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# NHC-Stabilized Gold(I) Complexes: Suitable Catalysts for 6-*exo*-dig Heterocyclization of 1-(*o*-Ethynylaryl)ureas

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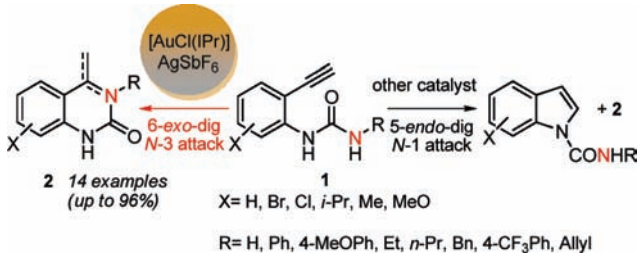
## ABSTRACT




**3-substituted 1-(*o*-ethynylaryl)ureas 1 selectively undergo either 6-*exo*-dig or 5-*endo*-dig cyclization (to give 4-methylene-3,4-quinazolin-2-ones 2 or indoles 3, respectively) depending on the choice of the metal, ligand, and reaction conditions. The best results (up to 96% yield) in the preparation of the hydroamination products 2 are achieved with the highly bulky NHC-stabilized cationic gold(I) complex $[Au(IPr)]^+$. Conversely, ureas bearing an internal alkyne lead to the 5-*endo*-dig cyclization mode regardless of the gold(I) complex employed. Whereas the nature of the substituent at *N*-3 does not have any influence on the regiochemistry observed, it does, in some cases, affect the efficiency of these transformations.**

A number of remarkable gold-catalyzed[1] hydroamination reactions have been successfully developed in the past few years.[2,3] Among these, annulation of *o*-alkynylaniline derivatives constitutes a well-established route to indole rings via a highly favored 5-*endo*-dig process.[4] In contrast, the possibility that such substrates could be used to access the less favored 6-*exo*-dig cyclization products has drawn relatively little attention.[5] Intrigued by the potential of such a reaction path, we focused our attention on the gold-catalyzed intramolecular hydroamidation reaction of 3-substituted 1-(*o*-alkynylaryl)ureas **1**, prepared from the readily accessible *o*-alkynylanilines and isocyanates.

Heterocyclization of substrate **1** may, in principle, lead to at least four different structures (see Figure 1),[6] namely, 4-ylidene-3,4-dihydroquinazolin-2-ones **2**[7−9] or their constitutional isomers 4-ylidene-benzoxazin-2-ylideneanilines **4** (path A), indoles **3** (path B), and benzodiazepin-2-ones **5** (path C).[10]

In the initial experiment, subjecting 1-(*o*-ethynylphenyl)-3-phenylurea (**1a**) to catalytic amounts of $NaAuCl_4$ (5 mol %) in

(1) For some selected reviews in gold catalysis, see: (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1776.

(2) For selected examples about gold-catalyzed hydroamination reactions, see: (a) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (b) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (c) Zhang, Y.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627. (d) Lalonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (e) Liu, X. Y.; Ding, P.; Huang, J. S.; Che, C. M. *Org. Lett.* **2007**, *9*, 2645. (f) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, *11*, 1767. (g) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887. (h) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (i) Giner, X.; Nájera, C. *Org. Lett.* **2008**, *10*, 2919. (j) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157. (k) Zhang, Z.; Lee, S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372. (l) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166. (m) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690. (n) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem.—Eur. J.* **2009**, *15*, 3056. (o) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182.

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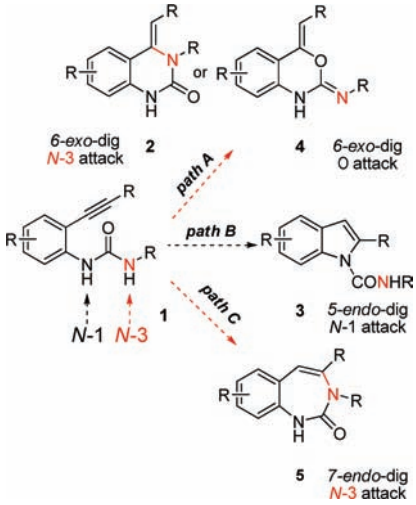



**Figure 1.** Possible main pathways for gold-catalyzed intramolecular hydroamidation reactions of ureas **1**.

ethanol afforded a 1:1 mixture of quinazolinone **2a** and indole **3a** after 3 h at room temperature (eq 1). The structure of **2a** was confirmed by single-crystal X-ray diffraction[11] (Figure 2). Compound **2** was found to form stacking N−H···OC hydrogen-bonded pairs in the solid state. The formation of either *N*-(4-methylene-1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-ylidene)aniline (product type **4**, path A) or 3-phenyl-1*H*-benzo[*d*][1,3]diazepin-2(3*H*)-one (hypothetical path C) was not detected.

(3) For general recent reviews about hydroamination reactions, see: (a) Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F. M.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407.

(4) (a) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, *4*, 610. (b) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265. (c) Arcadi, A.; Alfonsi, M.; Bianchi, G.; D'Anniballe, G.; Marinelli, F. *Adv. Synth. Catal.* **2006**, *348*, 331. (d) Ambrogio, I.; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2007**, *11*, 1775. (e) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284. (f) Zhang, Y.; Donahue, J.; Li, C. *Org. Lett.* **2007**, *9*, 627. (g) Nakamura, I.; Sato, Y.; Konta, S.; Terada, M. *Tetrahedron Lett.* **2009**, *50*, 2075.

(5) Ye, D.; Wang, J.; Zhang, X.; Zhou, Y.; Ding, X.; Feng, E.; Sun, H.; Liu, G.; Jiang, H.; Liu, H. *Green Chem.* **2009**, *11*, 1201.

(6) For gold-catalyzed reactions where a plausible competition between two nitrogen nucleophiles is present, see: (a) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661. (b) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (c) See ref 4. (d) Iglesias, A.; Muñiz, K. *Chem.—Eur. J.* **2009**, *15*, 10563.

(7) To the best of our knowledge, only two examples for the synthesis of the quinazolin-2-one core from 1-(*o*-alkynylaryl)ureas have been reported. (a) $Pd^{II}$-catalyzed: Costa, M.; Della Ca, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469. (b) TfOH-mediated: Wang, H.; Liu, L.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6841.

(8) Molina, P.; Conesa, C.; Alías, A.; Arques, A.; Velasco, M.; Llamas-Saiz, A. L.; Foces-Foces, C. *Tetrahedron* **1993**, *49*, 7599.

(9) Brack, A. *Lieb. Ann. Chem.* **1969**, *730*, 166.

(10) Benzooxazepin-2-amines arising from the nucleophilic attack of ureas **1** through their tautomeric carbamimidic forms could be also envisioned.

(11) X-ray data for compound **2a**: colorless lath, 0.25 × 0.12 × 0.05 mm size, monoclinic, $P2_1/c$, $a$ = 10.9132(5) Å, $b$ = 6.9003(3) Å, $c$ = 15.2690(7) Å, $\beta$ = 92.715(4)°, $V$ = 1148.53(9) Å$^3$, $Z$ = 4, $\rho_{calcd}$ = 1.366 g cm$^{-3}$, $\theta_{max}$ = 29.21, Mo Kα, $\lambda$ = 0.710 73 Å, $\omega$ scan, diffractometer Oxford Diffr. Gemini S Ultra, $T$ = 120(2) K, 11 878 reflections collected, of which 2768 were independent ($R_{int}$ = 0.0379), direct primary solution and refinement on $F^2$ (Sheldrick, G. M. *SHELXS-97* and *SHELXL-97*; University of Göttingen, Göttingen, Germany, 1997), 167 refined parameters, N−H hydrogen atom refined free, others *riding*, R1 [$I > 2\sigma(I)$] = 0.0361, wR2 (all data) = 0.0746, $\Delta\rho_{max}$ = 0.18 e Å$^{-3}$.

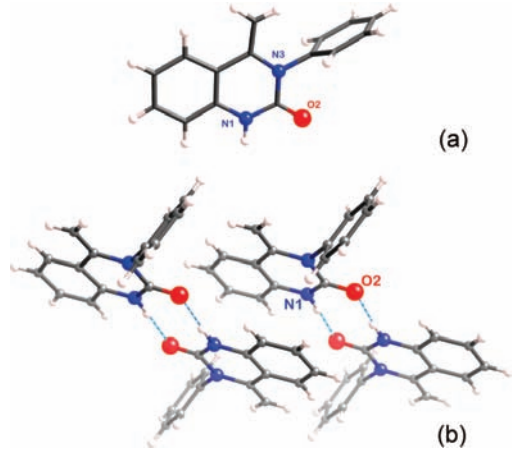
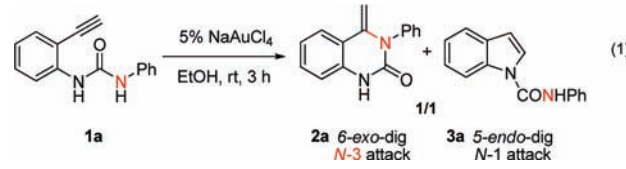
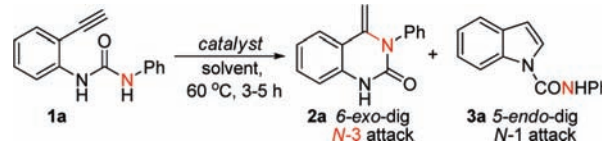



**Figure 2.** Single-crystal X-ray structure (a) of **2a** showing N−H···OC hydrogen-bonded pairs (b).




This preliminary result confirmed the ability of $NaAuCl_4$ to catalyze both 6-*exo*-dig and the highly competitive 5-*endo*-dig cyclization mode. In order to control the selectivity of heterocyclization of substrate **1a** in the preparation of 4-methylene-3,4-dihydroquinazolin-2-one derivatives **2**, we first explored different catalysts and conditions (Table 1).

**Table 1.** Screening of the Reaction Conditions To Control the Selectivity of the Intramolecular Gold(I)-Catalyzed Hydroamidation of Urea **1a**

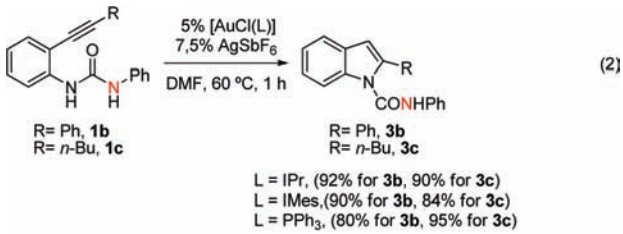



| catalyst [a] | solvent | **2a**/**3a** [b] | ligands |
|---|---|---|---|
| $NaAuCl_4$ | DMF | 5/1 | |
| $[AuCl(Ph_3P)]/AgSbF_6$ | DMF | 1/1.2 | |
| $[Au(L^1)(MeCN)]SbF_6$ | DMF | 1/1.5 | JonhPhos ($L^1$) |
| $[AuCl(Ph_3P)]/AgSbF_6$ | $CH_2Cl_2$ [c] | - | |
| $[Au(L^1)(MeCN)]SbF_6$ | $CH_2Cl_2$ [c] | - | |
| $[AuCl(L^2)]/AgSbF_6$ | DMF | 1/- | $R^1$ = *i*-Pr, $R^2$ = H ($L^2$); $R^1$ = $R^2$ = Me ($L^3$) |
| $[AuCl(L^3)]/AgSbF_6$ | DMF | 1/1.8 | |
| $PtCl_2/AgSbF_6$ | DMF | -/1 | |

[a] 5% Au or Pt catalyst. 7.5% Ag salt when indicated. [b] Determined by $^1$H NMR analysis of the crude reaction mixture. [c] Reaction carried out in a sealed tube.

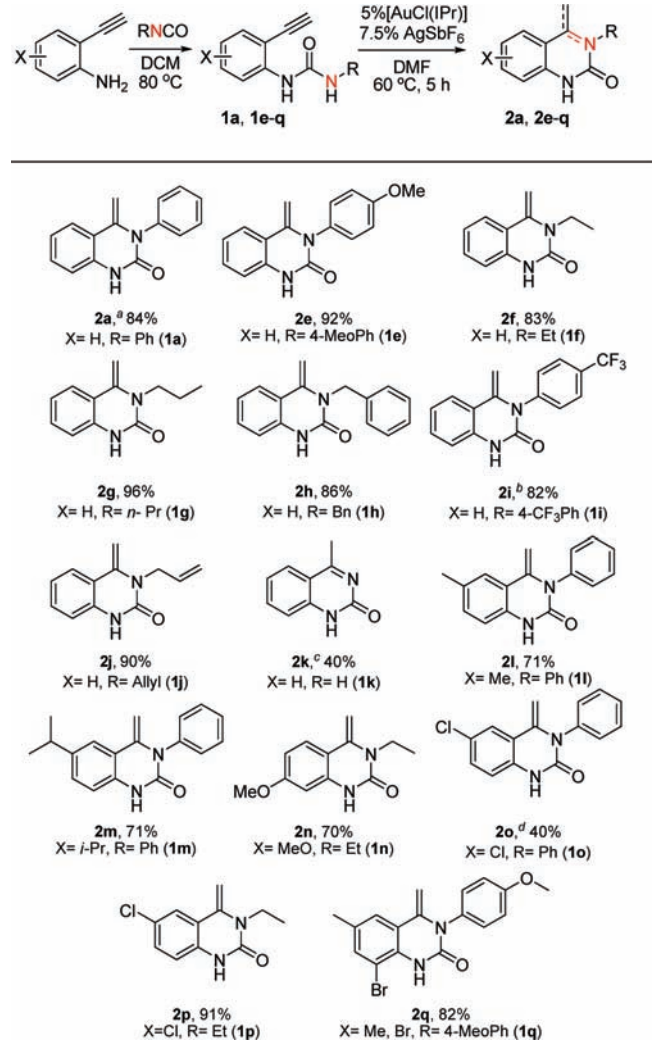
The **2a**/**3a** ratio increases up to 5:1 by carrying out the reaction under $NaAuCl_4$ catalysis in *N*,*N*-dimethylformamide (DMF) at 60 °C. The use of $[AuCl(Ph_3P)]/AgSbF_6$ or of the cationic $[Au(L^1)(MeCN)]^+$ complex led to a mixture enriched in indole **3a**. Phosphine-based catalysts in dichloromethane resulted in a very inefficient combination, probably as a result of the low solubility of ureas in this solvent. However, a mixture of 5% gold(I) carbene complex [AuCl(IPr)] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] and 7.5% $AgSbF_6$ in DMF (0.1 M in substrate **1a**) proved to be a very efficient catalyst, providing exclusively compound **2a**. Attempts to lower the gold catalyst loading to 2.5 mol % led to a sluggish reaction.[12,13] Because it has been suggested that the selectivity in catalytic applications in [Au(NHC)] systems may very well be controlled as a function of ligand sterics,[14] we examine how the selectivity was affected by decreasing of the bulk of the NHC ligand. Thus, when $[AuCl(IMes)]/AgSbF_6$ (IMes = 1,3-dimesitylimidazol-2-ylidine) was employed as the catalyst, a 1:1.8 mixture of quinazolinone **2a** and indole **3a** was observed (see Table 1). This result seems to confirm that the selectivity is, at least, affected by the steric hindrance of the NHC ligand on the gold(I) complex. An opposite selectivity was observed with a ligand-free cationic catalyst based on $Pt^{II}/Ag^{I}$, which led to indole **3a** as the only product.

Subsequently, a study with urea (**1b**) bearing an internal alkyne, with similar steric demand on opposite sides of the alkyne, was undertaken. In this case, the reaction leads to the 5-*endo*-dig cyclization mode[15] regardless of the electronic and steric properties of the ligand on the gold(I) complex (eq 2). When the phenyl substituent on the alkyne was replaced by an alkyl group in substrate **1c**, once again cyclization provides the corresponding indole derivative in every catalytic system studied. It is also worth mentioning that gold(I)-catalyzed heterocyclization of the *N*-3-unsubstituted urea **1d** also yields exclusively the indole ring **3d** (eq 3).




The results described so far point out the complete control exerted by the presence of an internal alkyne on the substrate toward -*endo*-dig cyclization in this process. At this point, encouraged by the excellent regio- and chemoselectivity exhibited by the $[Au(IPr)]SbF_6$ catalyst to perform the less favored, and therefore more challenging, 6-*exo*-dig cyclization with 3-substituted 1-(*o*-ethynylaryl)ureas, we sought to prepare a series of quinazolin-2-one derivatives **2** (Scheme 1) through the annulation reaction of a range of correspond-

**Scheme 1.** Gold(I)-Catalyzed 6-*exo*-dig Heterocyclization of 3-Substituted 1-(2-Ethynylaryl)ureas **1**




[a] All products were isolated with ≥95% purity. [b] The reaction ran over 18 h at 60 °C. [c] Conditions: 10% [AuCl(IPr)], 7.5% $AgSbf_6$, 80 °C, 24 h. [d] Determined by $^1H$ NMR analysis of the reaction mixture; a 21% yield of indole **3o** was also detected.

ing ureas, **1a** and **1e**−**1q**.[16] Indeed, the reaction proved equally efficient when applied to other ureas. First, we

(12) Given the well-documented tendency of diarylureas to behave as polymorphic structures because of their hydrogen-bonding patterns, we carried out the reaction under different concentrations (0.05 and 0.2 M in DMF). We found, no appreciable change in the conversion as a function of the concentration. (a) Dannecker, W.; Kopf, J.; Rust, H. *Cryst. Struct. Commun.* **1979**, *8*, 429. (b) Etter, M.; Panuto, T. *J. Am. Chem. Soc.* **1988**, *110*, 5896.

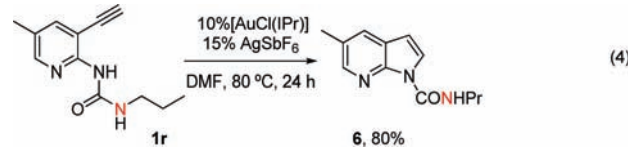
(13) The reaction was performed in the presence of 5% triflic acid, but no conversion of substrate **1a** was observed after 41 h at 100 °C. Because it is described that other coinage metal salts ($CuL_n$ and $AgL_n$) exhibit a significant coordination ability to C−C multiple bonds, we set up test experiments to catalyze the reaction with 5% $AgSF_6$ and 5% copper(II) salts, but in every case, the starting material remained unaltered.

(14) Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *24*, 2411–2418.

decided to evaluate the effect of substitution at *N*-3 in the urea moiety. Thus, substrate **1e** bearing a *p*-methoxy-substituted aryl ring at *N*-3 yielded a 92% dihydroquinazolinone **2e**.

Both aliphatic and benzylic 3-substituted 1-(*o*-ethynylphenyl)ureas (**1f**−**1h**) were easily transformed into the corresponding products **2f**, **2g**, and **2h** in 83, 96, and 86% yield, respectively (see Scheme 1). Even the clearly deactivated *N*-3-substituted [*p*-(trifluoromethyl)phenyl]urea **1i** was smoothly transformed into the corresponding quinazolin-2-one **2i** in a very good yield (82%) albeit within a longer reaction time. The reaction tolerates the presence of potential gold-coordinating functional groups, such as alkenes, at the urea moiety (see compound **2j**; Scheme 1). However, cyclization of the *N*-3- unsubstituted urea **1k** proved to be slower, and only 40% of tautomerized quinazolinone **2k** was obtained under slight forcing conditions. Nevertheless, from the point of view of regioselectivity control, the results described so far suggest that the substituent at *N*-3 does not have a significant influence on the competitive formation of compounds **2** and **3**.

The effect of substitution on the *N*-1-substituted aryl ring was also tested. The presence of electron-donating groups on the *N*-1-substituted aryl ring is tolerated in this heterocyclization; thus, reaction with ureas **1l**−**1n** leads to compounds **21**−**2n** in good yields. In contrast, the efficiency of the reaction decreased considerably when an electron-withdrawing chlorine atom was present on the *N*-1-substituted aryl ring. An enhancement of the basicity at the urea *N*-3 center increases the efficacy of the transformation and gives the product **2p** in very good yield (see Scheme 1). Particularly interesting is the reaction carried out with substrate **1r** in which the aryl ring bearing the alkyne is replaced by a more electron-deficient pyridine ring (eq 4).



(4)

In this case, formation of the expected 3,4-dihydropyridopyrimidin-2-one was not observed. Instead, the pyrrolopyridine **6** was obtained in 80% isolated yield. In addition, more drastic conditions (10% [Au(IPr)]$SbF_6$, 80 °C, 24 h) had to be used to ensure complete conversion. The slower rate of the reaction could be due to the potential substrate coordination to the cationic gold catalyst. The different course of cyclization could be explained by a reverse positive charge distribution in the gold-activated alkyne induced by the electron-deficient pyridine ring.

In conclusion, it was found that 1-(*o*-akynylaryl)ureas are privileged substrates that provide an adequate framework to explore alternative reaction pathways in the metal-catalyzed hydroamidation of alkynes. The new route disclosed allows for generation of the 4-methylene-3,4-dihydroquinazolin-2-one core and is synthetically valuable when compared with the multistep or harsh protocols previously reported for this interesting type of heterocycle. A detailed theoretical calculation study into the origins of the catalysts' ability to control the mode of cyclization in these interesting alternative transformations is currently ongoing in our group.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and CIF files giving crystal data for compounds **2a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The structure of indole **3b** was established by single-crystal X-ray diffraction; see Supporting Information.

(16) Ureas **1a**−**1c**, **1e**, **1h**−**1j**, **1l**, **1m**, **1o**, and **1q** were prepared by the reaction of *o*-alkynylanilines and isocyanates and used without further purification. The syntheses of **1f**, **1g**, **1n**, **1p**, and **1r** were run over 12 h, and 1.5 equiv of the corresponding isocyanate was needed to achieve complete conversion of the 2-ethynylaniline derivative. To avoid secondary reactions, these ureas were purified by column chromatography.