JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2018, 83, 8170−8182
Article
pubs.acs.org/joc

Gold-Catalyzed Post-Ugi Ipso-Cyclization with Switchable Diastereoselectivity

Anton A. Nechaev,[†] Kristof Van Hecke,[‡] Manzoor Zaman,[§] Stepan Kashtanov,[∥] Liviu Ungur,[⊥] Olga P. Pereshivko,[§] Vsevolod A. Peshkov,*[,§] and Erik V. Van der Eycken*[,†,#]

[†]Laboratory of Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium

[‡]XStruct, Department of Chemistry, Ghent University, Krijgslaan 281-S3, B-9000 Ghent, Belgium

[§]College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Dushu Lake Campus, Suzhou 215123, China

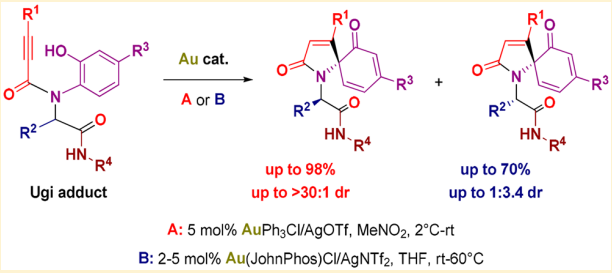
[∥]Institute of Functional Nano & Soft Materials (FUNSOM) and Jiangsu Key Laboratory for Carbon-Based Functional Materials & Devices, Soochow University, Suzhou 215123, China

[⊥]Theory of Nanomaterials Group, Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium

[#]Peoples' Friendship University of Russia (RUDN University), Miklukho-Maklaya Street 6, Moscow 117198, Russia

Supporting Information

ABSTRACT: A gold-catalyzed post-Ugi ipso-cyclization for the diastereoselective synthesis of spirocyclic pyrrol-2-one-dienone system is described. Tuning the catalytic system, solvent, and temperature allowed selectively attaining two sets of diastereoisomers. The scope of the process has been evaluated, and a putative mechanistic model was proposed.



INTRODUCTION

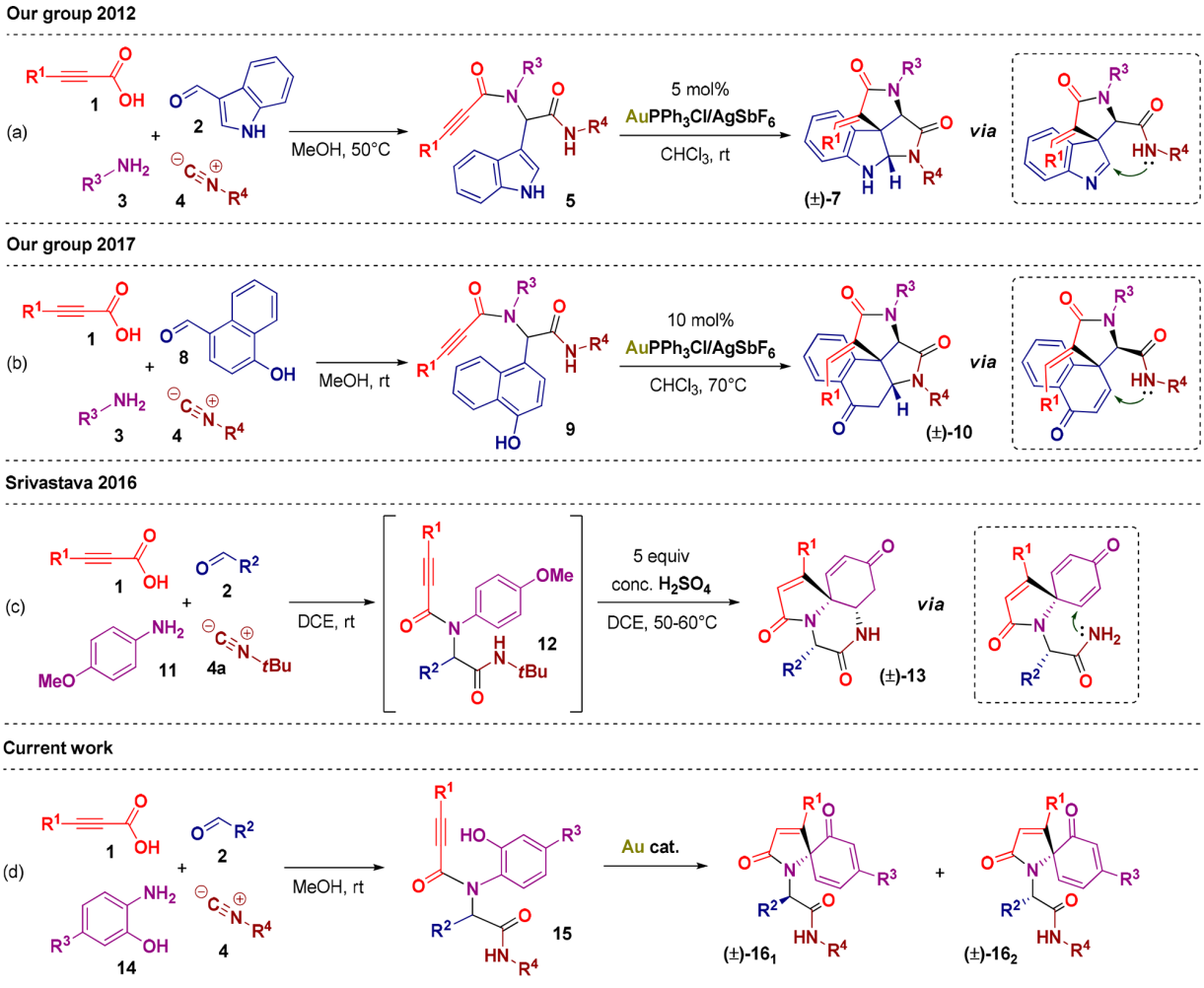
The intramolecular Friedel−Crafts reaction of electron rich arenes with alkynes activated by an electrophile, Brønsted or Lewis acid constitutes a versatile approach to assemble a wide array of polycyclic cores.[1,2] In general, depending on an arene substitution pattern, two kinds of reaction pathways are possible. The first one involves cyclization onto an *ortho*-position of the arene, leading to the formation of fused polycyclic compounds via direct triple bond hydroarylation.[3,4] Alternatively, the alkyne tether could engage into an ipso-cyclization involving dearomatization and the formation of spirocyclic molecules.[5−7] In certain cases, the initial ipso attack is followed by cationic skeletal rearrangement, restoring aromaticity and eventually leading to the formation of fused cycles.[8]

A four-component Ugi reaction is a practical venue to access precursors for diversity-oriented synthesis of heterocyclic libraries.[9,10] It permits a prompt installment of prerequisite functional groups in the resulting Ugi adducts, while simultaneously acting as a powerful diversification tool. For example, using alkynoic acids, the alkyne moiety could be introduced, which, given the presence of an appropriate nucleophilic site, opens the way toward a large variety of post-Ugi hetero-[11] and carbocyclizations.[12] In particular, a number of domino approaches were developed based on the following common scenario. The ipso-attack of an electron-rich arene onto a triple bond generates a novel electrophilic unit that undergoes subsequent trapping by the isocyanide-originated amide nitrogen producing a complex polycyclic framework (Scheme 1a−c). In 2012, our group exploited alkynoic acids **1** and indole-3-carbaldehyde (**2**) to assemble Ugi adducts **5** that could be readily transformed into polycyclic spiroindolinones **7** via a gold(I)-catalyzed diastereoselective domino cyclization process (Scheme 1a).[13] Analogously, replacement of indole-3-carbaldehyde (**2**) by 4-hydroxy-1-naphthaldehyde (**8**) gave rise to adducts **9** that underwent a cationic Au(I)-catalyzed domino 5-*exo*-*dig* cyclization/aza-Michael reaction yielding tetracyclic scaffolds **10** in a fully diastereoselective fashion (Scheme 1b).[14] Using an electron rich arene as amine component in the Ugi reaction uncovered another fascinating niche. In 2016, Srivastava and co-workers utilized 4-methoxyaniline (**11**) to attain Ugi products **12** that could be in situ converted into tricyclic structures **13** upon treatment with concentrated sulfuric acid (Scheme 1c).[15]

Received: April 16, 2018
Published: July 2, 2018

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

Scheme 1. Post-transformations of Alkynoic Acid Derived Ugi Adducts Generating Spirocyclic Architectures

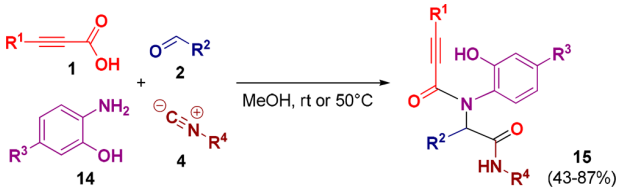


As a part of our efforts directed to the exploration of post-Ugi chemistry, we herein present a study on the cycloisomerization of 2-aminophenol-derived Ugi adducts **15** (Scheme 1d). In this case, the overall transformation did not affect the isocyanide-originated pendant, affording spirocyclic pyrrol-2-one-dienone system **16** as final product. Importantly, the diastereoselectivity[16] of this process could be efficiently modulated providing a selective access to both possible diastereomers. Considering the originality of such precedent for post-Ugi transformations and homogeneous gold catalysis, it became the major emphasis of the present investigation.

RESULTS AND DISCUSSION

First, a series of the required Ugi adducts **15** was conveniently prepared by reacting diverse alkynoic acids **1**, aldehydes **2**, 2-aminophenols **14** and isocyanides **4** in methanol at room temperature (Scheme 2). Then, the substrate **15a** was selected to perform a screening to identify the optimal conditions for the gold-catalyzed cycloisomerization into spiropyrrol-2-one-dienone **16a** (Table 1). To start, a number of preformed and in situ generated cationic gold(I) complexes featuring different ligands and counterions were evaluated using deuterated chloroform as solvent (Table 1, entries 1−6). To our delight, all reactions proceeded cleanly giving rise to the desired **16a** in

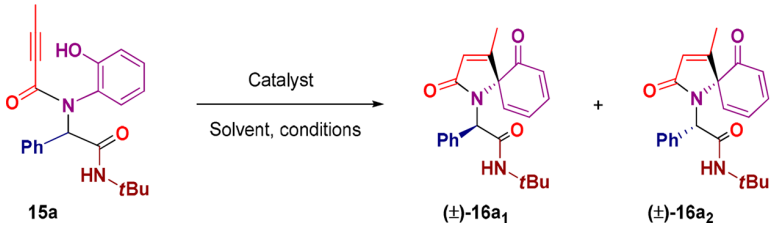
Scheme 2. Synthesis of Ugi Adducts 15



up to quantitative yield with different diastereomeric ratios. Using 5 mol % of the common $AuPPh_3Cl/AgOTf$ combination as precatalyst, a dr of 2:1 was obtained favoring the formation of the first diastereomer (entry 1). The reaction catalyzed by a preformed gold(I) complex bearing the bulky JohnPhos ligand required a longer time and led to a decreased dr of 1.4:1 (entry 2). Switching to Au complexes bearing a N-heterocyclic carbene as ligand resulted in a substantial improvement of the diastereoselectivity with the best result of 7:1 being obtained for the reaction with $AuIPrCl/AgNTf_2$ (entry 4). Next, we decided to evaluate the solvent effect keeping $AuPPh_3Cl/AgOTf$ as a standard precatalyst (entries 7−11 and 13−16). Moving from $CDCl_3$ to other chlorinated solvents such as DCM or 1,2-DCE did not provide much enhancement of the dr (entries 7 and 8 versus 1). Gratifyingly, improved results

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

Table 1. Screening of the Reaction Conditions for the Cyclization of Ugi Adduct 15a[a]



15a **(±)-16a$_1$** **(±)-16a$_2$**

entry	catalyst	solvent	conditions	conversion (%)[b]	yield (%)[c]	dr (1:2)[b]
Initial screening of cationic gold catalysts						
1	5 mol % $AuPPh_3Cl/AgOTf$	$CDCl_3$	rt, 5.5 h	100	quant	2:1
2	5 mol % $[Au(JohnPhos)(MeCN)]SbF_6$	$CDCl_3$	rt, 6.5 h	99	95	1.4:1
3	5 mol % AuIPrCl/AgOTf	$CDCl_3$	rt, 2 h	100	quant	5.9:1
4	5 mol % $AuIPrCl/AgNTf_2$	$CDCl_3$	rt, 2 h	100	quant	7:1
5	5 mol % $AuIPrCl/AgSbF_6$	$CDCl_3$	rt, 1.5 h	100	99	6.4:1
6	5 mol % $AuIPrCl/AgBF_4$	$CDCl_3$	rt, 1.5 h	100	quant	5.9:1
Solvent screening and identifying the optimal conditions for accessing the first diastereomer						
7	5 mol % $AuPPh_3Cl/AgOTf$	DCM	rt, 2 h	100	96	2.2:1
8	5 mol % $AuPPh_3Cl/AgOTf$	1,2-DCE	rt, 2.5 h	100	quant	2.3:1
9	5 mol % $AuPPh_3Cl/AgOTf$	CF_3CH_2OH	rt, 2.5 h	100	98	7.1:1
10	5 mol % $AuPPh_3Cl/AgOTf$	$MeNO_2$	rt, 2.5 h	100	quant	14.6:1
11	5 mol % $AuPPh_3Cl/AgOTf$	$MeNO_2$	2 °C, 5 h	100	quant	15.6:1
12	5 mol % $AuIPrCl/AgNTf_2$	$MeNO_2$	rt, 2 h	100	quant	5.3:1
13	5 mol % $AuPPh_3Cl/AgOTf$	MTBE	rt, 22 h	93	89	1.3:1
14	5 mol % $AuPPh_3Cl/AgOTf$	dioxane	rt, 4 h	96	95	1.3:1
15	5 mol % $AuPPh_3Cl/AgOTf$	2-MeTHF	rt, 22 h	87	81	1:1
16	5 mol % $AuPPh_3Cl/AgOTf$	THF	rt, 22 h	98	97	1:1.1
Identifying the optimal conditions for accessing the second diastereomer						
17	5 mol % $[Au(JohnPhos)(MeCN)]SbF_6$	THF	2 °C, 5 h	100	99	1:1.5
18	5 mol % $[Au(JohnPhos)(MeCN)]SbF_6$	THF	rt, 2 h	100	92	1:2.1
19	5 mol % $[Au(JohnPhos)(MeCN)]SbF_6$	THF	60 °C, 1 h	100	89	1:2.3
20	5 mol % Au(JohnPhos)Cl/AgOTf	THF	rt, 5 h	99	97	1:1.7
21	5 mol % $Au(JohnPhos)Cl/AgNTf_2$	THF	rt, 3 h	100	quant	1:2.3
22	5 mol % $Au(JohnPhos)Cl/AgNTf_2$	THF	60 °C, 1 h	100	89	1:2.4
23	2 mol % $Au(JohnPhos)Cl/AgNTf_2$	THF	rt, 4 h	100	97	1:2.7
24	1 mol % $Au(JohnPhos)Cl/AgNTf_2$	THF	rt, 24 h	99	97	1:2.8

[a]The reactions were run on a 0.2 mmol scale in 1 mL of solvent. [b]Determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [c]Combined yield of both diastereomers.

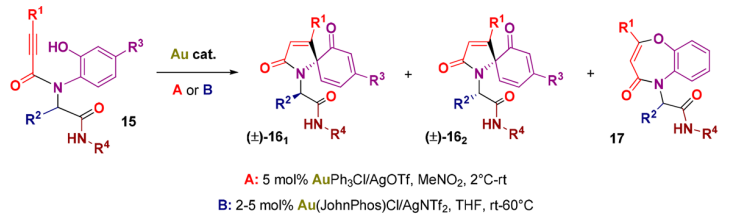
were obtained in protic and highly polar solvents such as trifluoroethanol and nitromethane (entries 9−11). For nitromethane, the dr could be further upgraded from 14.6:1 to 15.6:1 by moving from room temperature to 2 °C (entry 10 versus 11). However, no synergistic effect was observed when the reaction in nitromethane was conducted with AuIPrCl/$AgNTf_2$ precatalyst (entry 12). Several ethereal solvents were tested with the outcomes being not particularly diastereoselective (entries 13−16). However, when the reaction was performed in THF, a reversal of the diastereoselectivity to the second isomer was observed (entry 16). Enlightened by this result, we then focused our efforts on tuning the reaction parameters toward the formation of the second diastereomer, maintaining THF as the reaction medium (Table 1, entries 17−24). Much to our delight, the tangible progress could be quickly achieved using catalytic species bearing the bulky JohnPhos ligand, with the overall outcome being strongly affected by the reaction temperature and the catalyst loading. For example, the dr of $[Au(JohnPhos)(MeCN)]SbF_6$-catalyzed reactions steadily raised with temperature at the price of decreasing the overall yield of **16a** (entries 17−19). The same trend was observed for the reactions utilizing $Au(JohnPhos)Cl/AgNTf_2$ combination (entries 21 and 22). Finally, it was noted that the latter precatalytic system tended to provide a better selectivity upon reducing the catalyst loading, allowing to achieve up to a 1:2.8 dr with predominance of the second diastereomer (entries 21, 23 and 24).

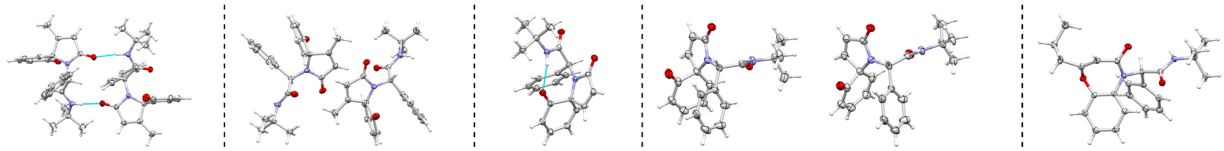
Encouraged by these results, we moved to exploring the scope and limitations of our process using a set of prepared Ugi adducts **15** (Table 2). Most of the reactions proceeded smoothly toward pyrrol-2-one-dienones **16** allowing to modulate the diastereoselectivity in accordance with the previously identified trend (conditions A and conditions B). Furthermore, in all instances the major isomers could be separated from the minor ones and from other byproducts.

At first, we have examined Ugi adducts **15a−e** derived from different alkynoic acids to check the influence of the R^1 substituent on the reaction outcome (Table 2, entries 1−5). The substrates **15c** and **15d** bearing a propyl or phenyl group on the triple bond, being subjected to the conditions B, also produced substantial amounts of O-cyclized benzo[*b*][1,4]-

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

Table 2. Scope of the Process[a]





16a$_1$ **16a$_2$** **16e$_1$** **16e$_2$** **17c**

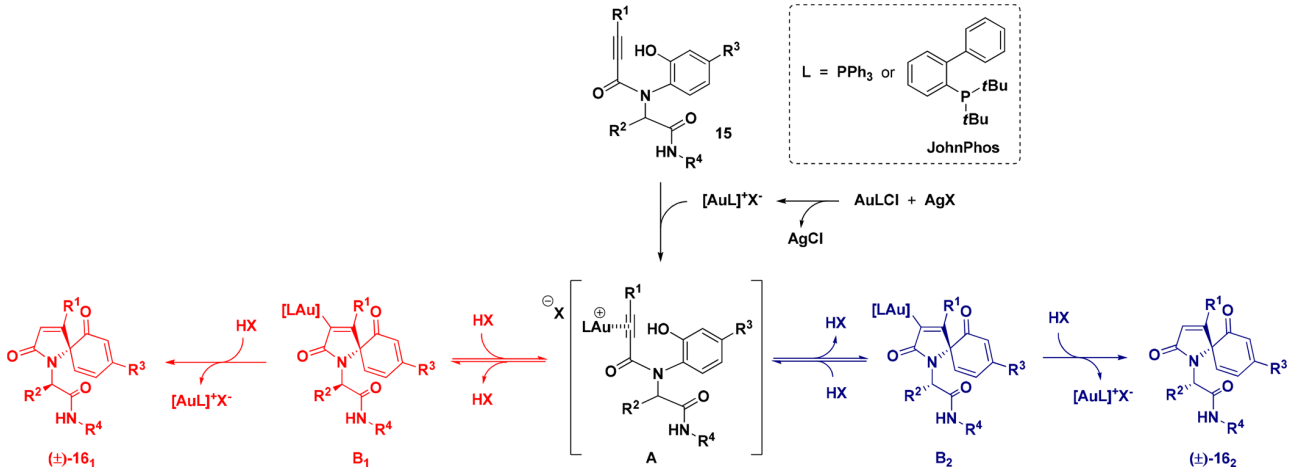
							yield[b]		
entry (**15**)	R^1	R^2	R^3	R^4	conditions	dr (1:2)	**16$_1$**	**16$_2$**	**17**
1 (**15a**)	Me	Ph	H	*t*Bu	**A**	15.6:1	**94**		
					B	1:2.3		**70**	
2 (**15b**)	Et	Ph	H	*t*Bu	**A**	4.7:1	77		
					B	1:3		**61**	
3 (**15c**)	Pr	Ph	H	*t*Bu	**A**	6.9:1	77		
					B	1:3.2		**43**	21
4 (**15d**)	Ph	Ph	H	*t*Bu	**A**	1.7:1	**51** (54)[c]		
					B	1:2.6		**44**	25
5 (**15e**)	H	Ph	H	*t*Bu	**A**	>30:1	**89**		
					B	1:1.2	36 (44)[c]	**48** (52)[c]	
6 (**15f**)	Me	4-CNC$_6$H$_4$	H	*t*Bu	**A**	5.2:1	**79**		
					B	1:2.5		**60** (72)[c]	
7 (**15g**)	Me	4-CF$_3$C$_6$H$_4$	H	*t*Bu	**A**	15.2:1	**92**		
					B	1:2.5		**60**	
8 (**15h**)	Me	4-MeOC$_6$H$_4$	H	*t*Bu	**A**	2.3:1	**66**		
					B	1:2.8		**65**	
9 (**15i**)	Me	Thiophen-2-yl	H	*t*Bu	**A**	1.6:1	**54**		
					B	1:2.1		**66**	
10 (**15j**)	Me	Cy	H	*t*Bu	**A**	30:1	**91**		
					B	2:1	50 (60)[c]	25 (30)[c]	
11 (**15k**)	Me	Ph	Me	*t*Bu	**A**	>30:1	**98**		
					B	1:2.4		**70**	
12 (**15l**)	Me	Ph	Cl	*t*Bu	**A**	7.4:1	**87**		
					B	1:2.8		**69**	
13 (**15m**)	Me	Ph	H	Cy	**A**	6:1	**85**		
					B	1:2.8		**60**	
14 (**15n**)	Me	Ph	H	1,1,3,3-Tetramethylbutyl	**A**	5.5:1	**75** (80)[c]		
					B	1:2.4		**65**	
15 (**15o**)	Me	Ph	H	Bn	**A**	2.4:1	**45** (65)[c]		
					B	1:3.4		**53** (68)[c]	
16 (**15p**)	Me	Ph	H	2-Naphtyl	**A**	7.7:1	**59** (67)[c]		
					B	1:3.2		**51**	

[a]The reactions were run on 0.4 mmol scale in 2 mL of solvent (MeCN for conditions A, THF for conditions B). [b]Isolated yields are reported. [c]When the purification or separation of isomers was difficult, the corresponding ^{1}H NMR yields are also given in parentheses (determined using 3,4,5-trimethoxybenzaldehyde as internal standard).

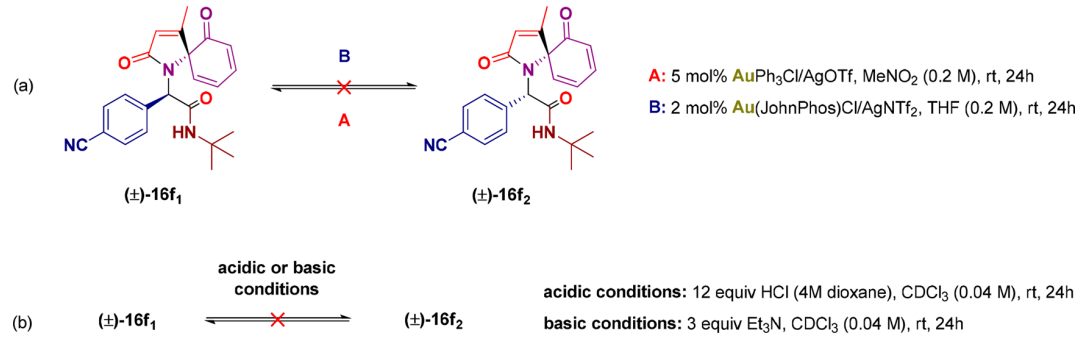
oxazepines **17** in addition to the expected pyrrol-2-one-dienones **16** (entries 3 and 4).[17] The reactions with Ugi adducts **15a** and **15b** with less crowded internal alkynes (entries 1 and 2) as well as with substrate **15e** bearing a terminal alkyne (entry 5) delivered no O-cyclized products **17**. Thus, it can be assumed that excessive steric hindrance is disadvantageous for the formation of the congested spiro framework **16**. Substrate **15e** gave the best diastereoselectivity under conditions A among all Ugi adducts with different R^1 group, while using conditions B the poorest dr in the series was observed (entry 5). The structures of representative pyrrol-2-one-dienones **16a$_1$**, **16a$_2$**, **16e$_1$**, **16e$_2$** and benzo[*b*][1,4]-oxazepine **17c** were established by X-ray crystallographic analysis.[18,19] Evaluating the substrates **15f–j** with different

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170–8182

Scheme 3. Mechanistic Model for a Gold(I)-Catalyzed Ipso-Cyclization of Ugi Adducts 15



Scheme 4. Control Experiments



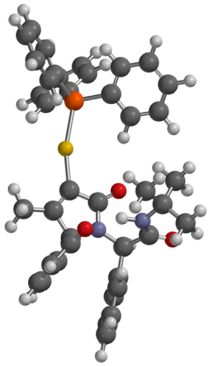
aldehyde-originated R^2 substituents (Table 2, entries 6−10) led to identifying an important limitation of the conditions B evoked by the unexpected inversion of the dr. Thus, the reaction with Ugi adduct **15j** bearing an aliphatic cyclohexyl group at the peptidyl position provided pyrrol-2-one-dienone **16j**$_1$ as the major product under either of tested conditions (entry 10). Reacting Ugi adducts **15h** and **15i** derived from electron rich (hetero)aromatic aldehydes produced pyrrol-2-one-dienones **16h** and **16i** with good diastereoselectivity under both conditions proving that our methodology does not suffer from the possible competition between two electron rich arene fragments (entries 8 and 9). The introduction of a methyl or chlorine group into the 2-aminophenol core was well tolerated, allowing to attain diastereoselective outcomes under both reaction settings (Table 2, entries 11−12). Finally, for the isocyanide-originated fragments, the R^4 substituent could be successfully represented by aliphatic, benzylic or aromatic groups (Table 2, entries 13−16), although in certain cases a drop of isolated yields for the desired isomers was observed due to the difficult purification.

A tentative mechanistic model for the gold(I)-catalyzed ipso-cyclization of Ugi adducts **15** is given in Scheme 3. When using the Au/Ag precatalytic combination, the process starts with the formation of an active catalytic species from a ligand-gold chloride complex and a silver(I) salt AgX, in which X represents a weakly coordinating counteranion such as triflate ($^-$OTf) or triflimide ($^-$NTf$_2$). The driving force of this anion exchange is the formation and the consequent precipitation of AgCl.[20] Once cationic gold is formed, it will π-coordinate to the triple bond of the substrate to form complex **A**. Next, the activated triple bond undergoes nucleophilic attack by the phenol moiety to form an intermediate vinyl gold complex **B**$_1$ or **B**$_2$. Finally, the cyclized product **16**$_1$ or **16**$_2$ is formed by protodeauration, releasing cationic gold and enabling turnover.

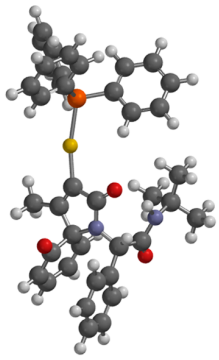
We assume that the protonolysis of **B** into **16** is not reversible as was supported by the control experiments in which no interconversion was observed when the diastereomer **16f**$_1$ was resubjected to conditions B, and the diastereomer **16f**$_2$ to conditions A (Scheme 4a). Likewise, the treatment of either of diastereomers with acid or base did not lead to equilibration (Scheme 4b), suggesting that the observed diastereomeric ratios were unlikely to be affected by the enolization-triggered epimerization of the stereocenter at the peptidyl position of **16**.[21] Therefore, we speculate that the diastereoselectivity of the process is defined during the reversible ring-closure of the π-complex **A** into the vinyl gold complex **B**. Conformational analysis and geometry optimization using SPARTAN program suite[22] revealed that the intermediates **B**$_{a1}$ and **B**$_{a1}$′ leading to the product **16a**$_1$ are more energetically favorable than the corresponding intermediates **B**$_{a2}$ and **B**$_{a2}$′ that are responsible for the formation of **16a**$_2$ (Table 3). In line with this, for the final pyrrol-2-one-dienone products, the first diastereomer **16a**$_1$ was found to be more energetically favorable as compared to the second isomer **16a**$_2$ (Table 3). These results point to the thermodynamic preference of the pathway generating products **16**$_1$.

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

Table 3. Gas Phase Optimized Geometries of Vinyl Gold Intermediates B_{a1} versus B_{a2} and Corresponding Pyrrol-2-one-dienones $16a_1$ versus $16a_2$



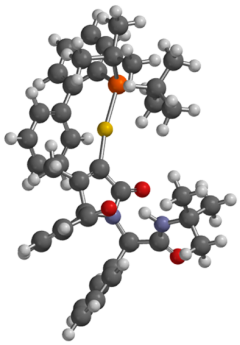
B_{a1} (L = PPh_3)



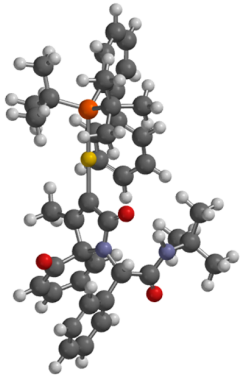
B_{a2} (L = PPh_3)

Method ωB97X-D/LANL2DZ

$\Delta E_{1\text{-}2}$ = -9.1 kJ/mol (gas phase); - 17.5 kJ/mol (in $MeNO_2$)



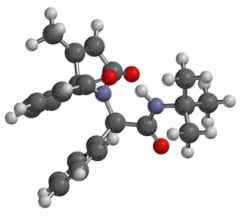
B_{a1}' (L = JohnPhos)



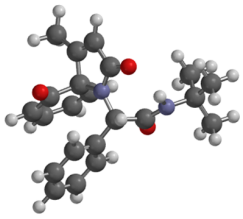
B_{a2}' (L = JohnPhos)

Method ωB97X-D/LANL2DZ

$\Delta E_{1\text{-}2}$ = - 4.8 kJ/mol (gas phase); - 10.4 kJ/mol (in THF)



$16a_1$



$16a_2$

Method ωB97X-D/6-31G*

$\Delta E_{1\text{-}2}$ = - 6.2 kJ/mol (gas phase)

CONCLUSIONS

In summary, we have found that Ugi adducts derived from alkynoic acids and 2-aminophenols could readily engage into gold-catalyzed intramolecular Friedel−Crafts reactions producing spirocyclic pyrrol-2-one-dienones. These reactions could be effectively directed to two different modes by choosing the appropriate catalytic system, providing a selective access to two sets of diastereomeric products. The crucial factors affecting the reaction outcome include the effect of the ligand and the counterion, as well as the influence of the solvent, the temperature, and the catalyst loading. The described findings could be useful for designing and optimizing novel stereoselective gold-catalyzed transformations.

EXPERIMENTAL SECTION

General Remarks. The starting materials and solvents were purchased from commercial sources and used as received. The ^1H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. HRMS ESI spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer. Samples were infused at 3 μL/min, and spectra were obtained in positive ionization mode with a resolution of 15 000 (fwhm) using leucine enkephalin as lock mass.

Synthesis of Ugi Adducts 15. Alkynoic acid **1** (2.0 mmol) was dissolved in methanol (8.0 mL) followed by the addition of aldehyde **2** (2 mmol), 2-aminophenol **14** (2 mmol) and isocyanide **4** (2 mmol). The reaction mixture was stirred at room temperature for 24 h. The resulting mixture was diluted with DCM. Then the silica gel was added, and the volatiles were removed under reduced pressure. Column chromatography with heptane/EtOAc (the ratio was adjusted according to TLC) as eluent delivered Ugi adduct **15**.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15a).** Yield: 561 mg, 77%; pale orange solid; ∼3:17 mixture of rotamers; ^1H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 0.85H), 10.78 (s, 0.15H), 7.54−7.37 (m, 0.75H), 7.29−7.08 (m, 4.4H), 7.08−6.97 (m, 1H), 6.92 (dd, *J* = 7.7, 1.6 Hz, 0.15H), 6.84 (dd, *J* = 8.2, 1.3 Hz, 0.85H), 6.77−6.68 (m, 0.15H), 6.46−6.34 (m, 1.7H), 5.87 (s, 0.85H), 5.53 (bs, 1H), 4.71 (s, 0.15H), 1.71 (s, 0.45H), 1.68 (s, 2.55H), 1.35 (s, 7.65H), 1.31 (s, 1.35H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 171.7, 156.3, 156.1, 133.0, 132.2, 130.2, 129.9, 129.1, 128.8, 125.2, 118.6, 117.6, 90.3, 73.5, 65.5, 52.8, 28.5, 4.0; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{25}N_2O_3^+$ calcd 365.1860, found 365.1855.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)pent-2-ynamide (15b).** Yield: 621 mg, 82%; pale orange solid; ∼3:17 mixture of rotamers; ^1H NMR (300 MHz, $CDCl_3$) δ 11.07 (s, 0.85H), 10.77 (s, 0.15H), 7.53−7.39 (m, 0.75H), 7.28−7.09 (m, 4.4H), 7.07−6.97 (m, 1H), 6.95−6.90 (m, 0.15H), 6.87−6.80 (m, 0.85H), 6.75−6.67 (m, 0.15H), 6.46−6.33 (m, 1.7H), 5.88 (s, 0.85H), 5.54 (bs, 1H), 4.73 (s, 0.15H), 2.05 (q, *J* = 7.5 Hz, 0.3H), 2.01 (q, *J* = 7.4 Hz, 1.7H), 1.35 (s, 7.65H), 1.31 (s, 1.35H), 0.83 (t, *J* = 7.5 Hz, 0.45H), 0.79 (t, *J* = 7.5 Hz, 2.55H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 171.7, 156.4, 156.1, 133.1, 132.3, 130.2, 130.0, 129.1, 128.9, 125.4, 118.6, 117.5, 95.6, 73.8, 65.4, 52.8, 28.5, 12.6, 12.5; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2009.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)hex-2-ynamide (15c).** Yield: 636 mg, 81%; pale orange solid; ∼7:43 mixture of rotamers; ^1H NMR (300 MHz, $CDCl_3$) δ 11.07 (s, 0.86H), 10.77 (s, 0.14H), 7.53−7.40 (m, 0.7H), 7.27−7.19 (m, 4.44H), 7.07−6.95 (m, 1H), 6.95−6.89 (m, 0.14H), 6.86−6.79 (m, 0.86H), 6.75−6.67 (m, 0.14H), 6.45−6.34 (m, 1.72H), 5.88 (s, 0.86H), 5.60−5.48 (m, 1H), 4.72 (s, 0.14H), 2.08−1.96 (m, 2H), 1.35 (s, 7.74H), 1.31 (s, 1.26H), 1.26−1.09 (m, 2H), 0.71−0.61 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 171.6, 156.3, 156.0, 132.9, 132.2, 130.1, 129.8, 129.0, 128.7, 125.2, 118.5, 117.4, 94.3, 74.4, 65.3, 52.7, 28.4, 21.0, 20.7, 13.1; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{29}N_2O_3^+$ calcd 393.2173, found 393.2170.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)-3-phenylpropiolamide (15d).** Yield: 461 mg, 54%; pale brown solid; ∼3:17 mixture of rotamers; ^1H NMR (300 MHz, $CDCl_3$) δ 11.16 (s, 0.85H), 10.86 (s, 0.15H), 7.59−7.42 (m, 0.75H), 7.35−6.97 (m, 10.55H), 6.94−6.86 (m, 0.85H), 6.82−6.74 (m, 0.15H), 6.53−6.44 (m, 1.7H), 5.95 (s, 0.85H), 5.58 (bs, 1H), 4.81 (s, 0.15H), 1.38 (s, 7.65H), 1.34 (s, 1.35H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 171.6, 156.7, 156.2, 133.0, 132.9, 132.5, 130.4, 130.2, 130.0, 129.3, 128.9, 128.3, 125.3, 120.3, 118.7, 117.6, 91.3, 82.0, 65.5, 52.9, 28.5; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{27}N_2O_3^+$ calcd 427.2016, found 427.2019.

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)propiolamide (15e).** Yield: 533 mg, 76%; pale brown solid; ~7:43 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.05 (s, 0.86H), 10.76 (s, 0.14H), 7.54−7.40 (m, 0.7H), 7.32−7.00 (m, 5.44H), 6.93 (dd, J = 7.8, 1.6 Hz, 0.14H), 6.86 (dd, J = 8.2, 1.3 Hz, 0.86H), 6.79−6.70 (m, 0.14H), 6.48−6.34 (m, 1.72H), 5.88 (s, 0.86), 5.58−5.49 (m, 1H), 4.74 (s, 0.14H), 2.81 (s, 0.14H), 2.76 (s, 0.86H), 1.36 (s, 7.74H), 1.32 (s, 1.26H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 171.3, 156.4, 154.8, 132.6, 132.2, 130.7, 130.0, 129.4, 129.0, 124.6, 118.8, 117.8, 79.5, 75.7, 65.6, 52.9, 28.5; HRMS (ESI, $[M + H]^+$) for $C_{21}H_{23}N_2O_3^+$ calcd 351.1703, found 351.1698.

***N*-(2-(*tert*-Butylamino)-1-(4-cyanophenyl)-2-oxoethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15f).** Yield: 670 mg, 86%; pale yellow solid; ~3:22 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.96 (s, 0.88H), 10.52 (s, 0.12H), 7.74 (d, J = 8.4 Hz, 0.24H), 7.64 (d, J = 8.3 Hz, 0.24H), 7.47 (d, J = 8.4 Hz, 1.76H), 7.31−7.23 (m, 1.88H), 7.10−6.99 (m, 1H), 6.89−6.82 (m, 1H), 6.78−6.70 (m, 0.12H), 6.50−5.41 (m, 0.88H), 6.37 (dd, J = 7.9, 1.7 Hz, 0.88H), 5.88 (s, 0.88H), 5.85 (bs, 1H), 4.78 (s, 0.12H), 1.72 (s, 0.36H), 1.67 (s, 2.64H), 1.36 (s, 7.92H), 1.32 (s, 1.08H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 170.7, 156.2, 156.1, 138.1, 132.6, 131.9, 130.8, 130.6, 124.6, 119.1, 118.1, 117.9, 113.2, 91.2, 73.2, 65.1, 53.1, 28.5, 4.0; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{24}N_3O_3^+$ calcd 390.1812, found 390.1807.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-(4-(trifluoromethyl)phenyl)-ethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15g).** Yield: 726 mg, 84%; white solid; ~4:21 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.97 (s, 0.84H), 10.64 (s, 0.16H), 7.71 (d, J = 8.5 Hz, 0.32H), 7.65 (d, J = 8.6 Hz, 0.32H), 7.43 (d, J = 8.1 Hz, 1.68H), 7.30−7.23 (m, 1.84H), 7.10−6.99 (m, 1H), 6.92−6.82 (m, 1H), 6.78−6.70 (m, 0.16H), 6.48−6.41 (m, 0.84H), 6.37 (dd, J = 7.9, 1.7 Hz, 0.84H), 5.89 (s, 0.84H), 5.60 (bs, 0.84H), 5.38 (bs, 0.16H), 4.78 (s, 0.16H), 1.73 (s, 0.48H), 1.68 (s, 2.52H), 1.36 (s, 7.56H), 1.33 (s, 1.44H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 170.9, 156.1, 156.0, 136.8, 131.9, 131.1 (q, J = 32.7 Hz), 130.5, 130.2, 125.6 (q, J = 3.6 Hz), 124.6, 123.6 (q, J = 272.4 Hz), 118.9, 117.7, 90.8, 73.2, 64.9, 52.9, 28.3, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{24}F_3N_2O_3^+$ calcd 433.1734, found 433.1730.

***N*-(2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15h).** The reaction was conducted on 3 mmol scale at 50 °C for 48 h. Yield: 604 mg, 51%; white solid; ~7:43 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 0.86H), 10.75 (s, 0.14H), 7.42 (d, J = 8.7 Hz, 0.28H), 7.26−7.18 (m, 0.14H), 7.07−6.95 (m, 2.72H), 6.92 (d, J = 8.9 Hz, 0.28H), 6.88 (dd, J = 7.8, 1.6 Hz, 0.14H), 6.83 (dd, J = 8.2, 1.3 Hz, 0.86H), 6.74−6.62 (m, 1.86H), 6.47−6.39 (m, 0.86), 6.36 (dd, J = 7.8, 1.7 Hz, 0.86H), 5.87 (s, 0.86H), 5.86 (bs, 0.86H), 5.57 (bs, 0.14H), 4.61 (s, 0.14H), 3.82 (s, 0.42H), 3.68 (s, 2.58H), 1.66 (s, 0.42H), 1.62 (s, 2.58H), 1.33 (s, 7.74H), 1.29 (s, 1.26H);^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 172.0, 159.9, 156.3, 156.0, 132.2, 131.1, 130.2, 125.3, 125.0, 118.7, 117.5, 114.1, 90.1, 73.6, 64.8, 55.2, 52.6, 28.5, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_4^+$ calcd 395.1965, found 395.1945.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-(thiophen-2-yl)ethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15i).** The reaction was conducted on 3 mmol scale at 50 °C for 48 h. Yield: 478 mg, 43%; biege solid; ~19:31 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 0.62H), 10.73 (s, 0.38H), 7.44−7.38 (m, 0.38H), 7.29−7.22 (m, 0.38H), 7.18−7.11 (m, 1H), 7.10−6.99 (m, 1.38H), 6.93−6.88 (m, 1H), 6.86 (dd, J = 8.2, 1.3 Hz, 0.62H), 6.80−6.70 (m, 1H), 6.59 (dd, J = 7.8, 1.7 Hz, 0.62H), 6.55−6.48 (m, 0.62H), 6.08 (s, 0.62H), 5.96 (bs, 0.62H), 5.85 (bs, 0.38H), 4.95 (s, 0.38H), 1.68 (s, 1.14H), 1.65 (s, 1.86H), 1.36 (s, 5.58H), 1.32 (s, 3.42H);^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 169.5, 156.3, 155.9, 155.1, 154.6, 136.0, 134.2, 132.1, 130.9, 130.5, 129.63, 129.62, 129.1, 128.9, 127.9, 127.2, 126.9, 124.9, 119.2, 118.7, 118.2, 117.6, 90.9, 90.5, 73.4, 73.2, 66.4, 60.3, 52.8, 52.7, 28.41, 28.39, 3.99, 3.97; HRMS (ESI, $[M + H]^+$) for $C_{20}H_{23}N_2O_3S^+$ calcd 371.1424, found 371.1435.

***N*-(2-(*tert*-Butylamino)-1-cyclohexyl-2-oxoethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15j).** Yield: 578 mg, 78%; pale brown solid; ~1:19 mixture of rotamers; ^{1}H NMR (400 MHz, $CDCl_3$, major rotamer) δ 11.73 (s, 1H), 7.30−7.18 (m, 1H), 7.11−7.03 (m, 1H), 7.03−6.95 (m, 1H), 6.84−6.74 (m, 1H), 5.80 (bs, 1H), 4.18 (d, J = 7.1 Hz, 1H), 1.82−1.73 (m, 1H), 1.72−1.34 (m, 17H), 1.14−0.80 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 173.0, 157.1, 156.5, 132.9, 130.8, 124.4, 118.4, 118.3, 90.7, 73.9, 67.7, 52.8, 36.7, 33.2, 29.5, 28.6, 26.1, 26.01, 25.97, 4.0; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{31}N_2O_3^+$ calcd 371.2329, found 371.2324.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxy-4-methylphenyl)but-2-ynamide (15k).** Yield: 643 mg, 85%; yellow solid; ~4:21 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.92 (s, 0.84H), 10.62 (s, 0.16H), 7.52−7.37 (m, 0.8H), 7.23−7.07 (m, 4.2H), 6.89−6.85 (m, 0.16H), 6.79 (d, J = 7.9 Hz, 0.16H), 6.69−6.63 (m, 0.84H), 6.56−6.49 (m, 0.16H), 6.27−6.19 (m, 1,68H), 5.87 (s, 0.84H), 5.51 (bs, 1H), 4.68 (s, 0.16H), 2.32−2.29 (m, 0.48H), 2.17−2.12 (m, 2.52H), 1.74 (s, 0.48H), 1.70 (s, 2.52H), 1.35 (s, 7.56H), 1.31 (s, 1.44H); ^{13}C NMR (151 MHz, $CDCl_3$, major rotamer) δ 171.7, 156.3, 155.8, 140.4, 133.1, 131.8, 130.0, 129.1, 128.8, 122.5, 119.6, 117.9, 90.2, 73.6, 65.4, 52.8, 28.5, 21.4, 4.1; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2016.

***N*-(2-(*tert*-Butylamino)-2-oxo-1-phenylethyl)-*N*-(4-chloro-2-hydroxyphenyl)but-2-ynamide (15l).** Yield: 622 mg, 78%; pale brown solid; ~3:22 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (s, 0.88H), 11.18 (s, 0.12H), 7.51−7.39 (m, 0.6H), 7.26−7.16 (m, 2.64H), 7.14−7.05 (m, 1.88H), 6.88−6.82 (m, 1H), 6.71 (dd, J = 8.3, 2.3 Hz, 0.12H), 6.41 (dd, J = 8.4, 2.3 Hz, 0.88H), 6.30 (d, J = 8.4 Hz, 0.88H), 5.85 (s, 0.88H), 5.54 (bs, 1H), 4.65 (s, 0.12H), 1.76 (s, 0.36H), 1.72 (s, 2.64H), 1.36 (s, 7.92H), 1.31 (s, 1.08H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 171.5, 157.1, 155.7, 135.3, 132.9, 132.6, 129.7, 129.3, 128.9, 123.9, 118.8, 117.8, 90.7, 73.2, 65.2, 52.8, 28.4, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{24}ClN_2O_3^+$ calcd 399.1470, found 399.1460.

***N*-(2-(Cyclohexylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15m).** Yield: 601 mg, 77%; dark pink solid; ~1:3 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.90 (s, 0.75H), 10.61 (s, 0.25H), 7.54−7.39 (m, 1.25H), 7.30−6.97 (m, 5H), 6.93 (dd, J = 7.7, 1.6 Hz, 0.25H), 6.86 (dd, J = 8.2, 1.4 Hz, 0.75H), 6.77−6.69 (m, 0.25H), 6.46−6.38 (m, 0.75H), 6.33 (dd, J = 7.9, 1.7 Hz, 0.75H), 6.00 (s, 0.75H), 5.66−5.52 (m, 1H), 4.77 (s, 0.25H), 3.96−3.76 (m, 1H), 2.09−1.93 (m, 1H), 1.90−0.90 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 171.4, 156.2, 156.0, 132.8, 132.1, 130.2, 129.9, 129.1, 128.7, 125.0, 118.6, 117.5, 90.3, 73.3, 64.8, 49.6, 32.5, 32.4, 25.4, 24.7, 24.6, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{27}N_2O_3^+$ calcd 391.2016, found 391.2013.

***N*-(2-Hydroxyphenyl)-*N*-(2-oxo-1-phenyl-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)but-2-ynamide (15n).** Yield: 732 mg, 87%; orange solid; ~6:19 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (s, 0.76H), 10.82 (s, 0.24H), 7.52−7.36 (m, 1.2H), 7.29−6.97 (m, 5.04H), 6.91 (dd, J = 7.8, 1.7 Hz, 0.24H), 6.86 (dd, J = 8.2, 1.3 Hz, 0.76H), 6.76−6.68 (m, 0.24H), 6.46−6.38 (m, 0.76H), 6.34 (dd, J = 7.8, 1.7 Hz, 0.76H), 5.86 (s, 0.76H), 5.67 (bs, 0.24H), 5.50 (bs, 0.76H), 4.68 (s, 0.24H), 1.77 (d, J = 15.0 Hz, 0.76H), 1.72 (s, 0.72H), 1.67 (s, 2.28H), 1.64 (d, J = 15.2 Hz, 0.24H), 1.56 (d, J = 15.0 Hz, 0.76H), 1.45−1.35 (m, 6.24H), 0.88 (s, 6.84H), 0.80 (s, 2.16H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 171.0, 156.3, 155.9, 132.7, 132.1, 130.1, 129.9, 129.0, 128.7, 125.1, 118.6, 117.4, 90.2, 73.4, 65.5, 56.7, 52.5, 31.5, 31.3, 28.8, 27.9, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{26}H_{33}N_2O_3^+$ calcd 421.2486, found 421.2479.

***N*-(2-(Benzylamino)-2-oxo-1-phenylethyl)-*N*-(2-hydroxyphenyl)but-2-ynamide (15o).** Yield: 606 mg, 76%; pale brown solid; ~1:4 mixture of rotamers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 0.8H), 10.43 (s, 0.2H), 7.56−7.49 (m, 0.4H), 7.43−7.37 (m, 0.6H), 7.34−6.99 (m, 10.2H), 6.94 (dd, J = 7.8, 1.6 Hz, 0.2H), 6.88 (dd, J = 8.2, 1.3 Hz, 0.8H), 6.79−6.71 (m, 0.2H), 6.48−6.40 (m, 0.8H), 6.36 (dd, J = 7.9, 1.7 Hz, 0.8H), 6.09−5.97 (m, 1.8H), 4.86 (s, 0.2H), 4.72−4.37 (m, 2H), 1.73 (s, 0.6H), 1.69 (s, 2.4H); ^{13}C NMR

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

(151 MHz, $CDCl_3$, major rotamer) δ 172.4, 156.1, 156.0, 137.0, 132.3, 132.1, 130.3, 130.0, 129.2, 128.8, 128.7, 127.7, 127.6, 124.9, 118.7, 117.5, 90.5, 73.3, 65.0, 44.2, 3.9; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{23}N_2O_3^+$ calcd 399.1703, found 399.1699.

***N*-(2-Hydroxyphenyl)-*N*-(2-(naphthalen-2-ylamino)-2-oxo-1-phenylethyl)but-2-ynamide (15p).** Yield: 504 mg, 58%; brown solid; ~3:22 mixture of rotamers; ^1H NMR (300 MHz, $CDCl_3$) δ 10.76 (bs, 1H), 8.75 (bs, 0.88H), 8.30−8.20 (m, 0.24H), 8.14 (d, J = 2.0 Hz, 0.88H), 8.10 (d, J = 2.1 Hz, 0.12H), 7.82−6.72 (m, 13.12H), 6.46−6.36 (m, 1.76H), 6.30 (dd, J = 7.9, 1.6 Hz, 0.88H), 5.05 (s, 0.12H), 1.73 (s, 0.36H), 1.70 (s, 2.64H); ^{13}C NMR (101 MHz, $CDCl_3$, major rotamer) δ 171.2, 156.4, 156.0, 134.7, 133.5, 132.04, 131.96, 130.8, 130.3, 130.1, 129.2, 128.8, 128.5, 127.7, 127.4, 126.3, 125.1, 119.8, 118.9, 117.5, 117.2, 91.2, 73.4, 66.0, 4.0; HRMS (ESI, $[M + H]^+$) for $C_{28}H_{23}N_2O_3^+$ calcd 435.1703, found 435.1689.

General Procedure for the Synthesis of Pyrrol-2-one-dienones 16_1 (First Diastereomer). An appropriate Ugi adduct **15** (0.4 mmol), $AuPPh_3Cl$ (5 mol %) and AgOTf (5 mol %) were placed to a glass vial followed by addition of cold nitromethane (0−5 °C, 2 mL). The mixture was allowed to react at the indicated temperature for the indicated time (see below for details). The resulting mixture was diluted with DCM. Then the silica gel was added and the volatiles were removed under reduced pressure. Column chromatography with heptane/EtOAc (the ratio was adjusted according to TLC) as eluent delivered pure pyrrol-2-one-dienones $\mathbf{16_1}$. For $\mathbf{16o_1}$, the crude mixture was not treated with silica gel prior to the loading onto chromatographic column.

(±)-(*R*)-*N*-*tert*-Butyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide ($\mathbf{16a_1}$). The reaction was conducted in fridge at 2 °C without stirring for 5 h. Yield: 137 mg, 94%; pale brown solid; mp 180−182 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.29−7.22 (m, 1H), 7.21−7.11 (m, 4H), 6.89 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.14 (dt, J = 9.8, 0.8 Hz, 1H), 6.06 (q, J = 1.5 Hz, 1H), 5.80 (ddd, J = 9.4, 6.1, 0.8 Hz, 1H), 5.59 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 5.23 (s, 1H), 1.72 (d, J = 1.5 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 172.3, 168.4, 156.8, 144.2, 140.8, 135.6, 130.2, 129.1, 128.6, 127.1, 124.6, 122.4, 78.2, 64.1, 51.4, 28.6, 12.1; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{25}N_2O_3^+$ calcd 365.1860, found 365.1859.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-4-ethyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide ($\mathbf{16b_1}$). The reaction was conducted in fridge at 2 °C without stirring for 24 h and then was additionally stirred at rt for 24 h. Yield: 117 mg, 77%; pale brown solid; mp 168−170 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (bs, 1H), 7.30−7.22 (m, 1H), 7.22−7.11 (m, 4H), 6.89 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.13 (dt, J = 9.8, 0.7 Hz, 1H), 6.07 (t, J = 1.9 Hz, 1H), 5.80 (ddd, J = 9.4, 6.0, 0.8 Hz, 1H), 5.62 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 5.21 (s, 1H), 2.14−1.81 (m, 2H), 1.43 (s, 9H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 172.4, 168.5, 163.1, 144.0, 140.9, 135.6, 130.1, 129.1, 128.6, 127.1, 122.6, 122.5, 88.0, 64.1, 51.4, 28.6, 19.1, 11.3; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2010.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-4-propyl-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide ($\mathbf{16c_1}$). The reaction was conducted in fridge at 2 °C without stirring for 24 h and then was additionally stirred at rt for 5 h. Yield: 121 mg, 77%; yellow solid; mp 131−133 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.29−7.21 (m, 1H), 7.21−7.13 (m, 4H), 6.89 (ddd, J = 9.8, 6.0, 1.8 Hz, 1H), 6.14 (dt, J = 9.9, 0.8 Hz, 1H), 6.06 (t, J = 1.8 Hz, 1H), 5.80 (ddd, J = 9.4, 6.0, 0.8 Hz, 1H), 5.60 (ddd, J = 9.4, 1.8, 0.8 Hz, 1H), 5.21 (s, 1H), 2.03−1.78 (m, 2H), 1.59−1.34 (m, 11H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 172.5, 168.5, 161.5, 144.2, 140.8, 135.5, 130.1, 129.1, 128.6, 127.1, 122.9, 122.5, 78.0, 64.0, 51.4, 28.6, 27.7, 20.3, 13.7; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{29}N_2O_3^+$ calcd 393.2173, found 393.2166.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide ($\mathbf{16d_1}$). The reaction was conducted in fridge at 2 °C without stirring for 24 h and then was additionally stirred at rt for 24 h. Yield: 87 mg, 51%; pale brown solid; mp 138−140 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 7.59 (bs, 1H), 7.43−7.15 (m, 11H), 6.81 (s, 1H), 6.38 (ddd, J = 9.4, 6.0, 0.7 Hz, 1H), 6.25 (dt, J = 9.9, 0.8 Hz, 1H), 6.11 (ddd, J = 9.4, 1.6, 0.8 Hz, 1H), 5.00 (s, 1H), 1.26 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 195.3, 170.9, 167.2, 157.5, 143.5, 138.9, 136.2, 130.6, 130.1, 128.7, 128.6, 128.0, 127.8, 127.2, 126.7, 125.6, 124.3, 74.3, 61.1, 50.5, 28.2; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{27}N_2O_3^+$ calcd 427.2016, found 427.2014.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide ($\mathbf{16e_1}$). The reaction was conducted at rt with stirring for 24 h. Yield: 125 mg, 89%; pale brown solid; mp 163−165 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (bs, 1H), 7.29−7.20 (m, 1H), 7.20−7.11 (m, 4H), 6.89 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.50 (d, J = 5.8 Hz, 1H), 6.33 (d, J = 5.8 Hz, 1H), 6.15 (dt, J = 9.9, 0.8 Hz, 1H), 5.69 (ddd, J = 9.3, 6.0, 0.8 Hz, 1H), 5.53 (ddd, J = 9.3, 1.8, 0.8 Hz, 1H), 5.28 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.2, 172.1, 168.1, 144.5, 143.9, 139.5, 135.3, 130.2, 129.2, 128.8, 128.6, 126.7, 121.5, 77.7, 64.1, 51.5, 28.6; HRMS (ESI, $[M + H]^+$) for $C_{21}H_{23}N_2O_3^+$ calcd 351.1703, found 351.1693.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-(4-cyanophenyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide ($\mathbf{16f_1}$). The reaction was conducted in fridge at 2 °C without stirring for 5 h. Yield: 123 mg, 79%; beige solid; mp 175−177 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.40 (bs, 1H), 7.07 (ddd, J = 9.9, 5.9, 1.8 Hz, 1H), 6.25−6.15 (m, 2H), 6.07 (q, J = 1.4 Hz, 1H), 5.82−5.73 (m, 1H), 5.07 (s, 1H), 1.79 (d, J = 1.5 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 172.4, 167.6, 157.3, 143.6, 140.6, 139.6, 132.3, 129.8, 127.5, 124.7, 124.4, 118.5, 112.5, 78.5, 63.6, 51.8, 28.5, 12.4; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{24}N_3O_3^+$ calcd 390.1812, found 390.1803.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-(4-(trifluoromethyl)phenyl)-acetamide ($\mathbf{16g_1}$). The reaction was conducted in fridge at 2 °C without stirring for 5 h. Yield: 159 mg, 92%; pale orange solid; mp 140−142 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.23 (bs, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.23−7.11 (m, 1H), 6.30−6.08 (m, 3H), 5.88−5.79 (m, 1H), 5.62 (s, 1H), 1.75−1.68 (m, 3H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.9, 172.0, 166.6, 157.4, 143.3, 142.3, 140.1, 129.0, 128.4 (q, J = 31.7 Hz), 127.2, 125.1 (q, J = 3.6 Hz), 124.1 (q, J = 272.1 Hz), 123.7, 123.2, 78.2, 59.1, 50.6, 28.2, 11.6; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{24}F_3N_2O_3^+$ calcd 433.1734, found 433.1733.

(±)-(*R*)-*N*-*tert*-Butyl-2-(4-methoxyphenyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide ($\mathbf{16h_1}$). The reaction was conducted in fridge at 2 °C without stirring for 48 h. Yield: 104 mg, 66%; biege solid; mp 197−198 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (bs, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.92 (ddd, J = 9.8, 6.0, 1.8 Hz, 1H), 6.68 (d, J = 8.7 Hz, 2H), 6.14 (dt, J = 9.9, 0.8 Hz, 1H), 6.04 (q, J = 1.4 Hz, 1H), 5.83 (ddd, J = 9.3, 6.1, 0.8 Hz, 1H), 5.59 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 5.18 (s, 1H), 3.75 (s, 3H), 1.72 (d, J = 1.5 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 172.0, 168.5, 160.3, 156.8, 144.5, 140.7, 131.3, 127.4, 126.7, 124.3, 121.8, 113.7, 77.9, 63.2, 55.2, 51.0, 28.3, 11.8; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_4^+$ calcd 395.1965, found 395.1956.

(±)-(*S*)-*N*-*tert*-Butyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-(thiophen-2-yl)acetamide ($\mathbf{16i_1}$). The reaction was conducted in fridge at 2 °C without stirring for 5 h and then was additionally stirred at rt for 14 h. Yield: 80 mg, 54%; biege solid; mp 70−71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.21 (dd, J = 5.1, 0.9 Hz, 1H), 6.98 (ddd, J = 9.8, 6.0, 1.7 Hz, 1H), 6.88−6.84 (m, 1H), 6.82 (dd, J = 5.1, 3.6 Hz, 1H), 6.19 (dt, J = 9.9, 0.8 Hz, 1H), 6.04 (q, J = 1.5 Hz, 1H), 5.93 (ddd, J = 9.3, 6.0, 0.7 Hz, 1H), 5.68 (ddd, J = 9.4, 1.6, 0.7 Hz, 1H), 5.50 (s, 1H), 1.75 (d, J = 1.5 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.0, 172.2, 167.5, 156.9, 143.9, 140.5, 137.4, 129.4, 127.2, 127.1, 124.5, 122.3, 78.2, 57.9, 51.5, 28.5, 12.2; HRMS (ESI, $[M + H]^+$) for $C_{20}H_{23}N_2O_3S^+$ calcd 371.1424, found 371.1440.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-cyclohexyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide ($\mathbf{16j_1}$). The reaction was conducted in fridge at 2 °C without stirring for 24 h. Yield: 135 mg, 91%; pale gray solid; mp 194−196 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (ddd, J = 9.9, 6.0, 1.7 Hz, 1H), 6.57 (ddd,

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

J = 9.5, 6.0, 0.8 Hz, 1H), 6,35 (bs, 1H), 6.22 (dt, J = 9.9, 0.7 Hz, 1H), 6.06 (ddd, J = 9.5, 1.6, 0.8 Hz, 1H), 5.98 (q, J = 1.5 Hz, 1H), 3.77 (d, J = 10.9 Hz, 1H), 2.21−2.01 (m, 1H), 1.80−1.55 (m, 8H), 1.34−1.02 (m, 12H), 1.02−0.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 173.3, 169.1, 156.9, 141.5, 138.5, 128.1, 125.4, 124.0, 78.0, 64.1, 51.6, 39.0, 29.8, 29.6, 28.7, 26.3, 25.8, 25.7, 12.2; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{31}N_2O_3^+$ calcd 371.2329, found 371.2324.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-4,8-dimethyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16k$_1$). The reaction was conducted in fridge at 2 °C without stirring for 5 h. Yield: 148 mg, 98%; yellow solid; mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (bs, 1H), 7.29−7.22 (m, 1H), 7.21−7.09 (m, 4H), 6.04 (q, J = 1.5 Hz, 1H), 6.01−5.97 (m, 1H), 5.61 (dd, J = 9.5, 1.4 Hz, 1H), 5.49 (d, J = 9.5 Hz, 1H), 5.22 (s, 1H), 1.94 (d, J = 1.3 Hz, 3H), 1.69 (d, J = 1.5 Hz, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 172.4, 168.6, 157.6, 157.0, 139.4, 135.4, 130.4, 129.0, 128.5, 126.0, 124.5, 124.4, 76.7, 64.3, 51.4, 28.6, 23.4, 12.2; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2013.

(±)-(*R*)-*N*-(*tert*-Butyl)-2-((*R*)-8-chloro-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16l$_1$). The reaction was conducted at rt with stirring for 24 h. Yield: 139 mg, 87%; pale brown solid; mp 174−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.38−7.26 (m, 1H), 7.25−7.12 (m, 4H), 6.33 (d, J = 1.5 Hz, 1H), 6.08 (q, J = 1.6 Hz, 1H), 5.75 (dd, J = 9.8, 1.8 Hz, 1H), 5.58 (d, J = 9.8 Hz, 1H), 5.28 (s, 1H), 1.73 (d, J = 1.6 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 172.0, 168.0, 156.4, 153.9, 140.8, 135.6, 130.1, 129.4, 128.7, 125.2, 124.9, 124.8, 76.5, 63.6, 51.4, 28.5, 12.1; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{24}ClN_2O_3^+$ calcd 399.1470, found 399.1468.

(±)-(*R*)-*N*-Cyclohexyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16m$_1$). The reaction was conducted at rt with stirring for 7 h. Yield: 133 mg, 85%; yellow solid; mp 138−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (d, J = 7.8 Hz, 1H), 7.32−7.15 (m, 5H), 7.11 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.18 (dt, J = 9.9, 0.8 Hz, 1H), 6.15 (q, J = 1.6 Hz, 1H), 6.03 (ddd, J = 9.4, 6.0, 0.7 Hz, 1H), 5.69 (ddd, J = 9.4, 1.7, 0.7 Hz, 1H), 5.53 (s, 1H), 3.61−3.42 (m, 1H), 1.80−1.59 (m, 7H), 1.58−1.45 (m, 1H), 1.36−1.07 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.7, 171.9, 166.9, 157.4, 143.8, 140.2, 136.9, 128.9, 128.2, 127.0, 123.3, 122.9, 78.0, 59.7, 47.3, 32.1, 32.1, 25.2, 24.1, 24.1, 11.5; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{27}N_2O_3^+$ calcd 391.2016, found 391.2009.

(±)-(*R*)-2-((*R*)-4-Methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)-acetamide (16n$_1$). The reaction was conducted at rt with stirring for 24 h. Yield: 126 mg, 75%; pale brown solid; mp 172−174 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (bs, 1H), 7.31−7.18 (m, 5H), 7.10 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.18 (dt, J = 9.8, 0.7 Hz, 1H), 6.13 (q, J = 1.6 Hz, 1H), 5.98 (ddd, J = 9.4, 6.0, 0.8 Hz, 1H), 5.70 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 5.40 (s, 1H) 1.75−1.59 (m, 5H), 1.34 (s, 3H), 1.30 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 196.0, 171.9, 167.2, 157.1, 144.0, 140.6, 136.8, 129.3, 128.2, 128.1, 126.8, 123.5, 122.6, 77.9, 60.9, 54.5, 51.5, 31.2, 31.1, 28.8, 27.6, 11.5; HRMS (ESI, $[M + H]^+$) for $C_{26}H_{33}N_2O_3^+$ calcd 421.2486, found 421.2483.

(±)-(*R*)-*N*-Benzyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16o$_1$). The reaction was conducted at rt with stirring for 2 h. Yield: 72 mg, 45%; yellow solid; mp 61−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29−8.16 (m, 1H), 7.41−7.22 (m, 6H), 7.21−7.11 (m, 4H), 6.89 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.11 (dt, J = 9.9, 0.8 Hz, 1H), 6.05 (q, J = 1.4 Hz, 1H), 5.82 (ddd, J = 9.3, 6.0, 0.8 Hz, 1H), 5.61 (ddd, J = 9.4, 1.8, 0.8 Hz, 1H), 5.43 (s, 1H), 4.63 (dd, J = 15.1, 6.0 Hz, 1H), 4.51 (dd, J = 15.0, 5.6 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 172.4, 169.6, 156.9, 144.2, 140.6, 138.4, 135.2, 130.2, 129.3, 128.7, 128.6, 127.8, 127.3, 127.1, 124.7, 122.6, 78.2, 63.4, 43.8, 12.2; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{23}N_2O_3^+$ calcd 399.1703, found 399.1697.

(±)-(*R*)-2-((*R*)-4-Methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-*N*-(naphthalen-2-yl)-2-phenylacetamide (16p$_1$). The reaction was conducted at rt with stirring for 96 h. Yield: 103 mg, 59%; brown solid; mp 96−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (bs, 1H), 8.48−8.43 (m, 1H), 7.83−7.74 (m, 4H), 7.47−7.34 (m, 2H), 7.33−7.23 (m, 3H), 7.22−7.13 (m, 2H), 6.95 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.24 (dt, J = 9.9, 0.7 Hz, 1H), 6.14 (q, J = 1.5 Hz, 1H), 5.82 (ddd, J = 9.4, 6.1, 0.8 Hz, 1H), 5.65 (ddd, J = 9.4, 1.7, 0.7 Hz, 1H), 5.55 (s, 1H), 1.79 (d, J = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 172.5, 168.1, 157.2, 144.9, 140.9, 135.8, 134.9, 134.1, 130.8, 130.3, 129.5, 128.9, 128.6, 127.9, 127.6, 127.1, 126.4, 124.9, 124.8, 122.5, 120.3, 116.7, 78.4, 64.6, 12.2; HRMS (ESI, $[M + H]^+$) for $C_{28}H_{23}N_2O_3^+$ calcd 435.1703, found 435.1694.

General Procedure for the Synthesis of Pyrrol-2-one-dienones 16$_2$ (Second Diastereomer). An appropriate Ugi adduct **15** (0.4 mmol), (2-biphenyl)di-*tert*-butylphosphine gold(I) chloride (2−5 mol %) and $AgNTf_2$ (2−5 mol %) were placed to a glass vial followed by addition of dry THF (2 mL). The mixture was sealed and kept with a stirring at indicated temperature for an indicated time (see below for details). The resulting mixture was diluted with DCM. Then the silica gel was added and the volatiles were removed under reduced pressure. Column chromatography with heptane/EtOAc (the ratio was adjusted according to TLC) as eluent delivered pure pyrrol-2-one-dienones **16$_2$**. For the substrates **15c** and **15d**, in addition to expected pyrrol-2-one-dienones **16**, the formation of substantial amount of *O*-cyclized benzo[*b*][1,4]oxazepines **17c** and **17d** was observed. The isolated products **17c** and **17d** were additionally washed with pentane after column chromatography. For the reactions with substrates **15e** and **15j**, in addition to expected second diastereomers, the formation of substantial amount of first diastereomers **16e$_1$** and **16j$_1$** was observed. These products were also isolated in 36% and 50% yields, respectively.

(±)-(*S*)-*N*-*tert*-Butyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16a$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 4 h. Yield: 102 mg, 70%; yellow solid; mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 6.98 (ddd, J = 9.9, 5.9, 1.8 Hz, 1H), 6.63 (bs, 1H), 6.35 (ddd, J = 9.5, 5.9, 0.8 Hz, 1H), 6.23 (ddd, J = 9.5, 1.8, 0.8 Hz, 1H), 6.05 (q, J = 1.5 Hz, 1H), 6.01 (dt, J = 9.9, 0.7 Hz, 1H), 4.83 (s, 1H), 1.76 (d, J = 1.6 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 172.1, 167.8, 156.4, 142.9, 140.3, 134.6, 130.4, 128.4, 128.3, 127.1, 125.1, 124.93, 124.92, 78.9, 62.8, 51.6, 28.6, 12.3; HRMS (ESI, $[M + H]^+$) for $C_{22}H_{25}N_2O_3^+$ calcd 365.1860, found 365.1860.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-4-ethyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16b$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at 60 °C for 72 h. Yield: 92 mg, 61%; white solid; mp 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5H), 6.98 (ddd, J = 9.9, 5.9, 1.8 Hz, 1H), 6.67 (bs, 1H), 6.34 (ddd, J = 9.5, 5.9, 0.8 Hz, 1H), 6.21 (ddd, J = 9.5, 1.8, 0.9 Hz, 1H), 6.07 (t, J = 1.9 Hz, 1H), 6.01 (dt, J = 9.9, 0.8 Hz, 1H), 4.79 (s, 1H), 2.23−1.84 (m, 2H), 1.37 (s, 9H), 1.07 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 172.1, 167.8, 162.6, 142.8, 140.4, 134.7, 130.36, 128.3, 128.3, 127.1, 125.1, 122.8, 78.7, 62.8, 51.6, 28.6, 19.4, 11.3; HRMS (ESI, $[M + H]^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2011.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-4-propyl-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16c$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at 60 °C for 8 h and then additionally at rt for 15 h. Yield: 68 mg, 43%; yellow solid; mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 5H), 6.98 (ddd, J = 9.9, 5.9, 1.8 Hz, 1H), 6.66 (bs, 1H), 6.34 (ddd, J = 9.5, 5.9, 0.8 Hz, 1H), 6.22 (ddd, J = 9.5, 1.8, 0.9 Hz, 1H), 6.06 (t, J = 1.8 Hz, 1H), 6.01 (dt, J = 9.9, 0.8 Hz, 1H), 4.80 (s, 1H), 2.10−1.80 (m, 2H), 1.60−1.20 (m, 11H), 0.87 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 172.2, 167.8, 161.0, 142.7, 140.4, 134.7, 130.4, 128.3, 128.2, 127.2, 125.1, 123.3, 78.6, 62.8, 51.6, 28.7, 28.1, 20.4, 13.7; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{29}N_2O_3^+$ calcd 393.2173, found 393.2168.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-4-phenyl-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16d$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at 60 °C for 24 h. Yield: 75 mg, 44%; pale gray solid; mp 194−196 °C;

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.61 (bs, 1H), 7.41−7.10 (m, 10H), 6.90−80 (m, 2H), 6.54 (ddd, J = 9.4, 1.7, 0.9 Hz, 1H), 6.35 (ddd, J = 9.5, 6.0, 0.7 Hz, 1H), 5.75 (dt, J = 9.9, 0.8 Hz, 1H), 5.22 (s, 1H), 1.23 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 195.0, 171.2, 167.8, 157.8, 141.9, 139.2, 133.7, 131.4, 130.6, 130.1, 128.7, 128.0, 127.4, 126.5, 126.3, 125.5, 124.0, 73.5, 60.9, 50.3, 28.3; HRMS (ESI, [M + H]$^+$) for $C_{27}H_{27}N_2O_3^+$ calcd 427.2016, found 427.2015.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16e$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 24 h and then additionally at 60 °C for 7 h. Yield: 67 mg, 48%; orange solid; mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 6.99 (ddd, J = 9.9, 4.8, 3.0 Hz, 1H), 6.63 (bs, 1H), 6.57 (d, J = 5.8 Hz, 1H), 6.35 (d, J = 5.8 Hz, 1H), 6.28−6.21 (m, 2H), 6.04 (dt, J = 9.9, 0.8 Hz, 1H), 4.89 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 171.8, 167.6, 144.1, 142.7, 139.3, 134.4, 130.4, 129.2, 128.5, 128.4, 127.1, 124.2, 78.4, 62.5, 51.7, 28.7; HRMS (ESI, [M + H]$^+$) for $C_{21}H_{23}N_2O_3^+$ calcd 351.1703, found 351.1700.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-(4-cyanophenyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide (16f$_2$). The reaction was conducted using 2 mol % of gold and silver precatalysts at rt for 4 h. Yield: 93 mg, 60%; beige solid; mp 212−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.86 (bs, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.11 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.40 (ddd, J = 9.4, 6.0, 0.8 Hz, 1H), 6.19 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 6.12 (q, J = 1.6 Hz, 1H), 6.02 (dt, J = 9.9, 0.7 Hz, 1H), 5.33 (s, 1H), 1.67 (d, J = 1.5 Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 195.8, 171.7, 166.8, 157.2, 143.1, 141.5, 139.6, 131.4, 130.9, 126.8, 125.2, 123.5, 118.7, 110.3, 77.6, 60.5, 50.5, 28.2, 11.6; HRMS (ESI, [M + H]$^+$) for $C_{23}H_{24}N_3O_3^+$ calcd 390.1812, found 390.1805.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-(4-(trifluoromethyl)phenyl)-acetamide (16g$_2$). The reaction was conducted using 2 mol % of gold and silver precatalysts at rt for 4 h. Yield: 104 mg, 60%; pale yellow solid; mp 170−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.11−7.00 (m, 1H), 6.44−6.33 (m, 1H), 6.29−6.21 (m, 1H), 6.16−6.08 (m, 1H), 5.98−5.89 (m, 1H), 5.35 (s, 1H), 1.70−1.61 (m, 3H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.7, 171.7, 167.1, 157.1, 143.0, 140.1, 139.8, 131.0, 128.2 (q, J = 31.6 Hz), 126.6, 125.0, 124.3 (q, J = 3.8 Hz), 124.2 (q, J = 272.4 Hz), 123.6, 77.6, 60.3, 50.4, 28.2, 11.5; HRMS (ESI, [M + H]$^+$) for $C_{23}H_{24}F_3N_2O_3^+$ calcd 433.1734, found 433.1729.

(±)-(*S*)-*N*-*tert*-Butyl-2-(4-methoxyphenyl)-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide (16h$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 4 h. Yield: 103 mg, 65%; white solid; mp 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 6.95 (ddd, J = 9.9, 5.7, 2.1 Hz, 1H), 6.75 (d, J = 8.8 Hz, 2H), 6.40 (bs, 1H), 6.36−6.25 (m, 2H), 6.03 (q, J = 1.5 Hz, 1H), 5.95 (dt, J = 9.9, 0.8 Hz, 1H), 4.87 (s, 1H), 3.76 (m, 3H), 1.74 (d, J = 1.5 Hz, 3H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 172.1, 168.2, 159.7, 156.4, 142.7, 140.6, 132.3, 127.0, 126.3, 124.9, 124.6, 113.5, 78.5, 61.9, 55.3, 51.5, 28.6, 12.2; HRMS (ESI, [M + H]$^+$) for $C_{23}H_{27}N_2O_4^+$ calcd 395.1965, found 395.1955.

(±)-(*R*)-*N*-*tert*-Butyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-(thiophen-2-yl)acetamide (16i$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 4 h. Yield: 98 mg, 66%; pale yellow solid; mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 5.2, 1.1 Hz, 1H), 7.06 (ddd, J = 9.9, 6.0, 1.7 Hz, 1H), 7.00−6.95 (m, 1H), 6.90 (bs, 1H), 6.87 (dd, J = 5.1, 3.6 Hz, 1H), 6.45 (ddd, J = 9.4, 6.0, 0.7 Hz, 1H), 6.22 (ddd, J = 9.5, 1.7, 0.7 Hz, 1H), 6.08 (dt, J = 9.9, 0.7 Hz, 1H), 6.03 (q, J = 1.5 Hz, 1H), 5.14 (s, 1H), 1.78 (d, J = 1.5 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.8, 171.9, 167.1, 156.6, 142.8, 139.8, 136.3, 129.9, 127.4, 127.2, 126.4, 125.5, 124.8, 78.7, 57.7, 51.7, 28.6, 12.4; HRMS (ESI, [M + H]$^+$) for $C_{20}H_{23}N_2O_3S^+$ calcd 371.1424, found 371.1443.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-cyclohexyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)acetamide (16j$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 24 h. Yield: 37 mg, 25%; yellow solid; mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (bs, 1H), 7.13 (ddd, J = 9.9, 6.0, 1.7 Hz, 1H), 6.60 (ddd, J = 9.5, 6.0, 0.7 Hz, 1H), 6.26 (dt, J = 9.9, 0.7 Hz, 1H), 6.05−5.94 (m, 2H), 2.75 (d, J = 11.3 Hz, 1H), 2.67−2.48 (m, 1H), 1.80−1.59 (m, 8H), 1.37−1.00 (m, 11H), 0.97−0.64 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 173.3, 169.5, 156.2, 141.8, 137.3, 127.7, 127.4, 125.6, 78.5, 70.6, 50.9, 36.5, 31.5, 29.9, 28.7, 26.4, 25.9, 25.8, 12.8; HRMS (ESI, [M + H]$^+$) for $C_{22}H_{31}N_2O_3^+$ calcd 371.2329, found 371.2326.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-4,8-dimethyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16k$_2$). The reaction was conducted using 2 mol % of gold and silver precatalysts at rt for 4 h. Yield: 106 mg, 70%; yellow solid; mp 166−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 6.86 (bs, 1H), 6.23 (dd, J = 9.6, 1.4 Hz, 1H), 6.09 (d, J = 9.6 Hz, 1H), 6.04 (q, J = 1.5 Hz, 1H), 5.95−5.91 (m, 1H), 4.68 (s, 1H), 2.07 (d, J = 1.4 Hz, 3H), 1.75 (d, J = 1.6 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 171.9, 167.6, 156.4, 156.1, 138.9, 135.1, 130.1, 129.2, 128.2, 124.9, 124.7, 77.8, 63.0, 51.5, 28.6, 23.4, 12.4; HRMS (ESI, [M + H]$^+$) for $C_{23}H_{27}N_2O_3^+$ calcd 379.2016, found 379.2010.

(±)-(*S*)-*N*-(*tert*-Butyl)-2-((*R*)-8-chloro-4-methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16l$_2$). The reaction was conducted using 2 mol % of gold and silver precatalysts at rt for 4 h. Yield: 110 mg, 69%; yellow solid; mp 200−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 6.55 (dd, J = 10.0, 0.5 Hz, 1H), 6.31 (dd, J = 10.0, 1.8 Hz, 1H), 6.30 (bs, 1H), 6.05 (q, J = 1.6 Hz, 1H), 5.96 (dd, J = 1.8, 0.5 Hz, 1H), 5.19 (s, 1H), 1.72 (d, J = 1.6 Hz, 3H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 172.2, 168.1, 156.3, 152.0, 141.1, 133.0, 131.3, 128.8, 128.2, 127.5, 125.0, 124.9, 76.3, 61.9, 51.7, 28.6, 12.3; HRMS (ESI, [M + H]$^+$) for $C_{22}H_{24}ClN_2O_3^+$ calcd 399.1470, found 399.1463.

(±)-(*S*)-*N*-Cyclohexyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16m$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 24 h. Yield: 94 mg, 60%; yellow solid; mp 201−203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 7.8 Hz, 1H), 7.28−7.09 (m, 5H), 6.91 (ddd, J = 9.8, 6.0, 1.8 Hz, 1H), 6.44 (ddd, J = 9.5, 1.7, 0.8 Hz, 1H), 6.26 (ddd, J = 9.5, 6.0, 0.7 Hz, 1H), 6.10 (q, J = 1.6 Hz, 1H), 5.71 (dt, J = 9.9, 0.7 Hz, 1H), 5.31 (s, 1H), 3.60−3.42 (m, 1H), 1.80−1.44 (m, 8H), 1.35−0.90 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.3, 171.8, 167.8, 157.0, 142.7, 140.5, 133.8, 131.3, 128.0, 127.4, 126.1, 123.9, 123.7, 77.2, 60.3, 47.7, 32.1, 25.2, 24.4, 24.3, 11.4; HRMS (ESI, [M + H]$^+$) for $C_{24}H_{27}N_2O_3^+$ calcd 391.2016, found 391.2013.

(±)-(*S*)-2-((*R*)-4-Methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-2-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)-acetamide (16n$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 72 h. Yield: 109 mg, 65%; yellow solid; mp 169−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.28 (m, 2H), 6.27−6.20 (m, 3H), 6.98 (ddd, J = 9.9, 5.9, 1.8 Hz, 1H), 6.51 (bs, 1H), 6.34 (ddd, J = 9.5, 5.9, 0.8 Hz, 1H), 6.22 (ddd, J = 9.4, 1.7, 0.8 Hz, 1H), 6.05 (q, J = 1.6 Hz, 1H), 5.99 (dt, J = 9.9, 0.8 Hz, 1H), 4.80 (s, 1H), 1.79 (d, J = 14.9 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.63 (d, J = 14.8 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 172.0, 167.3, 156.3, 142.8, 140.5, 134.6, 130.6, 128.4, 128.3, 127.1, 124.9, 78.9, 63.0, 55.7, 52.3, 31.6, 31.5, 28.8, 28.6, 12.3; HRMS (ESI, [M + H]$^+$) for $C_{26}H_{33}N_2O_3^+$ calcd 421.2486, found 421.2476.

(±)-(*S*)-*N*-Benzyl-2-((*R*)-4-methyl-2,10-dioxo-1-azaspiro-[4.5]deca-3,6,8-trien-1-yl)-2-phenylacetamide (16o$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at rt for 24 h. Yield: 84 mg, 53%; white solid; mp 141−143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (bt, J = 5.5 Hz, 1H), 7.35−7.07 (m, 10H), 6.93−6.82 (m, 1H), 6.56−6.43 (m, 1H), 6.29−6.19 (m, 1H), 6.14 (s, 1H), 5.70−5.62 (m, 1H), 5.43 (s, 1H), 4.31 (dd, J = 15.1, 5.9 Hz, 1H), 4.26 (dd, J = 15.2, 5.7 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.1, 172.1, 169.2, 157.1, 142.7, 140.7, 139.1, 132.9, 131.7, 128.4, 128.1, 127.4, 127.1, 126.7, 126.0,

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

123.7, 123.6, 77.1, 60.5, 42.2, 11.4; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{23}N_2O_3^+$ calcd 399.1703, found 399.1696.

(±)-(*S*)-2-((*R*)-4-Methyl-2,10-dioxo-1-azaspiro[4.5]deca-3,6,8-trien-1-yl)-*N*-(naphthalen-2-yl)-2-phenylacetamide (16p$_2$). The reaction was conducted using 5 mol % of gold and silver precatalysts at 60 °C for 24 h. Yield: 89 mg, 51%; dark brown solid; mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (bs, 1H), 8.33 (d, J = 1.8 Hz, 1H), 7.78−7.70 (m, 3H), 7.55 (dd, J = 8.8, 2.1 Hz, 1H), 7.46−7.28 (m, 7H), 7.13 (ddd, J = 9.9, 6.0, 1.8 Hz, 1H), 6.45 (ddd, J = 9.5, 6.0, 0.7 Hz, 1H), 6.24−6.14 (m, 2H), 6.11 (q, J = 1.6 Hz, 1H), 4.96 (s, 1H), 1.85 (d, J = 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 172.3, 167.1, 156.6, 143.5, 140.0, 135.8, 134.5, 134.0, 130.7, 130.1, 128.7, 128.60, 128.55, 127.8, 127.6, 127.4, 126.3, 125.7, 125.0, 124.8, 120.1, 116.6, 79.7, 63.4, 12.5; HRMS (ESI, $[M + H]^+$) for $C_{28}H_{23}N_2O_3^+$ calcd 435.1703, found 435.1696.

***N*-(*tert*-Butyl)-2-(4-oxo-2-propylbenzo[*b*][1,4]oxazepin-5(4*H*)-yl)-2-phenylacetamide (17c).** Yield: 33 mg, 21%; brown solid; mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.42 (m, 1H), 7.37−7.17 (m, 5H), 7.10−6.96 (m, 3H), 6.72 (bs, 1H), 5.69 (s, 1H), 5.40 (t, J = 0.8 Hz, 1H), 2.39−2.29 (m, 2H), 1.67 (sextet, J = 7.4 Hz, 2H), 1.39 (s, 9H), 0.95 (t, J = 7.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 169.1, 166.7, 154.1, 135.1, 134.3, 128.4, 127.9, 127.6, 126.4, 125.8, 125.3, 120.6, 107.0, 69.3, 51.6, 37.3, 28.6, 19.2, 13.6; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{29}N_2O_3^+$ calcd 393.2173, found 393.2164.

***N*-(*tert*-Butyl)-2-(4-oxo-2-phenylbenzo[*b*][1,4]oxazepin-5(4*H*)-yl)-2-phenylacetamide (17d).** Yield: 43 mg, 25%; white solid; mp 188−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.82 (m, 2H), 7.59−7.51 (m, 1H), 7.51−7.42 (m, 3H), 5.42−7.35 (m, 2H), 7.34−7.16 (m, 4H), 7.15−7.02 (m, 2H), 6.70 (bs, 1H), 6.15 (s, 1H), 5.80 (s, 1H), 1.42 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.1, 167.1, 166.4, 154.3, 135.1, 134.6 (bs), 132.9, 131.2, 129.0, 128.6, 128.2, 127.9, 126.6, 126.5, 126.1, 125.7, 120.8, 105.5, 69.3 (bs), 51.8, 28.8; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{27}N_2O_3^+$ calcd 427.2016, found 427.2012.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00953.

X-ray crystallographic analysis, conformational analysis and theoretical calculations, as well as the copies of ^{1}H and ^{13}C NMR spectra (PDF)
Crystal data for **16a$_1$** (CIF)
Crystal data for **16a$_2$** (CIF)
Crystal data for **16e$_1$** (CIF)
Crystal data for **16e$_2$** (CIF)
Crystal data for **17c** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: vsevolod@suda.edu.cn.
*E-mail: erik.vandereycken@kuleuven.be.

ORCID

Liviu Ungur: 0000-0001-5015-4225
Vsevolod A. Peshkov: 0000-0001-6649-2384
Erik V. Van der Eycken: 0000-0001-5172-7208

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support was provided by the Research Foundation − Flanders (FWO) and the Research Fund of the University of Leuven (KU Leuven). We acknowledge the support of RUDN University Program 5-100. A.A.N. is grateful to the European Community Mobility Programme "Erasmus Mundus Action 2, Strand 1" for providing a doctoral scholarship. K.V.H. thanks the Hercules Foundation (project AUGE/11/029 "3D-SPACE: 3D Structural Platform Aiming for Chemical Excellence") and the Special Research Fund (BOF) − UGent (project 01N03217) for funding. M.Z. is grateful to Chinese Scholarship Council (CSC) for providing a doctoral scholarship. M.Z., O.P.P., and V.A.P. acknowledge the financial support from the National Natural Science Foundation of China (grant 21650110445) and the Natural Science Foundation of Jiangsu Province of China (grants BK20160310 and BK20150317). S.K. thanks the Collaborative Innovation Center of Suzhou Nano Science & Technology (NANO−CIC) for support. Mass spectrometry was made possible by the support of the Hercules Foundation of the Flemish Government (grant 20100225−7).

■ REFERENCES

(1) Reviews: (a) Petrini, M. Regioselective Direct C-Alkenylation of Indoles. *Chem. - Eur. J.* **2017**, *23*, 16115−16151. (b) Yamamoto, Y. Synthesis of heterocycles *via* transition-metal-catalyzed hydroarylation of alkynes. *Chem. Soc. Rev.* **2014**, *43*, 1575−1600. (c) *Catalytic Hydroarylation of Carbon−Carbon Multiple Bonds*; Ackermann, L., Gunnoe, T. B., Habgood, L. G., Eds.; John Wiley & Sons, 2018; p 416.

(2) Selected examples: (a) Zhang, L.; Wang, Y.; Yao, Z.-J.; Wang, S.; Yu, Z.-X. Kinetic or Dynamic Control on a Bifurcating Potential Energy Surface? An Experimental and DFT Study of Gold-Catalyzed Ring Expansion and Spirocyclization of 2-Propargyl-β-tetrahydrocarbolines. *J. Am. Chem. Soc.* **2015**, *137*, 13290−13300. (b) Liddon, J. T. R.; James, M. J.; Clarke, A. K.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones. *Chem. - Eur. J.* **2016**, *22*, 8777−8780. (c) Liddon, J. T. R.; Clarke, A. K.; Taylor, R. J. K.; Unsworth, W. P. Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives. *Org. Lett.* **2016**, *18*, 6328−6331. (d) Fedoseev, P.; Van der Eycken, E. Temperature switchable Brønsted acid-promoted selective syntheses of spiro-indolenines and quinolines. *Chem. Commun.* **2017**, *53*, 7732−7735. (e) James, M. J.; Clubley, R. E.; Palate, K. Y.; Procter, T. J.; Wyton, A. C.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles. *Org. Lett.* **2015**, *17*, 4372−4375. (f) Shestakov, A. N.; Pankova, A. S.; Golubev, P.; Khlebnikov, A. F.; Kuznetsov, M. A. Brønsted acid mediated cyclizations of *ortho*-aryl(ethynyl)-pyrimidines. *Tetrahedron* **2017**, *73*, 3939−3948.

(3) For recent examples of Brønsted acid-promoted meta-cyclizations, see: (a) Otani, T.; Ueki, K.; Cho, K.; Kanai, K.; Tateno, K.; Saito, T. Construction of dibenzo-fused seven- to nine-membered carbocycles *via* Brønsted acid-promoted intramolecular Friedel−Crafts-type alkenylation. *Chem. Commun.* **2015**, *51*, 7895−7898. (b) Zhang, L.; Sun, J.; Kozmin, S. A. Brønsted acid-promoted cyclizations of siloxy alkynes with unactivated arenes, alkenes, and alkynes. *Tetrahedron* **2006**, *62*, 11371−11380.

(4) For recent examples of Lewis acid-catalyzed meta-cyclizations, see: (a) Vacala, T.; Bejcek, L. P.; Williams, C. G.; Williamson, A. C.; Vadola, P. A. Gold-Catalyzed Hydroarylation of *N*-Aryl Alkynamides for the Synthesis of 2-Quinolinones. *J. Org. Chem.* **2017**, *82*, 2558−2569. (b) Pflästerer, D.; Rettenmeier, E.; Schneider, S.; de Las Heras Ruiz, E.; Rudolph, M.; Hashmi, A. S. K. Highly Efficient Gold-Catalyzed Synthesis of Dibenzocycloheptatrienes. *Chem. - Eur. J.* **2014**, *20*, 6752−6755.

(5) For recent examples of Brønsted acid-promoted ipso-cyclizations, see refs 2d, f.

(6) For recent examples of Lewis acid-catalyzed ipso-cyclizations, see: (a) Cera, G.; Crispino, P.; Monari, M.; Bandini, M. Stereo-

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

selective synthesis of tetracyclic indolines *via* gold-catalyzed cascade cyclization reactions. *Chem. Commun.* **2011**, *47*, 7803−7805. (b) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. Enantioselective Gold-Catalyzed Synthesis of Polycyclic Indolines. *Org. Lett.* **2012**, *14*, 1350−1353. (c) Magné, V.; Blanchard, F.; Marinetti, A.; Voituriez, A.; Guinchard, X. Synthesis of Spiro-[piperidine-3,3′-oxindoles] *via* Gold(I)-Catalyzed Dearomatization of *N*-Propargyl- and *N*-Homoallenyl-2-bromotryptamines. *Adv. Synth. Catal.* **2016**, *358*, 3355−3361. (d) James, M. J.; Cuthbertson, J. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones: Direct Access to Spirocyclic Scaffolds. *Angew. Chem., Int. Ed.* **2015**, *54*, 7640−7643. (e) Nemoto, T.; Matsuo, N.; Hamada, Y. Gold-Catalyzed Carbocyclization of Phenols with a Terminal Alkyne *via* an Intramolecular *ipso*-Friedel−Crafts Alkenylation. *Adv. Synth. Catal.* **2014**, *356*, 2417−2421. (f) Clarke, A. K.; Liddon, J. T. R.; Cuthbertson, J. D.; Taylor, R. J. K.; Unsworth, W. P. Dearomatisation approaches to spirocyclic dienones *via* the electrophilic activation of alkynes. *Org. Biomol. Chem.* **2017**, *15*, 233−245. (g) Magné, V.; Marinetti, A.; Gandon, V.; Voituriez, A.; Guinchard, X. Synthesis of Spiroindolenines via Regioselective Gold(I)-Catalyzed Cyclizations of *N*-Propargyl Tryptamines. *Adv. Synth. Catal.* **2017**, *359*, 4036−4042. (h) Vacala, T. L.; Carlson, P. R.; Arreola-Hester, A.; Williams, C. G.; Makhoul, E. W.; Vadola, P. A. Gold-Catalyzed Dearomative Spirocyclization of *N*-Aryl Alkynamides for the Synthesis of Spirolactams. *J. Org. Chem.* **2018**, *83*, 1493−1501. (i) Shibuya, T.; Noguchi, K.; Tanaka, K. Dearomatization of Fused Arenes Using Platinum-Catalyzed Intramolecular Formation of Two C−C Bonds. *Angew. Chem., Int. Ed.* **2012**, *51*, 6219−6222.

(7) For examples of electrophile-mediated ipso-cyclizations, see: (a) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. Selective Synthesis of Spiro[4,5]trienyl Acetates via an Intramolecular Electrophilic *ipso*-Iodocyclization Process. *Org. Lett.* **2008**, *10*, 1063−1066. (b) Okitsu, T.; Nakazawa, D.; Kobayashi, A.; Mizohata, M.; In, Y.; Ishida, T.; Wada, A. *ipso*-Iodocyclization of Ethoxyethyl Ethers to Alkynes at the *ortho*-Position: An Efficient Synthesis of Functionalized Spiro Compounds. *Synlett* **2010**, *2010*, 203−206.

(8) For recent examples of ipso-cyclizations followed by skeletal rearrangements into fused cycles, see: (a) Suárez, A.; Suárez-Pantiga, S.; Nieto-Faza, O.; Sanz, R. Gold-Catalyzed Synthesis of 1-(Indol-3-yl)carbazoles: Selective 1,2-Alkyl vs 1,2-Vinyl Migration. *Org. Lett.* **2017**, *19*, 5074−5077. (b) Gruit, M.; Pews-Davtyan, A.; Beller, M. Platinum-catalyzed cyclization reaction of alkynes: synthesis of azepino[3,4-*b*]indol-1-ones. *Org. Biomol. Chem.* **2011**, *9*, 1148−1159. (c) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. Synthesis of Azocino[5,4-*b*]indoles *via* Gold-Catalyzed Intramolecular Alkyne Hydroarylation. *Adv. Synth. Catal.* **2012**, *354*, 2841−2848. For processes involving ring expansions, see: (d) Zhan, L.; Chang, L.; Hu, H.; Wang, H.; Yao, Z.-J.; Wang, S. Azocinoindole Synthesis by a Gold(I)-Catalyzed Ring Expansion of 2-Propargyl-β-Tetrahydrocarboline. *Chem. - Eur. J.* **2014**, *20*, 2925−2932.

(9) For reviews on post-Ugi chemistry, see: (a) Banfi, L.; Basso, A.; Riva, R. Synthesis of Heterocycles Through Classical Ugi and Passerini Reactions Followed by Secondary Transformations Involving One or Two Additional Functional Groups. *Top. Heterocycl. Chem.* **2010**, *23*, 1−39. (b) Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. Metal-mediated post-Ugi transformations for the construction of diverse heterocyclic scaffolds. *Chem. Soc. Rev.* **2015**, *44*, 1836−1860. (c) Zhang, Z.; Zheng, X.; Guo, C. Application of Ugi/De-Boc/Cyclization Strategy in the Synthesis of Nitrogen-Containing Heterocycles. *Youji Huaxue* **2016**, *36*, 1241−1265. (d) Li, X.; Jia, X.; Yin, L. Recent Progress on Post-Ugi Reaction. *Youji Huaxue* **2017**, *37*, 2237−2249. (e) Banfi, L.; Basso, A.; Lambruschini, C.; Moni, L.; Riva, R. Synthesis of seven-membered nitrogen heterocycles through the Ugi multicomponent reaction. *Chem. Heterocycl. Compd.* **2017**, *53*, 382−408.

(10) For recent examples of utilizing Ugi adducts to assemble complex spiro-fused architectures, see: (a) Santra, S.; Andreana, P. R. A Bioinspired Ugi/Michael/Aza-Michael Cascade Reaction in Aqueous Media: Natural-Product-like Molecular Diversity. *Angew. Chem., Int. Ed.* **2011**, *50*, 9418−9422. (b) Ghandi, M.; Zarezadeh, N.; Abbasi, A. One-pot synthesis of spiropyrroloquinoline-isoindolinone and their aza-analogs *via* the Ugi-4CR/metal-free intramolecular bis-annulation process. *Org. Biomol. Chem.* **2015**, *13*, 8211−8220. (c) Butani, H. H.; Vachhani, D. D.; Bhoya, U. E.; Shah, A. K.; Van der Eycken, E. V. Regio- and Chemoselective Formation of Spiroindolinone−Isoindolinone by a Palladium-Catalyzed Buchwald−Hartwig Addition−Elimination Sequence. *Eur. J. Org. Chem.* **2014**, *2014*, 6634−6638. (d) He, Y.; Li, Z.; Van Meervelt, L.; Van der Eycken, E. V. A Gold-Catalyzed Domino Cyclization Enabling Rapid Construction of Diverse Polyheterocyclic Frameworks. *Angew. Chem., Int. Ed.* **2018**, *57*, 272−276. (e) Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. Synthesis of polycyclic spiroindolines by highly diastereoselective interrupted Ugi cascade reactions of 3-(2-isocyanoethyl)indoles. *Chem. Commun.* **2016**, *52*, 12482−12485. (f) Mijangosa, M. V.; Miranda, L. D. Multicomponent access to indolo[3,3a-*c*]isoquinolin-3,6-diones: formal synthesis of (±)-plicamine. *Org. Biomol. Chem.* **2016**, *14*, 3677−3680.

(11) Peshkov, A. A.; Nechaev, A. A.; Pereshivko, O. P.; Goeman, J. L.; Van der Eycken, J.; Peshkov, V. A.; Van der Eycken, E. V. Gold- and Silver-Catalyzed 7-*endo-dig* Cyclizations for the Synthesis of Oxazepines. *Eur. J. Org. Chem.* **2015**, *2015*, 4190−4197.

(12) (a) Li, Z.; Kumar, A.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. Catalyst-controlled *exo*/*endo* selectivity in a post-Ugi intramolecular hydroarylation: synthesis of pyrrolopyridinones, pyrroloazepinones, and benzothienopyridines. *Tetrahedron* **2015**, *71*, 3333−3342. (b) Kumar, A.; Li, Z.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. Switching the regioselectivity *via* indium(III) and gold(I) catalysis: a post-Ugi intramolecular hydroarylation to azepino- and azocino-[*c*,*d*]indolones. *Chem. Commun.* **2013**, *49*, 6803−6805.

(13) (a) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Meervelt, L. V.; Van der Eycken, E. V. A Diversity-Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization. *Angew. Chem., Int. Ed.* **2012**, *51*, 9572−9575. For an analogous approach using propargylamines as a triple bond source, see: (b) Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. Post-Ugi gold-catalyzed diastereoselective domino cyclization for the synthesis of diversely substituted spiroindolines. *Beilstein J. Org. Chem.* **2013**, *9*, 2097−2102. For a supported silver nanoparticle-catalyzed ipso-cyclization of indole-3-carbaldehyde derived Ugi adducts that is not accompanied by the second cyclization, see: (c) Schröder, F.; Sharma, U. K.; Mertens, M.; Devred, F.; Debecker, D. P.; Luque, R.; Van der Eycken, E. V. Silver-Nanoparticle-Catalyzed Dearomatization of Indoles toward 3-Spiroindolenines via a 5-*exo*-dig Spirocyclization. *ACS Catal.* **2016**, *6*, 8156−8161.

(14) He, Y.; Li, Z.; Tian, G.; Song, L.; Van Meervelt, L.; Van der Eycken, E. V. Gold-catalyzed diastereoselective domino dearomatization/*ipso*-cyclization/aza-Michael sequence: a facile access to diverse fused azaspiro tetracyclic scaffolds. *Chem. Commun.* **2017**, *53*, 6413−6416.

(15) (a) Yugandhar, D.; Kuriakose, S.; Nanubolu, J. B.; Srivastava, A. K. Synthesis of Alkaloid-Mimicking Tricyclic Skeletons by Diastereo- and Regioselective Ugi/*ipso*-Cyclization/Aza-Michael Cascade Reaction in One-Pot. *Org. Lett.* **2016**, *18*, 1040−1043. For related ipso-iodocyclization that is not accompanied by the second cyclization, see: (b) Yugandhar, D.; Srivastava, A. K. Efficient Construction of Azaspiro[4.5]trienone Libraries via Tandem Ugi 4CC/Electrophilic *ipso*-Iodocyclization in One-Pot. *ACS Comb. Sci.* **2015**, *17*, 474−481.

(16) For recent examples of highly diastereoselective Ugi and post-Ugi processes, see: (a) Ramanivas, T.; Parameshwar, M.; Gayatri, G.; Nanubolu, J. B.; Srivastava, A. K. Asymmetric Synthesis of Functionalized 2,5-Pyrrolidinediones and β-Lactams through Diastereospecific Cycloisomerization/Rearrangement of Chiral Ethanolamine-Derived Ugi Adducts. *Eur. J. Org. Chem.* **2017**, *2017*, 2245−

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182

2257. (b) Zarezin, D. P.; Khrustalev, V. N.; Nenajdenko, V. G. Diastereoselectivity of Azido-Ugi Reaction with Secondary Amines. Stereoselective Synthesis of Tetrazole Derivatives. *J. Org. Chem.* **2017**, *82*, 6100−6107. (c) Srinivasulu, V.; Sieburth, S. McN.; El-Awady, R.; Kariem, N. M.; Tarazi, H.; O'Connor, M. J.; Al-Tel, T. H. Post-Ugi Cascade Transformations for Accessing Diverse Chromenopyrrole Collections. *Org. Lett.* **2018**, *20*, 836−839. (d) Caputo, S.; Basso, A.; Moni, L.; Riva, R.; Rocca, V.; Banfi, L. Diastereoselective Ugi reaction of chiral 1,3-aminoalcohols derived from an organocatalytic Mannich reaction. *Beilstein J. Org. Chem.* **2016**, *12*, 139−143. (e) Nenajdenko, V. G.; Gulevich, A. V.; Chernichenko, K.; Yu; Sokolova, N. V.; Balenkova, E. S. *R*-α-Phenylglycinol and *R*-α-phenylglycinamide as novel chiral templates in diastereoselective Ugi reaction. *Mendeleev Commun.* **2011**, *21*, 245−246.

(17) In the course of our study selective protocols for both 6-*exo-dig* and 7-*endo-dig* O-cyclizations of Ugi adducts derived from 2-aminophenol and 3-aryl propiolic acids were reported; see: Singh, K.; Malviya, B. K.; Roy, T. K.; Mithu, V. S.; Bhardwaj, V. K.; Verma, V. P.; Chimni, S. S.; Sharma, S. Catalyst-Controlled Structural Divergence: Selective Intramolecular 7-*endo-dig* and 6-*exo-dig* Post-Ugi Cyclization for the Synthesis of Benzoxazepinones and Benzoxazinones. *J. Org. Chem.* **2018**, *83*, 57−68.

(18) CCDC 1826895 (for $\mathbf{16a_1}$), 1826896 (for $\mathbf{16a_2}$), 1826897 (for $\mathbf{16e_1}$), 1826898 (for $\mathbf{16e_2}$), and 1826899 (for **17c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(19) The structures of diastereomeric pyrrol-2-one-dienones $\mathbf{16_1}$ and $\mathbf{16_2}$ were assured through the comparison of proton chemical shifts of the cyclohexadienone ring with the products $\mathbf{16a_1}$, $\mathbf{16a_2}$, $\mathbf{16e_1}$, and $\mathbf{16e_2}$ whose structures were established by X-ray analysis.

(20) In some instances, the role of silver cocatalyst proved to be more significant. See for example: Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. "Silver Effect" in Gold(I) Catalysis: An Overlooked Important Factor. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.

(21) It is well-known that the Ugi adducts derived from (hetero) aromatic aldehydes, aryl glyoxals or ethyl glyoxylate could undergo enolization-triggered cyclizations or boron-complexation. For selected recent examples, see: (a) Polindara-García, L. A.; Montesinos-Miguel, D.; Vazquez, A. An efficient microwave-assisted synthesis of cotinine and iso-cotinine analogs from an Ugi-4CR approach. *Org. Biomol. Chem.* **2015**, *13*, 9065−9071. (b) Abdessalem, A. B.; Abderrahim, R.; Agrebie, A.; Dos Santos, A.; El Kaïm, L.; Komesky, A. Formal [3 + 2] cycloaddition of Ugi adducts towards pyrrolines. *Chem. Commun.* **2015**, *51*, 1116−1119. (c) Ghabraie, E.; Balalaie, S.; Mehrparvar, S.; Rominger, F. Synthesis of Functionalized β-Lactams and Pyrrolidine-2,5-diones through a Metal-Free Sequential Ugi-4CR/Cyclization Reaction. *J. Org. Chem.* **2014**, *79*, 7926−7934. (d) Nechaev, A. A.; Peshkov, A. A.; Peshkov, V. A.; Van der Eycken, E. V. The Application of Multicomponent Ugi and Passerini Reactions for the One-Pot Synthesis of Pyrrolones and Butenolides. *Synthesis* **2016**, *48*, 2280−2286. (e) Zeng, X.-H.; Yan, Y.-M.; Wu, L.; Ding, M.-W. One-pot regioselective synthesis of β-lactams by a tandem Ugi 4CC/S_N cyclization. *Tetrahedron* **2014**, *70*, 3647−3652. (f) Wei, H.; Wang, G.; Wang, Y.; Li, B.; Huang, J.; Kashtanov, S.; Van Hecke, K.; Pereshivko, O. P.; Peshkov, V. A. Boron Complexes of Glyoxal-Derived Ugi Adducts as a New Class of Aggregation-Induced Emission Photoluminescent Materials. *Chem. - Asian J.* **2017**, *12*, 825−829.

(22) *Spartan2*; Wavefunction, Inc: Irvine, CA. See Supporting Information for details.

DOI: 10.1021/acs.joc.8b00953
J. Org. Chem. 2018, 83, 8170−8182