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Highly Efficient Access to Bi- and Tricyclic Ketals through Gold-Catalyzed Tandem Reactions of 4-Acyl-1,6-diynes

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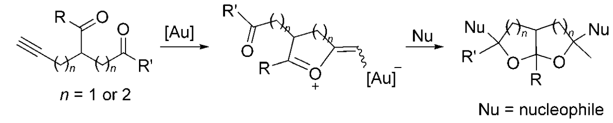
In the past few years, reports on gold-catalyzed organic transformations have increased substantially because various organic transformations and several total syntheses of natural products have been accessible under facile conditions with both high yields and chemoselectivity.[1] In gold-catalyzed organic reactions, the cyclization reactions of alkynyl ketones/aldehydes have emerged as a powerful strategy for the construction of various cyclic ring systems.[1,2] These reactions are generally believed to proceed via an electrophilic furylium (or pyrylium) ion, generated through intramolecular nucleophilic attack of the carbonyl-oxygen atom to the Au-coordinated carbon–carbon triple bond, which is trapped by various nucleophiles to afford the corresponding products. Recently, Michelet and Genêt reported the synthesis of strained bicyclic ketals via gold-catalyzed cycloisomerization of bis-homopropargylic diols with hydroxy oxygen atom as internal nucleophile.[3] It was predicted that, based on these reactions, a fused bicyclic ketal/acetal derivative, which exists in many biologically active and structurally diverse natural products,[4,5] could be constructed in a domino fashion if another tethered oxygen can be incorporated as an internal nucleophile (Scheme 1). However, such an approach requires systematic evaluation.

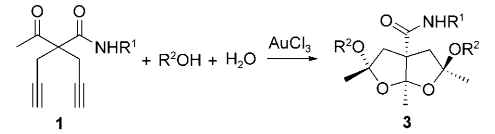


Scheme 1.

In chemistry, one-pot domino synthesis is a strategy to improve the efficiency of a chemical reaction whereby multiple bonds and stereocenters are formed in a single step without the isolation of intermediates.[6] During our research focused on transformations using relatively simple substrates to reasonably complex products,[7] very recently, several routes were developed for the synthesis of furo[2,3-*b*]quinolines[8a] and other quinoline derivatives[8b,c] starting from easily accessible acetoacetanilide derivatives. Encouraged by these results,[7,8] together with the significance of gold-catalyzed reactions[1–3] and the synthetic versatility of functionalized 1,6-diynes,[9] we focused our attention on the metal-catalyzed heteroannulation reactions of the readily available 4-acyl-1,6-diynes **1** (Table 1) and **4** (Table 2). Herein, we wish to report the highly efficient, atom-economical, highly regio- and diastereoselective approach to polyfunctionalized fused bicyclic ketals **3** and bridged tricyclic ketals **5** via $AuCl_3$-catalyzed multicomponent domino reactions of 4-acyl-1,6-diynes **1** and **4** with H_2O and alkanols, respectively.

In the initial experiment, the reactions of 1,6-diyne **1a** (obtained in 98% yield from the reaction of 3-oxo-*N*-phe-

Table 1. $AuCl_3$-catalyzed synthesis of hexahydrofuro[2,3-*b*]furans **3**.[a]



Entry	Substrate	R^1	R^2	*t* [h]	Yield[b] [%]
1	**1a**	C_6H_5	$CH_2C{\equiv}CH$	4	**3ca** (93)
2	**1b**	$4\text{-}ClC_6H_4$	$CH_2C{\equiv}CH$	4	**3cb** (85)
3	**1c**	$2\text{-}ClC_6H_4$	$CH_2C{\equiv}CH$	4	**3cc** (90)
4	**1d**	$4\text{-}MeOC_6H_4$	$CH_2C{\equiv}CH$	4	**3cd** (90)
5	**1e**	$2\text{-}MeOC_6H_4$	$CH_2C{\equiv}CH$	4	**3ce** (92)
6	**1f**	$4\text{-}MeC_6H_4$	$CH_2C{\equiv}CH$	4	**3cf** (83)
7	**1g**	$4\text{-}EtOC_6H_4$	$CH_2C{\equiv}CH$	4	**3cg** (90)
8	**1h**	H	$CH_2C{\equiv}CH$	4	**3ch** (78)
9	**1a**	C_6H_5	$CH_2CH{=}CH_2$	4	**3da** (82)
10	**1b**	$4\text{-}ClC_6H_4$	$CH_2CH{=}CH_2$	4	**3db** (91)
11	**1d**	$4\text{-}MeOC_6H_4$	$CH_2CH{=}CH_2$	4	**3dd** (88)

[a] Conditions: **1** (1.0 equiv), 3 mol% $AuCl_3$ in alkanol/H_2O (8.0 mL; 25:1). [b] Isolated yields.

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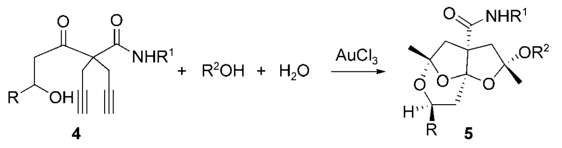
Table 2. $AuCl_3$-catalyzed synthesis of tricyclic ketals **5**.[a]



Entry	Substrate	R	R^1	R^2	*t* [h]	Yield[b] [%]	d.r.[d]
1	**4a**	2-ClC_6H_4	4-EtOC_6H_4	$CH_2C{\equiv}CH$	10	**5ca** (52)	10:90
2	**4b**	4-FC_6H_4	4-EtOC_6H_4	$CH_2C{\equiv}CH$	10	**5cb** (45)	10:90
3	**4c**	C_6H_5	4-EtOC_6H_4	$CH_2C{\equiv}CH$	10	**5cc** (43)	20:80
4	**4d**	$3,4\text{-CH}_2O_2C_6H_3$	4-EtOC_6H_4	$CH_2C{\equiv}CH$	10	**5cd** (40)	14:86
5	**4e**	2-ClC_6H_4	C_6H_5	$CH_2C{\equiv}CH$	10	**5ce** (44)	10:90
6[c]	**4a**	2-ClC_6H_4	4-EtOC_6H_4	Me	10	**5aa** (46)	12:88
7[c]	**4a**	2-ClC_6H_4	4-EtOC_6H_4	Et	10	**5ba** (42)	15:85
8	**4a**	2-ClC_6H_4	4-EtOC_6H_4	$CH_2CH{=}CH_2$	10	**5da** (50)	9:91

[a] Conditions: **4** (1.0 equiv), 5 mol% $AuCl_3$ in alkanol/H_2O (8.0 mL; 25:1). [b] Isolated yields. [c] Conditions: **4** (1.0 equiv), alkanols (3.0 equiv), H_2O (5.0 equiv), 5 mol% $AuCl_3$ in CH_2Cl_2 (8.0 mL). [d] Diastereomeric ratios were determined by the ^{1}H NMR spectra of **5**.

nylbutanamide and propargyl bromide, see Supporting Information) were examined in the presence of different metal catalysts and solvents (Table 3). With anhydrous MeOH as the solvent and $PdCl_2$ (5 mol%) or $Pd(OAc)_2$ (5 mol%) as the catalyst, no reaction was observed at room temperature for 24 h (Table 3, entries 1 and 2). To our delight, under otherwise identical conditions as above, the reaction of **1a** (1.0 mmol and 5.0 mL MeOH) could easily proceed to give exclusively the oxacyclization product **2aa** (Figure 1) in 95% yield (a mixture of mainly two diastereoisomers, a major (**2aa**) and a minor in a 6:4 ratio confirmed by ^{1}H NMR) in the presence of 3 mol% of $AuCl_3$ for 4 h (Table 3, entry 3).[10] Interestingly, when the reaction was performed in wet methanol (MeOH/H_2O 50:1), except **2aa** (in 89% yield), a fused bicyclic ketal, hexahydrofuro[2,3-*b*]furan **3aa** was isolated in 8% yield (Table 3, entry 4). Fortunately, the product selectivity could be controlled by the MeOH/H_2O ratio and catalyst loading. For example, **3aa** could be obtained as the major product in high yields and in a regio- and diastereoselective manner by increasing the catalyst loading and the ratio of H_2O/MeOH (Table 3, entries 5 and 6). However, further increase of $AuCl_3$ and the ratio of H_2O/MeOH did not improve the selectivity and the yield of **3aa** (Table 3, entries 7 and 8). Similarly, under otherwise identical conditions as above, when the reaction was carried out in anhydrous EtOH, the tetrahydrofuran **2ba** was produced exclusively in 92% yield (a mixture of mainly two diastereoisomers, a major (**2ba**) and a minor product in a 7:3 ratio confirmed by ^{1}H NMR, Table 3, entry 9); whereas, when the reaction was performed in EtOH/H_2O, the hexahydrofuro[2,3-*b*]furan **3ba** was obtained as the major product in 70% yield (Table 3, entry 10).

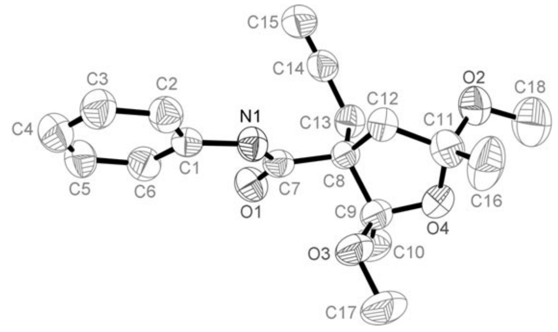
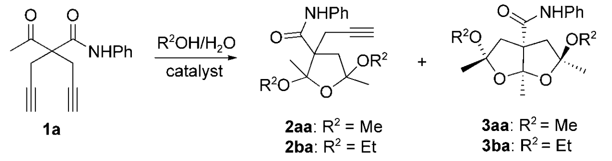


Figure 1. ORTEP drawing of **2aa**.

Gratifyingly, when propargyl alcohol was used as the external nucleophile, the reaction of **1a** could proceed smoothly with complete product selectivity to give hexahydrofuro[2,3-*b*]furan **3ca**. In the presence of 3 mol% of $AuCl_3$ in propargyl alcohol/H_2O (8.0 mL; 25:1) at room temperature under air for 4 h, **3ca** was produced exclusively in 93% isolated yield (Table 1, entry 1). Encouraged by these results, the scope of the reaction was investigated further and the results are summarized in Table 1. It is obvious that this multicomponent domino reaction shows wide applicability for various aryl substituents in diynes **1**. All selected substrates **1a–g**, bearing an aryl group (with either electron-donating or electron-withdrawing group on the phenyl ring) at the nitrogen, could efficiently undergo the $AuCl_3$-catalyzed domino reaction to give the corresponding hexahydrofuro-[2,3-*b*]furans **3ca–g** in high to excellent yields under very mild conditions (Table 1, entries 1–7). Notably, in the case of **1h**, the domino reaction also worked well, yielding the desired product **3ch** in 78% (Table 1, entry 8). Similarly, the allyl alcohol prove to be an effective external nucleophile

Table 3. Experimental results of 1,6-diyne **1a**.



Entry	Catalyst (mol%)	Solvent	*t* [h]	**2**	**3**
				(yield[a] [%])	
1	$PdCl_2$ (5)	MeOH	24	–	–
2	$Pd(OAc)_2$ (5)	MeOH	24	–	–
3	$AuCl_3$ (3)	MeOH	4	**2aa** (95)	**3aa** (0)
4	$AuCl_3$ (3)	MeOH/H_2O (50:1)	4	**2aa** (89)	**3aa** (8)
5	$AuCl_3$ (3)	MeOH/H_2O (15:1)	4	**2aa** (25)	**3aa** (60)
6	$AuCl_3$ (5)	MeOH/H_2O (15:1)	4	**2aa** (10)	**3aa** (75)
7	$AuCl_3$ (5)	MeOH/H_2O (10:1)	4	**2aa** (11)	**3aa** (72)
8	$AuCl_3$ (7)	MeOH/H_2O (15:1)	4	**2aa** (10)	**3aa** (73)
9	$AuCl_3$ (3)	EtOH	4	**2ba** (92)	**3ba** (0)
10	$AuCl_3$ (5)	EtOH/H_2O (15:1)	4	**2ba** (12)	**3ba** (70)

[a] Isolated yields.

and the corresponding hexahydrofuro[2,3-*b*]furans **3da**, **3db** and **3dd** were also obtained in high to excellent yields (Table 1, entries 9–11).[11] In addition, according to ^{1}H and ^{13}C NMR spectroscopic data of hexahydrofuro[2,3-*b*]furans **3**, it was found that the domino reaction proceeds in a highly regio- and diastereoselective manner[12] and the structure of fused bicyclic ketals **3** was finally established by the X-ray diffraction analysis of **3cd** (Figure 2).[13]

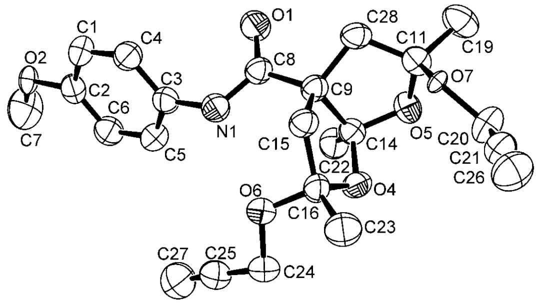
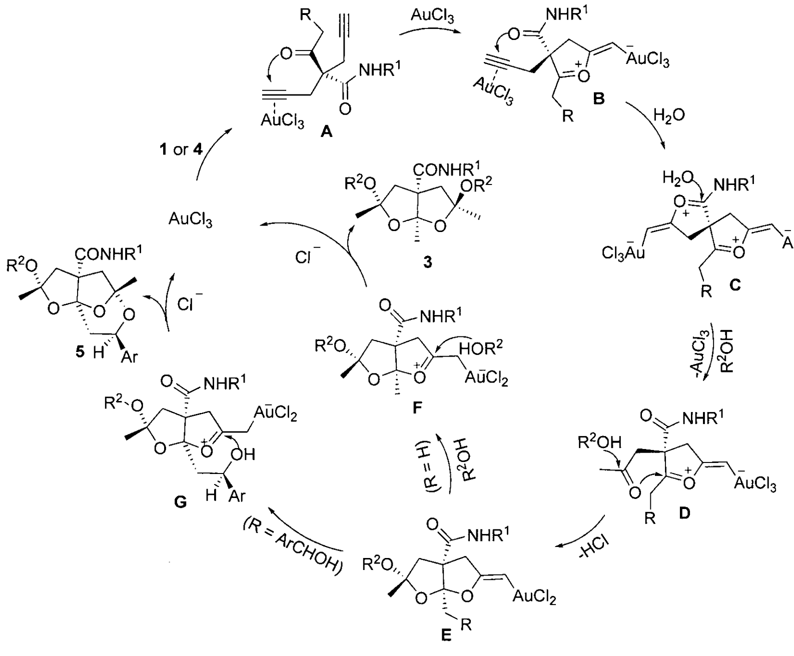


Figure 2. ORTEP drawing of **3cd**.

On the basis of the above experimental results together with the related reports,[1–3,14] a mechanism for the formation of **3** involving five C−O bond formation in a single step is proposed (Scheme 2). Initially, the chemo- and regiospecific attack of the acetyl carbonyl-oxygen of **1** on the electrophilic π-alkyne moiety of gold complex **A** generates the electrophilic furylium intermediate **B**, where the preferred intramolecular oxo-assisted alkyne hydration (**B**→**C**→**D**)[14] leads to the formation of dicarbonyl intermediate **D**. Then, the facilitated intramolecular cyclization of **D** followed by addition of the alkanol in a stereospecific manner (induced by the chiral center of intermediate **D**) gives the intermediate auric ate complex **E**. Hexahydrofuro[2,3-*b*]furans **3** are finally produced via isomerization of **E** and further alkanolysis. This explains the excellent diastereoselectivity observed in the reaction sequence with four chiral centers, which can possibly be rationalized by a series of the intramolecular chiral inductions.

According to the mechanism described above (Scheme 2), it is obvious that, 1) under the reaction conditions mentioned above (Table 1 or 3), the carbonyl oxygen of the acetyl group of **1** is more reactive than the amide oxygen toward the Au-coordinated carbon−carbon triple bond because the two oxygen atoms of the fused bicyclic ring system of **3** are generated from the two acetyl groups although the second acetyl functionality is created from the intramolecular oxo-assisted alkyne hydration (Scheme 2, **B**→**C**→**D**);[14] 2) both water and the OH group of an alkanol play an important but different role at different stages in the transformation process. Thus, tetrahydrofurans **2** and hexahydrofuro[2,3-*b*]furans **3** can be synthesized, respectively, by variation of the ratio of water and alkanol. Following the success of the evaluation (Tables 1 and 3; Schemes 1 and 2), we then turned our focus towards a solution that would work for a broad spectrum of substrates and lead to structures of high molecular complexity from relatively simple starting materials.[15] Therefore, the domino reactions of 1,6-diynes **4** (obtained in 55–85% yields by the aldol reaction of 1,6-diynes **1** and aromatic aldehydes, see Supporting Information) with H_2O and alkanols were investigated.

It was found that, under essentially the identical conditions as above (Table 1), when the 1,6-diyne **4a** was treated with wet propargyl alcohol in the presence 5% $AuCl_3$ at room temperature for 10 h, the bridged tricyclic ketal **5ca** was obtained in 52% yield (Table 2, entry 1) along with the recovery of **4a** (36%). Under otherwise identical reaction conditions, it was noted that, 1) increasing the amount of $AuCl_3$ (8 mol%) or reaction time (20 h) did not improve the yield of **5ca** (53 and 50%, respectively); 2) decreasing the loading of $AuCl_3$ (3 mol%) led to lower product yields (35%); and 3) elevated temperatures (40 °C) resulted in the formation of a complex mixture. All results indicate that under the optimized reaction conditions (Table 2, entry 1), the conversion yield of the domino reaction is high. With these results in hand, similarly, under the optimized conditions, the generality of the reaction was examined by select-



Scheme 2. Proposed mechanisms for the formation of **3** and **5**.

ed 1,6-diynes **4** and the results are summarized in Table 2. It was found that, the precursors **4** with either electron-donating or electron-withdrawing group on the phenyl ring (R= Ar) could undergo efficiently $AuCl_3$-catalyzed domino reaction with H_2O and propargyl alcohol in the presence 5% $AuCl_3$ to give the corresponding bridged tricyclic ketals **5ca–e** in good yields (Table 2, entries 1–5). In addition to propargyl alcohol, a variety of alcohols, such as methanol, ethanol, and allyl alcohol, also worked well as external nucleophiles, and the corresponding tricyclic ketals **5aa**, **5ba** and **5da** were obtained in good yields (Table 2, entries 6–8). In addition, according to ^1H and ^{13}C NMR data of tricyclic ketals **5**, it was found that the domino reaction proceeds in a highly regio- and diastereoselective manner (Table 2) and the structure of **5** was finally established by the X-ray diffraction analysis of **5ca** (Figure 3).[16]

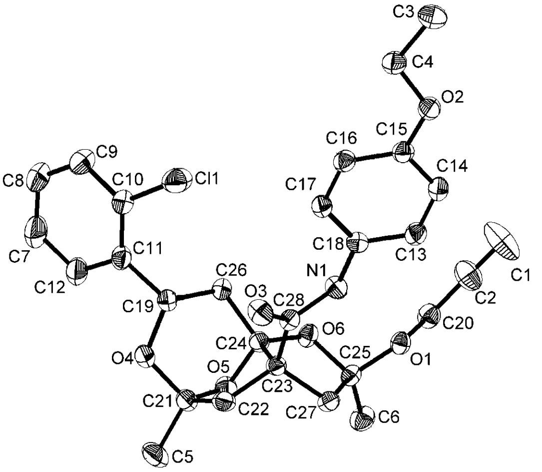


Figure 3. ORTEP drawing of **5ca**.

It should be noted that fused bicyclic ketal/acetal derivatives, especially dioxabicyclo[3.2.1]octanes, exist in many biologically active and structurally diverse natural products.[17] General synthetic methods for dioxabicyclo[3.2.1]octanes involve mainly the intramolecular acetalization of ketodiols,[5a,17] and ketalization/ring-closing metathesis of diene diol and alkenyl ketones developed recently.[18] Additionally, alternative strategies have been explored, for example, the intramolecular double alkoxylation of alkyne diols in the presence of transition-metal complexes, including Pt[5b] and Pd.[19] Recently, Shi and co-workers reported the gold(I)-catalyzed cycloisomerization of propargylic alcohols with oxirane to fused bicyclic ketals,[20] whereas, the reaction needs to be performed in the presence of co-catalysts. Undoubtedly, the above $AuCl_3$-catalyzed domino reactions (Tables 1 and 2) provide a facile and efficient access to fused bicyclic ketals **3** and bridged tricyclic ketals **5** from readily available starting materials under mild reaction conditions. Moreover, to the best of our knowledge, products **5** show the first example of the novel bridged tricyclic ketals with the basic structure of either dioxabicyclo[3.2.1]octane[5a–c,17–20] and hexahydrofuro[2,3-*b*]furan.[4,5d]

On the basis of the above experimental results together with the related reports,[1–3,14] the formation of **5** is believed to be similar to hexahydrofuro[2,3-*b*]furans **3** (Scheme 2). However, when the R substituent is ArCHOH, the attack of intramolecular hydroxyl group of intermediate **E** from substrates **4** would be more favorable than the corresponding intermolecular mode (Scheme 2).

In conclusion, we have shown the novel gold-catalyzed tandem reactions, that is, the cycloisomerization, intramolecular oxo-assisted alkyne hydration, cycloisomerization, alkanolysis, isomerization, and alkanolysis (intermolecular or intramolecular) sequence. These approaches allow the formation of either fused bicyclic ketals **3** or bridged tricyclic ketals **5** in good to excellent yields. In addition, these new transformations have the advantages of high regio- and diastereoselectivity in a single reaction step under mild reaction conditions and lead to structures of high molecular complexity from simple starting materials in an atom economic way.

Experimental Section

General procedure for the synthesis of 3: $AuCl_3$ (9.1 mg, 0.03 mmol) was added in one portion to a stirred solution of **1a** (253 mg, 1.0 mmol) in propargyl alcohol/H_2O (8.0 mL, 25:1). The reaction mixture was stirred for 4 h at room temperature. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (10 mL ×3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the corresponding crude product, which was purified by silica gel chromatography (diethyl ether/hexane 1:12) to give **3ca** (356 mg, 93%) as a white solid. M.p. 79–81 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ=1.53 (s, 3H), 1.55 (s, 3H), 1.65 (s, 3H), 2.16 (d, J=13.0 Hz, 1H), 2.38 (s, 1H), 2.40 (s, 1H), 2.83 (d, J=14.0 Hz, 1H), 2.96 (d, J=14.5 Hz, 1H), 3.17 (d, J=13.5 Hz, 1H), 4.20–4.42 (m, 4H), 7.10 (d, J=7.0 Hz, 1H), 7.31 (t, J=8.0 Hz, 2H), 7.67 (d, J=8.5 Hz, 2H), 9.66 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.7, 22.1, 23.8, 47.8, 49.5, 49.7, 49.8, 63.1, 73.4, 74.8, 79.4, 80.6, 108.8, 109.5, 119.8, 119.9, 121.0, 123.9, 128.5 (2C), 138.3, 169.8 ppm; IR (KBr): $\tilde{\nu}$=3286, 2924, 2156, 1686, 1555, 1446, 1378, 1212, 1177, 1049, 953 cm^{-1}; MS (ESI) m/z: 406 $[M+23]^+$; elemental analysis calcd (%) for $C_{22}H_{25}NO_5$: C 68.91, H 6.57, N 3.65; found: C 68.74, H 6.51, N 3.53.

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Keywords: asymmetric synthesis · cyclization · domino reactions · gold

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[10] Crystal data for **2aa**: $C_{18}H_{23}NO_4$, white crystal, $M=317.37$, monoclinic, $P21/c$, $a=8.641\ (5)$, $b=19.242(10)$, $c=10.537(6)$ Å, $\alpha=90.000(5)$, $\beta=92.623(9)$, $\gamma=90.000(5)°$, $V=1750.2(14)$ Å^3, $Z=4$, $T=273(2)$ K, $F_{000}=680$, $R_1=0.0710$, $wR_2=0.1610$. CCDC 702106 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[11] In addition, the reaction of 4-acetyl-4-ethoxycarbonyl-1,6-heptdiyne (1.0 mmol) was attempted in propargyl alcohol/H_2O (8.0 mL; 25:1) in the presence of 3 mol% of $AuCl_3$. However, a complex mixture was observed.

[12] According to the ^{1}H NMR spectra of products **3**, it was found that the diastereoselectivity of the reaction is excellent and their diastereomers could not be observed.

[13] Crystal data for **3cd**: $C_{23}H_{27}NO_6$, white crystal, $M=413.46$, triclinic, $P\bar{1}$, $a=10.043(3)$, $b=11.098(3)$, $c=11.241(3)$ Å, $\alpha=68.102(4)$, $\beta=88.496(4)$, $\gamma=68.688(4)°$, $V=1074.3(5)$ Å^3, $Z=2$, $T=273(2)$ K, $F_{000}=440$, $R_1=0.0502$, $wR_2=0.1153$. CCDC 702107 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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[16] Crystal data for **5ca**: $C_{28}H_{30}ClNO_6$, white crystal, $M=511.98$, monoclinic $C2/c$, $a=50.358(9)$, $b=10.427(2)$, $c=10.0136(18)$ Å, $\alpha=90.00$, $\beta=99.318(3)$, $\gamma=90.00°$, $V=5188.4(17)$ Å^3, $Z=8$, $T=293(2)$, $F_{000}=2160$, $R_1=0.0586$, $wR_2=0.1525$. CCDC 705786 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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