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Gold Catalyzed Cyclization of Alkyne-Tethered Dihydropyrimidones

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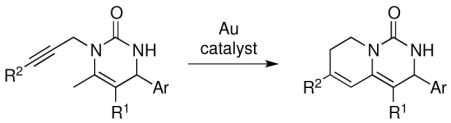
Abstract



Dihydropyrimidones are an important class of biologically active heterocycles accessible from the multicomponent Biginelli condensation. Further manipulation of the dihydropyrimidone skeleton gives access to unique heterocycles. Presented herein is a Au-catalyzed cyclization of alkyne-tethered dihydropyrimidinones to yield pyridopyrimidones.

Dihydropyrimidinones (DHPMs), the products of the classic Biginelli three-component reaction,[1] possess a wide range of intriguing pharmacological properties and thusly have attracted great synthetic interest.[2] Following our development of an organocatalytic route to access either enantiomer of the DHPM core and enantioenriched DHPM library collections,[3] we have been pursuing methods to further manipulate the scaffold. In addition to our discovery of a DHPM-derived guanidine chemotype which exhibits intriguing activity against select geographic isolates of *P. falciparum*,[4] we also recently reported the synthesis and identification of a DHPM-derived pyridopyrimidone that exhibits broad-spectrum acitivity against orthopoxviruses.[5] Herein we describe the discovery of a Au-catalyzed cyclization of propargyl-tethered DHPMs that gives rise to the tetrahydropyridopyrimidone motif.

Initial efforts focused on probing the intramolecular reactivity of DHPM derivatives **2** and **3** possessing alkynes attached to the N1 enamide nitrogen (Figure 1). Our initial screen[6] included a selection of alkynophilic metal catalysts, two different solvents (polar and nonpolar) and three different reaction conditions. All reactions were analyzed by TLC as well as UPLC/MS/ELSD. While substrate **2** was unreactive under all conditions screened, we were pleased to observe that a common product was formed when **1** was heated in the presence of gold or platinum, as well as in trace amounts with $GaCl_3$. The products of the

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Supporting Information Available Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

reaction were determined to be compound **3** by UPLC-MS and 2D NMR; compounds bearing a unique bicyclic tetrahydropyridopyrimidinone structural framework.[7]

Dihydropyrimidones analogous to **1** possessing N1 propargyl groups were synthesized to be evaluated in the cyclization reaction. However, our ablility to prepare substrates with our previous methodology was limited by the necessity of employing propargyl isocyanates: preparation of low molecular weight isocyanates is inconvenient due to both volatility and the use of phosgene. Since the commercial availability of propargylic isocyanates and ureas is limited, substrate synthesis necessitated a more general route to N1-propargylated DHPMs.

Kappe and coworkers developed N1-selective alkylation of DHPMs using a Mitsunobu reaction employing TMAD and TBP.[8] While the reaction worked quite well for some substrates, in our hands the reaction proved problematic for the range of alkynols we utilized giving mixtures of N1 and N3 alkylation products. We therefore developed a modified protocol employing N3-acylated DHPMs **5-8**,[9] thus avoiding the inherent selectivity issue and making use of readily available propargylic alcohols.[10] Furthermore, by decreasing the pKa of the N1 proton, we are able to use common Mitsunobu reagents, instead of TMAD and pyrophoric TBP.[11] As depicted in Table 1, the protocol was employed to synthesize alkyne cyclization precursors from both known and novel DHPMs.[12]

Additional substrates were synthesized by subjecting compound **1** to hydrolysis/amide formation (**18**), *N*3-alkylation (**19**), and reduction (**20**) (Scheme 1).

We then set out to determine the generality of the cyclization reaction. During the initial optimization using substrate **1**, we determined that 10 mol % AuCl provided the optimal yield. However, across AuCl sources we encountered a wide variance in reactivity on repetition of the parent reaction. Reproducibility issues led us to undergo a second screen of gold catalysts and conditions. We determined that for consistently productive yields, certain substrates required increased catalyst loading up to 30 mol %. We also identified $HAuCl_4$ as a similarly active and more dependable catalyst for a number of substrates.[13] Interestingly, while $AuClPPh_3$ alone gave trace product, cationic gold catalyst systems such as $AuClPPh_3$/AgOTf and $AuClPPh_3/AgBF_4$ were wholly unreactive for substrates **1** and **14**.

Table 2 depicts the scope and limitations of the reaction. Aliphatic, aromatic and silyl alkynes all cyclized in good to excellent yields (entries 1-2, 4-7). Notably, silyl alkynes **9** and **14** demonstrated the most efficient cyclization; while compound **1** required prolonged heating to induce cyclization, silyl alkyne **14** showed 91% conversion after 14 hours at room temperature (20 mol % $HAuCl_4$, percent converson determined by crude ^1H NMR).

The functionality at C5 proved to be critical to the outcome of the reaction. In addition to ester and ketone substrates, amide **18** (entry 11) cyclized in low yield, while substrates lacking a carbonyl (entries 16, 20) failed to cyclize. We also investigated the effect of substituents at N3 position of the DHPM. Acylated and alkylated substrates cyclized but with consistently lower conversions (entries 12, 14-15) and often requiring increased catalyst loading.

While substitution of the alkyne was widely tolerated, terminal alkynes **10** and **15** showed erratic reactivity, with conversions generally below 5%. However, the target pyridopyrimidone products of these cyclizations could be reliably accessed via AgF-mediated desilylation[14] of cyclized vinylsilanes **23** and **27**.[5] Lastly, we observed that substitution of an ethyl group C6-DHPM position also shuts down the reaction (Entry 10).

Our attention next turned to elucidating the mechanism of this transformation. A search for similar cyclizations of alkynyl enamides to give six-membered rings gave only one example: an undesired side reaction in the Au-catalyzed cycloisomerization of propargylated enamides to give pyrroles.[15] In addition, a number of examples of nucleophilic C-C bond formation at activated alkynes have been recently disclosed, employing β-dicarbonyls, silyl and alkyl enol ethers, and enamines as carbon nucleophiles.[16] There exist far fewer instances of such reactions employing unactivated enolizable carbonyls; the recent disclosure by Davies[17] is a notable example. For our system, we propose a vinylogous Conia-ene reaction[18] with dual activation, both oxophilic and alkynophilic, by the gold catalyst,[19] as depicted in Figure 2. A 6-*endo-dig* cyclization followed by protodemetallation and double bond isomerization gives rise the observed product.

To investigate the proposed mechanism, we performed deuterium labeling experiments (Scheme 2). We first prepared deuterated substrate **19-d_3**, which cyclized in 14% yield with deuterium distribution as depicted. In addition, we performed the cyclization of compound **1** in the presence of D_2O. From these experiments, we can conclude that: 1) significant enolization occurs prior to cyclization, as evidenced by the percent deuterium incorporation at the non-acidic γ-positions of **29-d_6** and **3-d_6**; 2) deuterium depletion at the acidic γ-protons of recovered starting materials **19-d_3** and **1-d_3** is suggestive of equilibration with the ε-protons of their respective cyclization products; and 3) the enolization of both **1** and **3** are gold-promoted, as there is no deuterium incorporation seen at any C-H position in two control experiments performed in the absence of catalyst.

Intrigued by the notion that the gold catalyst may serve a dual function in promoting the reaction, we then undertook a kinetic study to gain further insight. The third-order rate plot of the room-temperature cyclization of substrate **14** in the presence of auric acid is depicted in Figure 3. Kinetic data clearly indicates a multiple-order dependence on catalyst, supporting our proposed dual catalyst activation. The apparent third-order dependence in catalyst is intriguing and may arise from binuclear Au(III) Lewis acid activation of the carbonyl (Figure 4).[20]

We hypothesize that the challenges of reproducibility result from the relatively low catalytic activity of unstabilized gold (I) and (III) species under harsh reaction conditions, which is well-documented.[22] While gold is not generally known to cycle between oxidation states, AuCl will disproportionate to $AuCl_3$ and colloidal Au_0 upon heating.[23] The π-acidity of Au(I) and Au(III) are both well-established, calculations demonstrate Au(III) to be a superior oxophilic Lewis acid. Phosphine-ligated Au(I) salts, more broadly utilized due to their increased stability, may not be sufficiently oxophilic to promote the requisite enolization.[24]

In summary, we have discovered an interesting gold catalyzed cyclization of alkyne-tethered dihydropyrimidones. An effective protocol employing the Mitsunobu reaction was also developed to prepare a wide panel of reaction precursors. Mechanistic experiments suggest a dual role for the gold catalyst in this reaction, activating both the alkyne and nucleophile towards the desired reaction. Further studies, including applicability of this reaction to library synthesis and further biological evaluation of the pyridopyrimidones are currently under investigation and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

(1). Biginelli P. Gazz. Chim. Ital. 1893; 23:360–416.

(2) (a). Kappe CO. Tetrahedron. 1993; 49:6937–6963.(b) Kappe CO. Acc. Chem. Res. 2000; 33:879–888. [PubMed: 11123887] (c) Kappe CO. Eur. J. Med.Chem. 2000; 35:1043–1058. [PubMed: 11248403] (d) Borowsky B, Durkin MM, Ogozalek K, Marzabadi MR, Deleon J, Lagu B, Heurich R, Lichtblau H, Shaposhnik Z, Daniewska I, Blackburn TP, Branchek TA, Gerald C, Vaysse PHJ, Forray C. Nat. Med. 2002; 8:825–830. [PubMed: 12118247]

(3) (a). Lou S, Taoka BM, Ting A, Schaus SE. J. Am. Chem. Soc. 2005; 127:11256–11257. [PubMed: 16089450] (b) Lou S, Dai P, Schaus SE. J. Org. Chem. 2007; 72:9998–10008. [PubMed: 18047372]

(4). Brown LE, Cheng KC-C, Wei W-G, Yuan P, Dai P, Trilles R, Ni F, Yuan J, MacArthur R, Guha R, Johnson RL, Su X.-z. Dominguez MM, Snyder JK, Beeler AB, Schaus SE, Inglese J, Porco JA Jr. Proc. Nat. Acad. Sci. 2011; 108:6775–6780. [PubMed: 21498685]

(5). Dower, K.; Filone, CM.; Hodges, EN.; Bjornson, ZB.; Rubins, KH.; Brown, LE.; Schaus, SE.; Hensley, L.; Connor, JH. 2011. submitted for review

(6). Beeler AB, Su S, Singleton CA, Porco JA Jr. J. Am. Chem. Soc. 2007; 129:1413–1419. [PubMed: 17263426]

(7). For the synthesis of DHPM-derived hexahydropyridopyrimidines, see: Singh K, Singh S. Tetrahedron. 2008; 64:11718–11723.

(8). Dallinger D, Kappe CO. Synlett. 2002; 11:1901–1903.

(9) (a). Dallinger D, Gorobets NY, Kappe CO. Mol. Div. 2003; 7:229–245.(b) Kosolov MA, Orlov VD. Zh. Org. Farm. Khim. 2005; 3:17–22.(c) Mobinikhaledi A, Forughifar N, Habibi M, Kalate Z. Asian J. Chem. 2007; 19:219–222.

(10). A method for selective N1 DHPM alkylation employing alkyl bromides has also been disclosed: Singh K, Arora D, Poremsky E, Lowery J, Moreland RS. Eur. J. Med. Chem. 2009; 44:1997–2001. [PubMed: 19008020]

(11). Koppel I, Koppel J, Degerbeck F, Grehn L, Ragnarsson U. J. Org. Chem. 1991; 56:7172–7174.

(12)(a). Kappe CO, Stadler A. Org. React. 2004; 63:1.(b) Kappe CO, Roschger P. J. Het. Chem. 1989; 26:55–64.(c) Hu EH, Sidler DR, Dolling U-H. J. Org. Chem. 1998; 10:3454–3457.(d) Perez R, Beryozkina T, Zbruyev O, Haas W, Kappe CO. J. Comb. Chem. 2002; 4:501–510. [PubMed: 12217023]

(13) (a). For examples of $HAuCl_4$-mediated reactions of alkynes, see: Arcadi A, Alfonsi M, Chiarini M, Marinelli F. J. Organomet. Chem. 2009; 694:576–582. Shu X-Z, Liu X-Y, Xiao H-Q, Ji K-G, Guo L-N, Liang Y-M. Adv. Synth. Catal. 2008; 350:243–248. Ji K-G, Shen Y-W, Shu X-Z, Xiao

H-Q, Bian Y-J, Liang Y-M. Adv. Synth. Catal. 2008; 350:1275–1280. Wegner HA, Ahles S, Neuburger M. Chem.-Eur. J. 2008; 14:11310–11313. [PubMed: 19006147] Georgy M, Boucard V, Campagne J-M. J. Am. Chem. Soc. 2005; 127:14180–14181. [PubMed: 16218601] Belting V, Krause N. Org. Lett. 2006; 8:4489–4492. [PubMed: 16986932] Kato K, Teraguchi R, Kusakabe T, Motodate S, Yamamura S, Mochida T, Akita H. Synlett. 2007:63–66.

(14) (a). Furstner A, Radkowski K. Chem. Commun. 2002:2182–2193.(c) Trost BM, Osipov M, Dong G. Org. Lett. 2010; 12:1276–1279. [PubMed: 20148531]

(15). Saito A, Konishi T, Hanzawa Y. Org. Lett. 2010; 12:372–374. [PubMed: 20025257]

(16) (a). Denes F, Perez-Luna A, Chemla F. Chem. Rev. 2010; 110:2366–2447. [PubMed: 20196544] (b) Kennedy-Smith JJ, Staben ST, Toste FD. J. Am. Chem. Soc. 2004; 126:4526–4527. [PubMed: 15070364] (c) Staben ST, Kennedy-Smith JJ, Toste FD. Angew Chem. Int. Ed. 2004; 43:5350–5352.(d) Dankwardt JW. Tetrahedron Lett. 2001; 42:5809–5812.(e) Staben ST, Kennedy-Smith JJ, Huang D, Corkey BK, LaLonde RL, Toste FD. Angew. Chem. Int. Ed. 2006; 45:5991–5994.(f) Lee K, Lee PH. Adv. Synth. Catal. 2007; 349:2092–2096.(g) Minnihan EC, Colletti SL, Toste FD, Shen HC. J. Org. Chem. 2007; 72:6287–6289. [PubMed: 17625890] (h) Nevado C, Cárdenas DJ, Echavarren AM. Chem. Eur. J. 2009; 9:2627–2635. [PubMed: 12794906] (i) Abbiati G, Arcadi A, Bianchi G, Di Giuseppe S, Marinelli F, Rossi E. J. Org. Chem. 2003; 68:6959–6966. [PubMed: 12946136] (j) Harrison TJ, Dake GR. Org. Lett. 2004; 6:5023–5026. [PubMed: 15606126] (k) Belmont P, Belhadj T. Org. Lett. 2005; 7:1793–1795. [PubMed: 15844908] (l) Binder JT, Crone B, Haug TT, Menz H, Kirsch SF. Org. Lett. 2008; 10:1025–1028. [PubMed: 18232707] (m) Yang T, Ferrali A, Campbell L, Dixon DJ. Chem . Commun. 2008:2923–2925.(n) Montaignac B, Vitale MR, Michelet V, Ratovelomanana-Vidal V. Org. Lett. 2010; 12:2582–2585. [PubMed: 20462188] (o) Montaignac B, Vitale MR, Ratovelomanana-Vidal V, Michelet V. J. Org. Chem. 2010; 75:8322–8325. [PubMed: 21062095]

(17). Davies PW, Detty-Mambo C. Org. Biomol. Chem. 2010; 8:2918–2922. [PubMed: 20498915]

(18). Kende AS, Newbold RC. Tetrahedron Lett. 1989; 30:4329–4332.

(19) (a). Yamamoto Y. J. Org. Chem. 2007; 72:7817–7831. [PubMed: 17579452] (b) Duschek A, Kirsch SF. Angew. Chem. Int. Ed. 2008; 47:5703–5705.

(20). DeHaan FP, Brown HC. J. Am. Chem. Soc. 1969; 91:4844–4850.

(21)(a). Gorin DJ, Sherry BD, Toste FD. Chem. Rev. 2008; 108:3351–3378. [PubMed: 18652511] (b) Gorin DJ, Toste FD. Nature. 2007; 446:395–403. [PubMed: 17377576]

(22)(a). Vogler A, Kunkely H. Coord. Chem. Rev. 2001; 219:489–507.(b) Wabnitz TC, Yu J-Q, Spencer JB. Chem. Eur. J. 2004; 10:484–493. [PubMed: 14735517] (c) Lemiere G, Gandon V, Agenet V, Goddard J-P, de Kozak A, Aubert C, Fensterbank L, Malacria M. Angew Chem. 2006; 118:7758–7761.

(23). Straub BF. Chem. Commun. 2004:1726–1728.

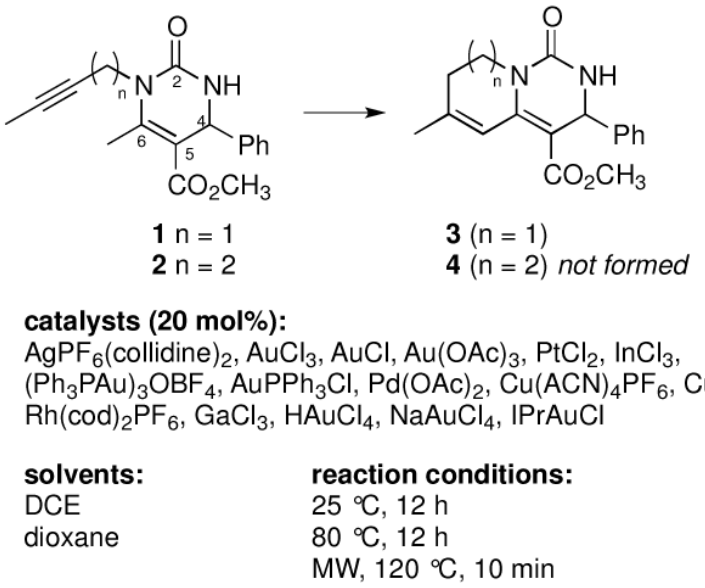


Figure 1.
Screened catalysts and conditions

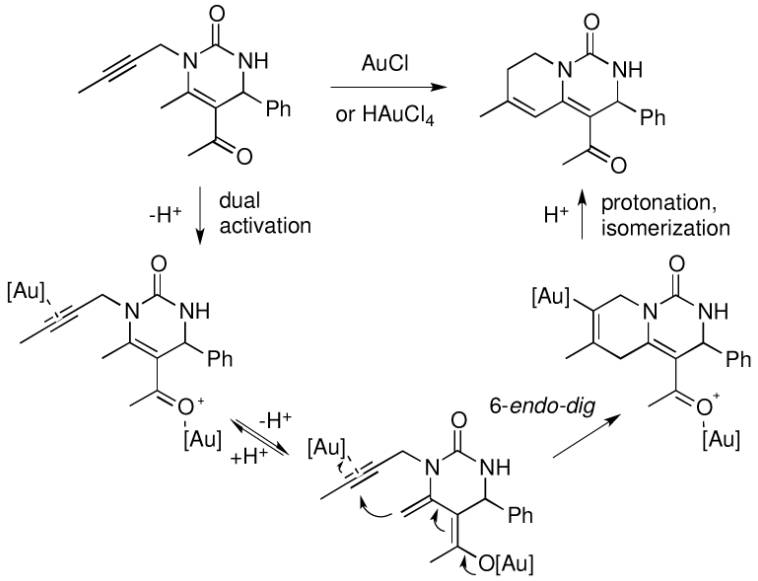


Figure 2.
Proposed mechanism for pyridopyrimidone formation

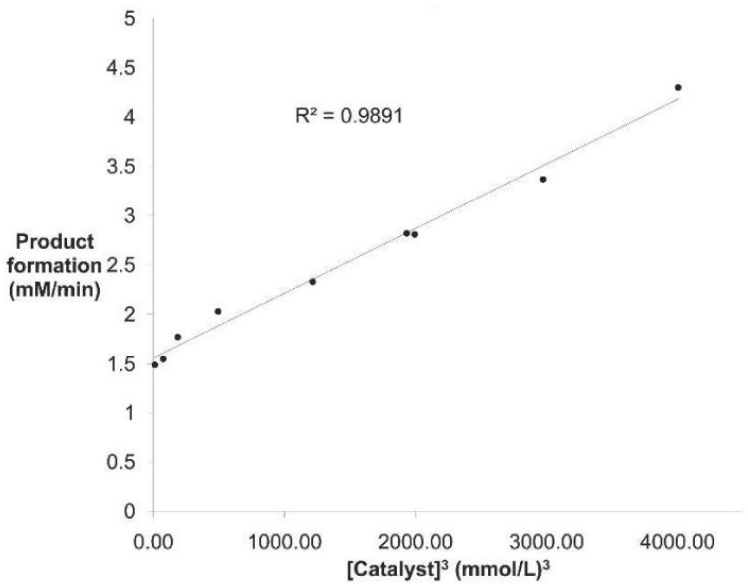


Figure 3.

Plot of the steady-state intial rate of product formation vs auric acid concentration cubed for the conversion of **14** to **27** ($ClCH_2CH_2Cl$, 25 °C)

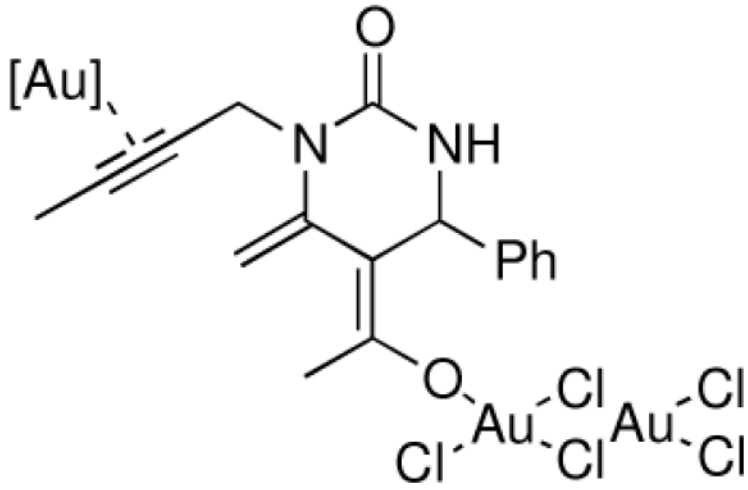
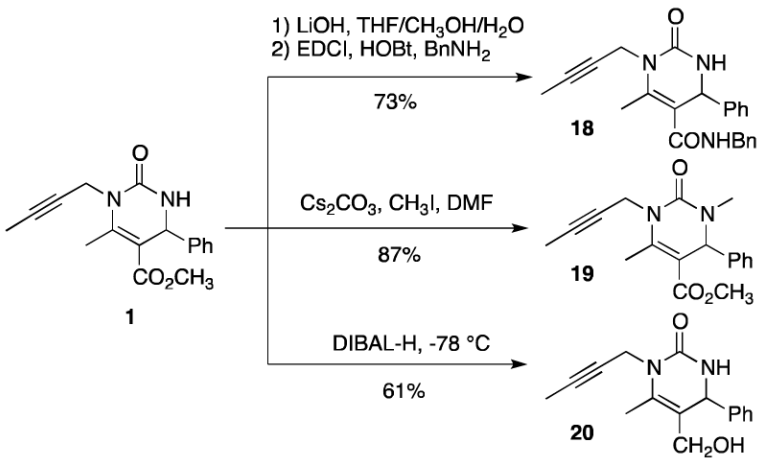
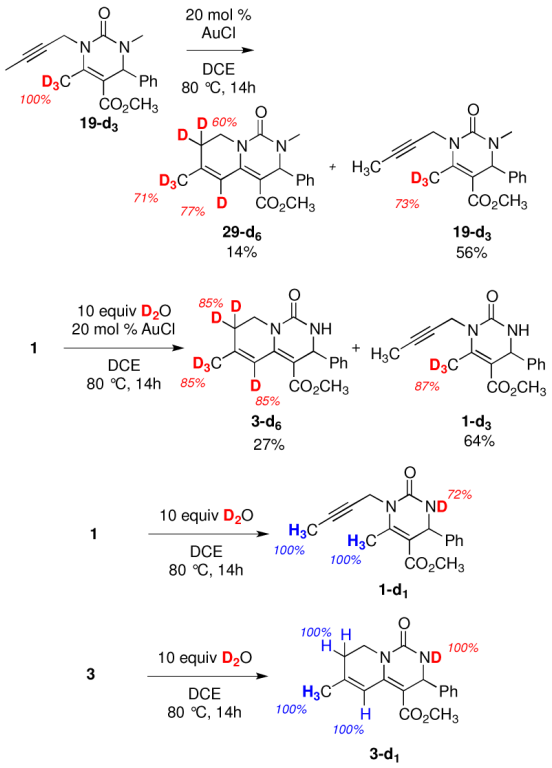


Figure 4.
Proposed bimetallic Au(III) carbonyl activation



Scheme 1.

Synthesis of additional substrates for reaction screen



Scheme 2.
Deuterium labeling studies

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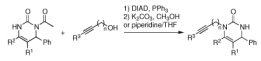
Table 1

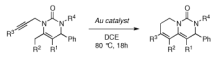
Synthesis of N1-propargylated DHPMs



DHPM	R_1	R_2	R_3	n	product	yield (%)
5	CO_2CH_3	CH_3	CH_3	1	**1**	69
5	CO_2CH_3	CH_3	CH_3	2	**2**	56
5	CO_2CH_3	CH_3	TMS	1	**9**	67
5	CO_2CH_3	CH_3	H	1	**10**	85
5	CO_2CH_3	CH_3	Ph	1	**11**	46
5	CO_2CH_3	CH_3	C_5H_{11}	1	**12**	84
6	$COCH_3$	CH_3	CH_3	1	**13**	68
6	$COCH_3$	CH_3	TMS	1	**14**	76
6	$COCH_3$	CH_3	H	1	**15**	73
7	CN	CH_3	CH_3	1	**16**	72
8	CO_2CH_3	CH_2CH_3	CH_3	1	**17**	83

Table 2

Substrate scope of gold-mediated cyclization



entry	substrate	catalyst[a,b]	product (yield)
1	**1**	C	**3** (63%)
2	**9**	B	**23** (93%)
3	**10**	A, B, C, D, E	No reaction
4	**11**	B	**24** (57%)
5	**12**	A	**25** (58%)
6	**13**	C	**26** (65%)
7	**14**	D	**27** (94%)
8	**15**	A, B, C, D, E	No reaction
9	**16**	B, D	No reaction
10	**17**	B, D	No reaction
11	**18**	E	**28** (27%)
12	**19**	E	**29** (20%)
13	**20**	B, D	Decomposed
14	**21** (R_1 = $COCH_3$, R_2 = H, R_3 = CH_3, R_4 = Ac)	C	**30** (50%)
15	**22** (R_1 = $COCH_3$, R_2 = H, R_3 = TMS, R_4 = Ac)	B	**31** (20%)

*a)*Catalyst loadings: A: 10 mol % AuCl; B: 20 mol % AuCl; C: 10 mol % $HAuCl_4$-$3H_2O$; D: 20 mol % $HAuCl_4$-$3H_2O$; E: 30 mol % AuCl.

*b)*Loadings reported are for optimized yields.