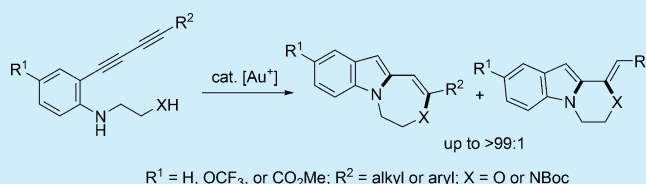


Direct Construction of Fused Indoles by Gold-Catalyzed Cascade Cyclization of Conjugated Diynes

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Supporting Information

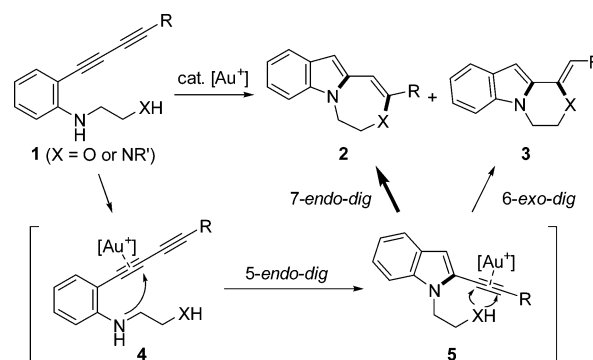
ABSTRACT: A gold-catalyzed cascade cyclization of aniline derivatives bearing a conjugated diyne moiety was developed. Following the 5-*endo-dig* indole formation, subsequent 7-*endo-dig* cyclization predominated over 6-*exo-dig* cyclization to give the indole fused with a seven-membered ring in good yields.



Homogeneous gold catalysis has recently garnered much interest in organic chemistry.¹ The versatile reactivity of gold catalysts enables the design of cascade reactions for atom- and step-economical direct syntheses of complex molecules.² Although many gold-catalyzed cascade reactions of alkynes have been reported,³ there have been few studies of the reactions of conjugated diynes. Recently, some useful gold-catalyzed reactions of conjugated diynes have been reported, including [4 + 3] annulation of conjugated diynyl esters,⁴ double nucleophilic addition for pyrrole/furan syntheses,⁵ and double hydroarylation to form highly fused rings.⁶ Banwell et al. reported a gold-catalyzed consecutive hydroamination of phenylurea derivatives bearing a terminal conjugated diyne moiety at the *ortho*-position.⁷ This reaction proceeds through indole formation followed by 5-*exo*- or 6-*endo-dig* cyclization, depending on the substrate structure. Gold-catalyzed reactions of conjugated diynes have great potential for ring construction including indoles.^{8a} However, to the best of our knowledge, 7-*endo* selective cyclization using conjugated diynes is unprecedented.

We recently developed a gold-catalyzed nucleophilic addition and hydroarylation cascade using unconjugated diynes for construction of fused rings such as carbazoles and naphthalenes.^{8b–e} When the reactions were applied to polyyne derivatives, highly fused rings were efficiently produced.⁹ Given our interest in the reactivity of conjugated diynes, we designed a gold-catalyzed intramolecular consecutive cyclization of conjugated diyne **1** bearing two nucleophilic functionalities, such as an amino alcohol and diamine (Scheme 1). The potential issues associated with this reaction were regioselectivity in the second cyclization (6-*exo-dig* vs 7-*endo-dig*) and reactivity of conjugated diynes toward indole formation. It is well-known that gold-catalyzed cyclizations of alkynes usually favor 6-*exo-dig* over 7-*endo-dig*,¹⁰ except for some limited cases using terminal^{11,12} and arylated alkynes.¹³ In the reaction of the intermediate **5**, the 6-*exo* cyclization might be promoted by the electron-donating nature of the indole ring, which can effectively stabilize a developing positive charge at the neighboring alkyne carbon when activated

Scheme 1. Gold(I)-Catalyzed Intramolecular Consecutive Cyclization of a Conjugated Diyne



by a gold catalyst. Here, we report a gold-catalyzed synthesis of oxepino- and diazepino[1,7-*a*]indole derivatives **2**. These are important structural motifs found in hepatitis C virus polymerase¹⁴ and dopamine receptor-binding compounds.¹⁵ The reaction proceeds through regioselective 7-*endo-dig* cyclization starting from conjugated diynes **1**.

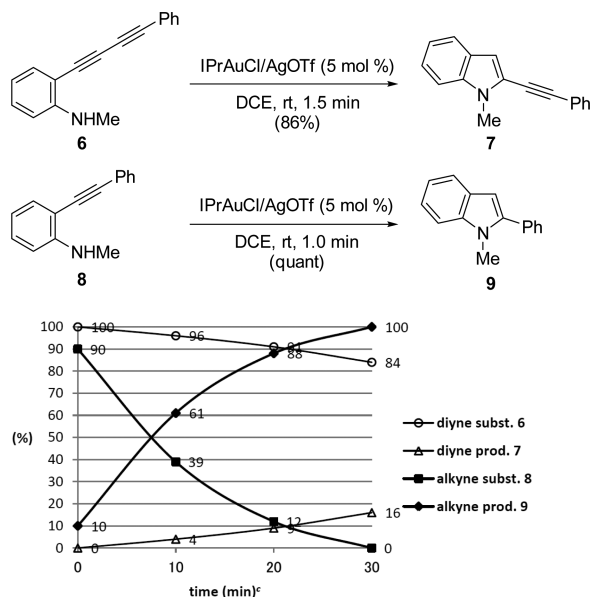
On initiation of this work, no information was available on the reactivity of conjugated diynes toward indole formation. For a feasibility study of the working hypothesis, the gold-catalyzed reaction of the conjugated diyne **6** bearing an *N*-methylamino group was examined. Indole formation proceeded smoothly to give the alkynylindole **7** in 86% yield after treatment of **6** with IPrAuCl/AgOTf (5 mol %) in DCE at rt for 1.5 min. Interestingly, indole formation from 2-alkynylaniline **8** was significantly faster than that from **6**, which reached completion within 1.0 min under identical conditions.¹⁷ This is in contrast to the steric effect, where conjugated diyne derivatives would have a positive effect on the coordination to gold catalysts compared to 2-(phenylethynyl)anilines. The relatively lower reactivity of

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diyne **6** compared with alkyne **8** toward indole formation can be more clearly seen in the competition experiment shown in Scheme 2.

Scheme 2. Comparison of the Reactivities toward Indole Formation between Diynyl- and (Phenylethynyl)anilines^{a,b}



^aRatios were determined by ¹H NMR. ^bThe competition experiment was conducted with IPrAuCl/AgOTf (5 mol %) in DCE at -20 °C. ^cThe horizontal axis indicates the time of NMR measurement.¹⁶

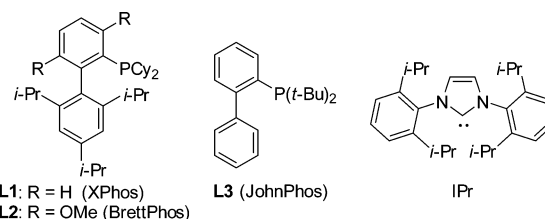
The conjugated diyne has a sufficient level of reactivity for gold-catalyzed indole formation, although it is relatively lower than that of the isolated alkyne. A search for suitable catalysts and solvents for the intramolecular consecutive cyclization of **1a** was then conducted (Table 1). When conjugated diyne **1a** was treated with PPh₃AuCl/AgOTf (5 mol %) in DCE at 50 °C, the desired fused indole derivatives **2a/3a** and alkynylindole derivative **10a** were obtained in 28% and 56% yields, respectively (entry 1). The ratio of **2a/3a** was determined by ¹H NMR after purification of **2a/3a** as an isomeric mixture. Surprisingly, 7-*endo-dig* cyclization preferentially proceeded in the second cyclization (**2a/3a** = 85/15). The reactions using XPhos (**L1**) or BrettPhos (**L2**) in place of PPh₃ gave the fused indoles **2a/3a** in 48% and 27% yield, respectively (entries 2 and 3). Use of JohnPhos (**L3**) resulted in efficient conversion to give a good yield of fused indoles **2a/3a** (76%, entry 4). The most efficient conversion was observed when an *N*-heterocyclic carbene ligand, IPr, was used (86%, entry 6). Compared with AgOTf (entry 6), other silver salts such as AgNTf₂, AgOTs, and AgBF₄ were less effective (entries 7–9). Of the four solvents tested (DCE, toluene, MeCN, and EtOH), DCE was the best (entries 6 and 10–12). The reaction at lower temperature (rt) reduced the yield slightly (73%, entry 13). Use of AgOTf alone produced the alkynylindole **10a** in 58% yield (entry 14). The reactions using AuCl, AuCl₃ without any phosphine or carbene ligands, or PtCl₄ were unsuccessful (entries 15–17).

With the conditions optimized (Table 1, entry 6), the cascade reaction was investigated using various substrates (Table 2). The reaction of **1b** and **1c** with electron-donating or -withdrawing groups at the *para*-position of the amino group (R¹) gave the desired double cyclization products **2b/3b** (86%) and **2c/3c**

Table 1. Optimization of the Reaction Conditions^a

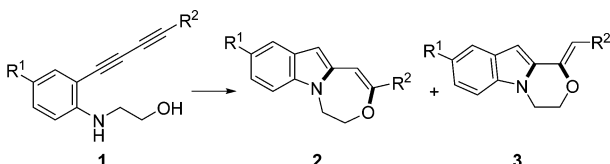
entry	catalysts (5 mol %)	solvent (0.1 M)	time (h)	% yield (%) ^c	
				2a/3a (ratio ^b)	10a
1	Ph ₃ PAuCl/AgOTf	DCE	5	28 (85/15)	56
2	L1AuCl/AgOTf	DCE	10	48 (91/9)	14
3	L2AuCl/AgOTf	DCE	5	27 (85/15)	43
4	L3AuCl/AgOTf	DCE	2	76 (93/7)	—
5	L3Au(MeCN)SbF ₆	DCE	5	3 (93/7)	39
6	IPrAuCl/AgOTf	DCE	2	86 (88/12)	—
7	IPrAuCl/AgNTf ₂	DCE	8	32 (85/15)	ca. 33
8	IPrAuCl/AgOTs	DCE	6	57 (95/5)	—
9	IPrAuCl/AgBF ₄	DCE	5	29 (98/2)	trace
10	IPrAuCl/AgOTf	toluene	2	<47 (93/7)	—
11	IPrAuCl/AgOTf	MeCN	6	trace	trace
12	IPrAuCl/AgOTf	EtOH	2	<17 (93/7)	—
13 ^d	IPrAuCl/AgOTf	DCE	8	73 (92/8)	trace
14 ^e	AgOTf	DCE	24	—	58
15 ^e	AuCl	DCE	4	N.R. ^f	—
16 ^e	AuCl ₃	DCE	4	N.R. ^f	—
17 ^e	PtCl ₄	DCE	4	N.R. ^f	—

^aReaction was carried out using **1a** (0.15 mmol) and catalyst (5 mol %) at 0.1 M at 50 °C. ^bRatios were determined by ¹H NMR analysis. ^c(Combined) isolated yields. ^dThe reaction was conducted at rt. ^e0.1 mmol of **1a** was used. ^fN.R. = No reaction.



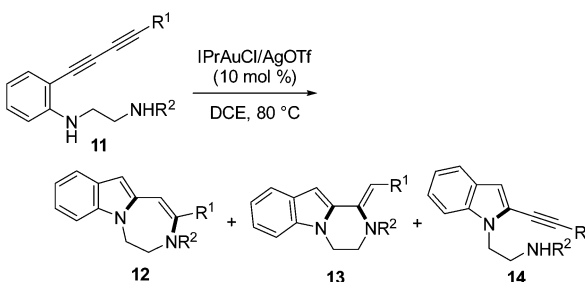
(88%), respectively (entries 2 and 3). In both cases, the 7-*endo* product was obtained with good selectivities (>90/10). A range of substituents at the conjugated diyne terminus (R²) were tolerated, including benzene rings bearing an electron-donating or -withdrawing group (entries 4 and 5). The observed low regioselectivity of the reaction of **1e** (R² = 4-(MeO₂C)C₆H₄) might result from the activation of 6-*exo* cyclization by the electron-deficient phenyl group. Interestingly, use of **1f** bearing an alkyl group exclusively afforded the 7-*endo*-product **2f** in 78% yield (entry 6).

Preliminary results of the reaction of diamine derivatives **11** are shown in Table 3. These reactions required an increased loading of the catalyst (10 mol %) and higher temperature (80 °C) because of the low reactivity. The reaction of **11a** bearing a free primary amino group (R² = H) was unsuccessful and produced a complex mixture of unidentified products (entry 1). The reaction of the corresponding carbamate derivative **11b** (R² = Boc) was slow to give the alkynylindoles **14b** (entry 2). Due to

Table 2. Reaction of Various Conjugated Diynes^a


entry	subst.	R ¹	R ²	time (h)	yield (%) ^b	ratio (2/3) ^c
1	1a	H	Ph	2	86	88/12
2	1b	OCF ₃	Ph	2	86	91/9
3	1c	CO ₂ Me	Ph	1.5	88	90/10
4	1d	H	4-(MeO)C ₆ H ₄	2	90	94/6
5	1e	H	4-(MeO ₂ C)C ₆ H ₄	1	71–92 ^d	56–61/44–39
6	1f	H	<i>n</i> -Pr	1	78	100/0

^aReaction conditions: IPrAuCl/AgOTf (5 mol %) in DCE (0.1 M) at 50 °C. ^bCombined isolated yields. ^cRatios were determined by ¹H NMR analysis after purification of the isomeric mixture. ^dLow reproducibility due to the products instability.

Table 3. Reaction of Ethylenediamine-Type Substrates^a


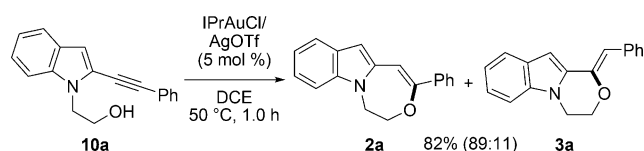
entry	subst.	R ¹	R ²	time (h)	% yield ^b (ratio ^c)	
					12/13	14
1	11a	Ph	H	24	complex mixture	–
2	11b	Ph	Boc	24	trace	79
3	11c	<i>n</i> -Pr	Boc	8	49–73 ^d (82–85/18–15)	–

^aReaction conditions: IPrAuCl/AgOTf (10 mol %) in DCE (0.1 M) at 80 °C. ^bCombined isolated yields. ^cRatios were determined by ¹H NMR analysis. ^dLow reproducibility due to the products instability.

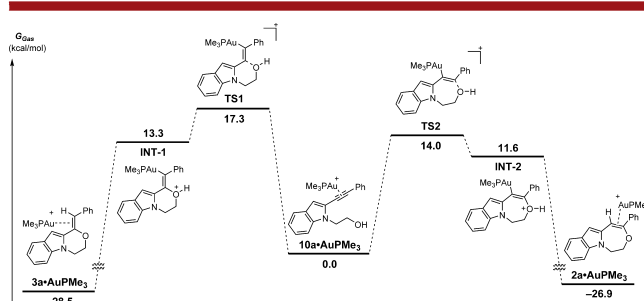
speculation that steric repulsion between R¹ and R² groups obstructs progress of the second cyclization, the reaction of the aliphatic diyne derivative **11c** was examined (R¹ = *n*-Pr). This reaction led to the desired fused indole products **12c/13c** in 49–73% yields (entry 3). The observed low reproducibility is because of the instability of **12c/13c** bearing a sterically congested enamine structure. Thus, the 1,2-diamine derivatives have proven to be less suitable substrates for the present gold-catalyzed cascade cyclization.

To obtain some insight of the reaction mechanism and regioselectivity, we investigated the second cyclization of the possible intermediate **10a** (Scheme 3). Also in this case, the seven-membered ring formation predominated to give a mixture of **2a** and **3a** in an 89:11 ratio, essentially the same as the original reaction of diyne **1a** (entry 1, Table 2).¹⁸ We then undertook a

Scheme 3. Reaction of the Possible Intermediate 10a



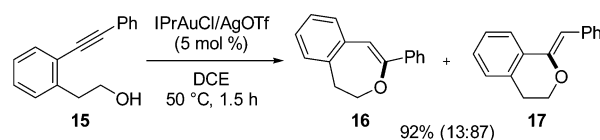
density functional theory (DFT) based exploration of the origin of the regioselectivity (Figure 1). The energy diagram clearly

Figure 1. DFT calculations on cyclization of **10a** [M06-2X/6-31G(d,p) & SDD(Au)].

suggests that the kinetically and thermodynamically more favorable pathway is the 7-*endo-dig* cyclization. Both cyclizations from the starting complex **10a**·AuPMe₃¹⁹ proceed smoothly, and 7-*endo-dig* cyclization requires a lower activation energy (14.0 kcal/mol) than that of 6-*exo-dig* (17.3 kcal/mol). However, the cyclizations are remarkably both highly endothermic processes and retro-cyclizations should occur very smoothly. Thus, an equilibration between INT-1 and INT-2 via **10a**·AuPMe₃ should exist and the seven-membered ring formation proceeds preferentially through INT-2, which is more stable than INT-1 by 1.7 kcal/mol.

We assumed that the thermodynamic preference for INT-2 may result from ring strain of the six-membered ring in INT-1 fused with the indole ring. To evaluate this possibility, we investigated the reaction of alkynylbenzene derivative **15** (Scheme 4, a benzene congener of the alkynylindole intermediate **10a**). In this case, the ring strain for the 6-*exo-dig* cyclization would be considerably less compared with that from **10a**. As expected, the 6-*exo-dig* cyclization product **17** was preferentially produced (**16/17** = 13/87) from **15**, which partially supports our assumption. However, at the present stage

Scheme 4. Reaction of the Benzene Congener 15



of our understanding, we cannot rule out another possibility that the protodeauration step might control the regioselectivity of the second cyclization. Further calculations to elucidate the protodeauration pathways from INT-1 and INT-2 are now underway.

In summary, a novel gold-catalyzed cascade cyclization of conjugated diynes was developed. This reaction provides direct access to oxepino[1,7-*a*]indole derivatives with good functional group tolerance. The observed 7-*endo*-selectivity was well rationalized by DFT calculations: the second ring formation proceeds through a more stable intermediate. Further development and application of this transformation in natural product syntheses are underway in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, characterization data for all new compounds, details of kinetic experiments, and computational investigations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For recent reviews, see: (a) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462–1479. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712. (c) Cera, G.; Bandini, M. *Isr. J. Chem.* **2013**, *53*, 848–855. (d) Nunes dos Santos Comprido, L.; Hashmi, A. S. K. *Isr. J. Chem.* **2013**, *53*, 883–891. (e) Gatineau, D.; Goddard, J.-P.; Mouriès-Mansuy, V.; Fensterbank, L. *Isr. J. Chem.* **2013**, *53*, 892–900. (f) Brand, J. P.; Waser, J. *Isr. J. Chem.* **2013**, *53*, 901–910.
- (2) For recent reviews, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462. (b) Rodeíguez, F.; Fañanás, F. J. *Synlett* **2013**, *24*, 1757–1771. (c) Zhang, Y.; Luo, T.; Yang, Z. *Nat. Prod. Rep.* **2014**, *31*, 489–503.
- (3) For recent reviews, see: (a) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009. (b) Ohno, H. *Isr. J. Chem.* **2013**, *53*, 869–882.
- (4) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480–14481.
- (5) (a) Lavallo, V.; Frey, G. D.; Donnadiou, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, S224–S228. (b) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758–2761. For related pyrrole syntheses using other transition metals, see: (c) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541–9544. (d) Zheng, Q.; Hua, R. *Tetrahedron Lett.* **2010**, *51*, 4512–4514.
- (6) Mo, J.; Eom, D.; Lee, E.; Lee, P. H. *Org. Lett.* **2012**, *14*, 3684–3687.
- (7) (a) Sharp, P. P.; Banwell, M. G.; Renner, J.; Lohmann, K.; Willis, A. C. *Org. Lett.* **2013**, *15*, 2616–2619. For a related gold-catalyzed 6-*endo* cyclization of alkynylindoles bearing a urea moiety, see: (b) Gupta, S.; Koley, D.; Ravikumar, K.; Kundu, B. *J. Org. Chem.* **2013**, *78*, 8624–8633.
- (8) (a) Matsuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Oho, H. *Chem.—Eur. J.* **2015**, *21*, 1463–1467. (b) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368–372. (c) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212–1227. (d) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907–4916. (e) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326–329.
- (9) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068–9080. See also ref 8c and 8d.
- (10) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (d) Patil, N. T.; Singh, V. J. *Organomet. Chem.* **2011**, *696*, 419–432.
- (11) (a) Wilckens, K.; Uhlemann, M.; Czekelius, C. *Chem.—Eur. J.* **2009**, *15*, 13323–13326. (b) Wilckens, K.; Lentz, D.; Czekelius, C. *Organometallics* **2011**, *30*, 1287–1290.
- (12) For related 7-*endo-dig* cyclization using other metals, see: (a) Bera, M.; Roy, S. *J. Org. Chem.* **2009**, *74*, 8814–8817. (b) Tsukano, C.; Yokouchi, S.; Girard, A.-L.; Kuribayashi, T.; Sakamoto, S.; Enomoto, T.; Takemoto, Y. *Org. Biomol. Chem.* **2012**, *10*, 6074–6786. (c) Girard, A.-L.; Enomoto, T.; Yokouchi, S.; Tsukano, C.; Takemoto, Y. *Chem.—Asian J.* **2011**, *6*, 1321–1324.
- (13) (a) Zhang, L.; Ye, D.; Zhou, Y.; Liu, G.; Feng, E.; Jiang, H.; Liu, H. *J. Org. Chem.* **2010**, *75*, 3671–3677. (b) Pan, B.; Lu, X.; Wang, C.; Hu, Y.; Wu, F.; Wan, B. *Org. Lett.* **2014**, *16*, 2244–2247.
- (14) (a) Ikegashira, K.; Oka, T.; Hirashima, S.; Noji, S.; Yamanaka, H.; Hara, Y.; Adachi, T.; Tsuruhashi, J.; Doi, S.; Hase, Y.; Noguchi, T.; Ando, I.; Ogura, N.; Ikeda, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 6950–6953. (b) Zheng, X.; Hudyma, T. W.; Martin, S. W.; Bergstrom, C.; Ding, M.; He, F.; Romine, J.; Poss, M. A.; Kadow, J. F.; Chang, C.-H.; Wan, J.; Witmer, M. R.; Morin, P.; Camac, D. M.; Sheriff, S.; Beno, B. R.; Rigat, K. L.; Wang, Y.-K.; Fridell, R.; Lemm, J.; Qiu, D.; Liu, M.; Voss, S.; Pelosi, L.; Roberts, S. B.; Gao, M.; Knipe, J.; Gentles, R. G. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2925–2929. (c) Sofia, M. J.; Chang, W.; Furman, P. A.; Mosley, R. T.; Ross, B. S. *J. Med. Chem.* **2012**, *55*, 2481–2531. (d) Ding, M.; He, F.; Hudyma, T. W.; Zheng, X.; Poss, M. A.; Kadow, J. F.; Beno, B. R.; Rigat, K. L.; Wang, Y.-K.; Fridell, R. A.; Lemm, J. A.; Qiu, D.; Liu, M.; Voss, S.; Pelosi, L. A.; Roberts, S. B.; Gao, M.; Knipe, J.; Gentles, R. G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2866–2871.
- (15) Kraxner, J.; Hübner, H.; Gmeiner, P. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 287–292.
- (16) Because the reaction partially proceeds before the NMR measurement even when the catalyst was added at a low temperature, the ratio at the zero time is slightly variable for every experiment.
- (17) For a review on gold-catalyzed indole formation of alkynylaniline derivatives, see: (a) Abbiati, G.; Marinelli, F.; Rossi, E.; Arcadi, A. *Isr. J. Chem.* **2013**, *53*, 856–868. For trapping of vinyl gold intermediates in related reactions, see: (b) Hashmi, A. S. K.; Ramamurthi, T. D.; Romingera, F. *Adv. Synth. Catal.* **2010**, *352*, 971–975.
- (18) The reaction of a possible intermediate **14c** showed slightly low regioselectivity (**12c**:**13c** = 75:25; see Supporting Information).
- (19) We confirmed that Me₃PAuCl/AgOTf shows similar regioselectivity (**2a**:**3a** = 82:18) although the reactivity was considerably decreased (<6% yield of **2a**/**3a**; 45% of **10a** after 24 h at 50 °C).