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Highly Regioselective Au(I)-Catalyzed Hydroamination of Ynamides and Propiolic Acid Derivatives with Anilines

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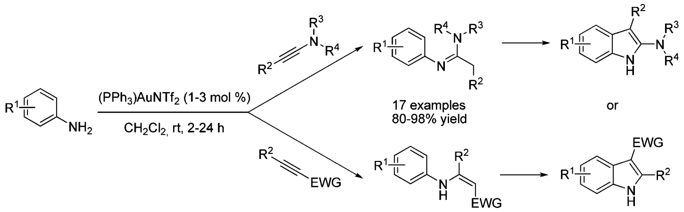
ABSTRACT



A highly regioselective hydroamination of unsymmetrical electron-poor and electron-rich alkynes with anilines catalyzed by Au(I) under mild conditions is reported. In addition, applications toward indole syntheses are presented including an example of a one-pot synthesis from a nonfunctionalized aniline.

Intermolecular hydroaminations and hydrations of alkynes have received much attention in the recent literature, representing an efficient means of accessing substituted amines and imines or ketones. A common feature in these reactions is the use of transition-metal catalysts (e.g., Ti, Ta, Pd, Au),[1,2] although in these cases usually elevated temperatures and long reaction times are required. Problems with regioselectivity are often avoided using symmetrical or terminal alkynes, with the latter predominantly giving rise to the Markovnikov product. On the other hand, the attempts with unsymmetrical internal alkynes have been restricted to alkyl arylacetylenes, which again lead to the product of Markovnikov addition. Whereas this predominantly gives the desired regioisomer, the substrate scope is quite narrow.

Herein, we report a fully regioselective and high-yielding protocol for the hydroamination of unsymmetrical internal alkynes represented by ynamides and propiolates/propiolamides with anilines under mild reaction conditions with the

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(1) Hydroaminations. Gold: (a) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (b) Bertrand, G.; Donnadieu, B.; Kinjo, R.; Frey, G. D.; Zeng, X. *J. Am. Chem. Soc.* **2009**, *131*, 8690. (c) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem.—Eur. J.* **2009**, *15*, 3056. (d) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (e) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645. Titanium: (f) *Synthesis* **2005**, *7*, 1200. (g) Ackermann, L. *Organometallics* **2003**, *22*, 4367. (h) Schafer, L. L.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4733. (i) Bytschkov, I.; Siebeneicher, H.; Doye, S. *Eur. J. Org. Chem.* **2003**, 2888. (j) Cao, C.; Shi, Y.; Odom, A. L. *Org. Lett.* **2002**, *4*, 2853. (k) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, 9541. (l) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011. Palladium: (m) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670. (n) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. Cobalt: (o) Liu, C.-C.; Korivi, R. P.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 9503. Silver: (p) Lingaiah, N.; Babu, N. S.; Reddy, K. M.; Prasad, P. S. S.; Suryanarayana, I. *Chem. Commun.* **2007**, 278. (q) Luo, Y.; Li, Z.; Li, C.-J. *Org. Lett.* **2005**, *7*, 2675. Tantalum: (r) Bergman, R. G.; Arnold, J.; Anderson, L. L. *Org. Lett.* **2004**, *6*, 2519. Review: (s) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *6*, 3079.

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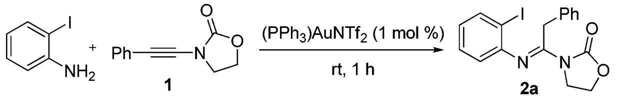
Gagosz catalyst ($(PPh_3)AuNTf_2$).[3] Furthermore, it was found that the electronics of the alkyne can be used to ensure full regioselectivity overruling sterical effects. Finally, applications of the resulting products for the preparation of 2,3-disubstituted indoles will be presented.

Ynamides have become an increasingly popular reagent in numerous synthetic transformations.[4−6] Their high interest can undoubtedly be linked to the development of more efficient protocols for their access, notably from the groups of Hsung, Danheiser, and others.[7] In connection with our work on the application of ynamides for the synthesis of 2-amidoindoles,[5a] we examined the possibility of exploiting gold catalysis[8] for the hydroamination of terminally substituted ynamides to prepare precursors for 3-substituted 2-amidoindoles.

The preliminary results from the hydroamination of iodoaniline with the model ynamide **1** using $(PPh_3)AuNTf_2$ as the catalyst revealed fast conversion to a single regioisomer in dichloromethane even at low catalyst loading (Table 1, entry 2). Of the solvents tried, only DMF was incompatible (entry 6), while the reaction in dioxane required higher catalyst loading and longer reaction time (entry 5). Support for the regioselectivity was obtained from the X-ray structure of the resulting imidoyl **2a** (Figure 1).

Table 1. Solvent Screening



entry	solvent	conversion[a] (%)
1	DCE	89
2	CH_2Cl_2	88
3	MeCN	84
4	toluene	78
5	dioxane	>95[b]
6	DMF	13[b]

[a] Conversion was determined by ^{1}H NMR of the crude reaction mixture. [b] 2 mol %, 4 h.

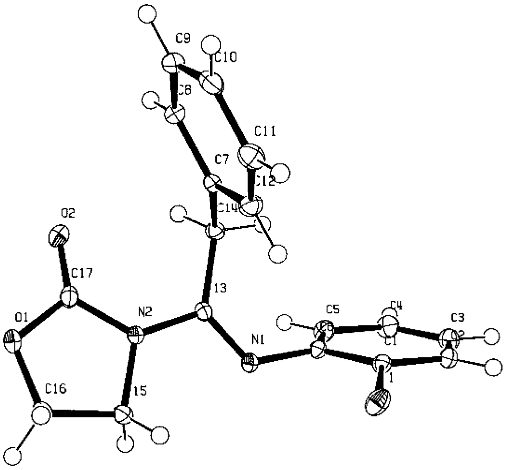
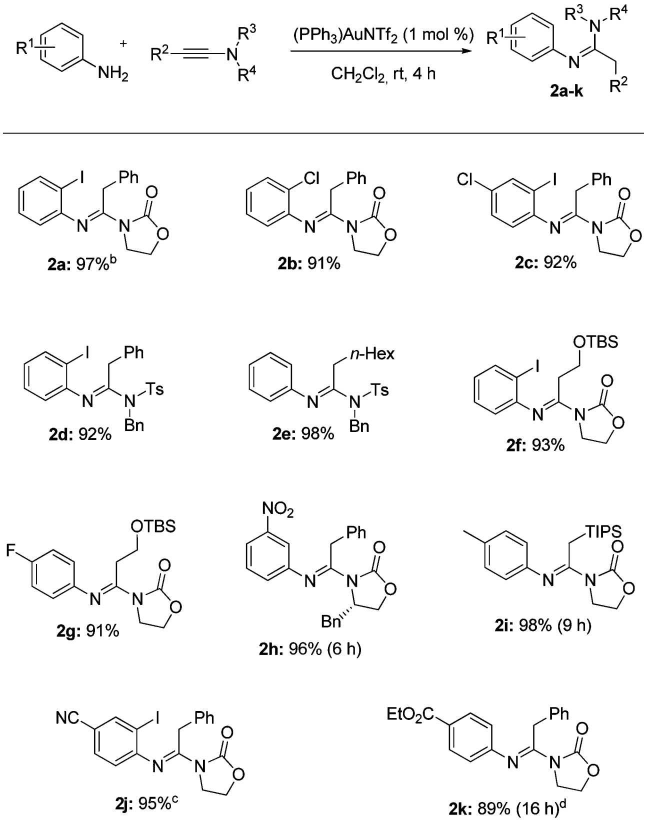


Figure 1. X-ray crystal structure of **2a**.

The scope of this hydroamination with various anilines and ynamides is illustrated in Scheme 1. These electron-rich alkynes led to exclusively one regioisomer of the hydroamination products, and full conversion was achieved at room temperature within a few hours.[9,10] It was noted though, that electron-withdrawing groups on the aniline led to longer reaction times for completion. In one attempt, we

Scheme 1. Hydroamination with Ynamides[a]



[a] Isolated yields after column chromatography. [b] 3.7 mmol scale. On the standard scale, 91% was isolated after 2 h. [c] 2 mol %. [d] 3 mol %.

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(3) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

(4) For a special issue dedicated ynamides, see: (a) *Tetrahedron-Symposium-In-Print*: "Chemistry of Electron-Deficient Ynamines and Ynamides." *Tetrahedron* **2006**, *62*, Issue No. 16. For reviews on ynamides, see: (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. L. *Tetrahedron* **2001**, *57*, 7575. (c) Zhang, Y.; Hsung, R. P. *ChemTracts* **2004**, *17*, 442. (d) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

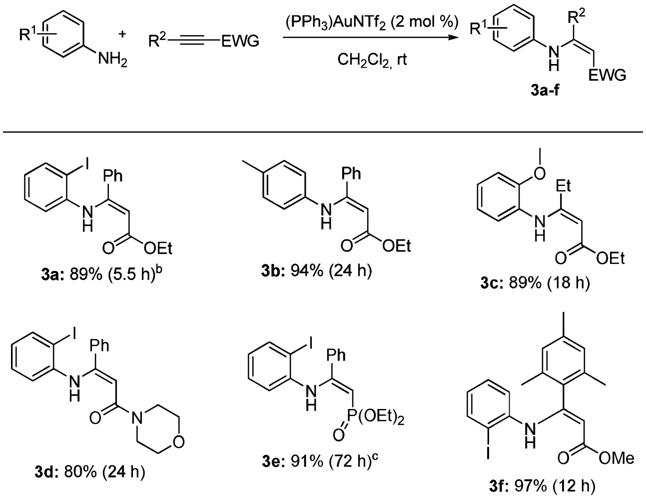
(5) For some recent examples, see: (a) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221. (b) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (c) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (d) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (e) Hashmi, S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672. (f) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (g) Tanaka, K.; Takeishi, K. *Synlett* **2007**, 2920. (h) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815. (i) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (j) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586.

scaled up the hydroamination of **1** with 2-iodoaniline to 3.75 mmol. In this case, it was possible to lower the catalyst loading to 0.5 mol %, although a longer reaction time (7 h) was required for completion.

Unfortunately, when iodopyridinamines were used no conversion to the desired product was observed. Instead, a heavy precipitation was seen in the reaction mixtures possibly due to strong coordination of these pyridinamines to Au(I).

Electron-poor alkynes were also examined and generally displayed a lower reactivity (Scheme 2). Longer reaction times were thus required for these substrates, but in all cases tested, high yields of the products were obtained. Only the *Z*-enamines were observed as products.[11] In principle, these products could also arise from a Michael addition. However, this was ruled out by control experiments at 60 °C for 24 h without the catalyst showing no conversion.

Scheme 2. Hydroamination with Electron-Poor Alkynes[a]

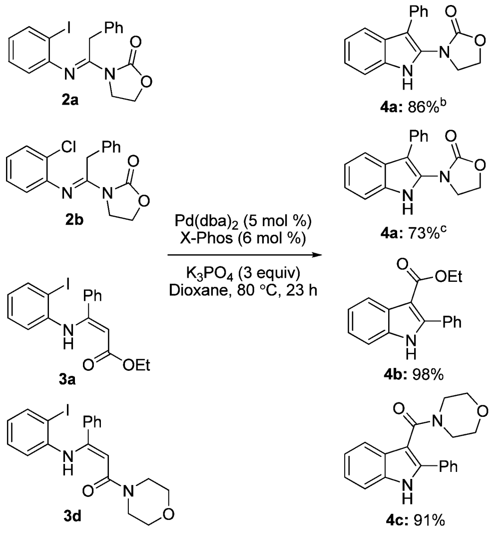


[a] Isolated yields after column chromatography. [b] 1 mol %. [c] 1:1 mixture of imine/enamine.

Interestingly, when comparing the electron-rich and the electron-poor alkynes, a complete switch in selectivity was observed. These observations show how the electronics of the internal alkyne strongly influence the regioselectivity in the intermolecular Au(I)-catalyzed hydroaminations. The difference in regioselectivity between **2a** and **3d** demonstrates this effect by reversing the order of the nitrogen and the carbonyl on the sp carbon leading to opposite regioisomers. Also, products **2e** and **3f** examplify the strong electronic effect by only yielding the product resulting from attack on the more sterically hindered carbon.

Next, the application toward indole syntheses was attempted. To our delight, this proved possible in high yields using a Pd(0)-catalyzed ring closing (Scheme 3). Optimization studies on the iodide **2a** showed that the catalytic system consisting of Pd(dba)$_2$, X-Phos, and K$_3$PO$_4$ in dioxane at 80 °C with a reaction time of 23 h gave the indoles in good to excellent yields.[12]

Scheme 3. Pd(0)-Catalyzed Indole Synthesis[a]



[a] Isolated yields after column chromatography. [b] 2 equiv of K$_3$PO$_4$. [c] 100 °C.

Surprisingly, we also found that by exploiting the Larock indole synthesis,[13] with the ynamide **1**, we could access the opposite regioisomer, the 3-amidoindole **5**, as the major product (Scheme 4).

Recently, Yu et al. revealed how *N*-arylenamines can be cyclized to indoles under oxidizing conditions with PhI-

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(6) Recent applications of ynamides from the group of R. P. Hsung: (a) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899. (b) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *65*, 5001. (c) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (d) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780. (e) Zhang, X.; Hsung, R. P.; Li, H.; Zhang, Y.; Johnson, W. L.; Figueroa, R. *Org. Lett.* **2008**, *10*, 3477. (f) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661. (g) Li, H.; You, L.; Zhang, X.; Johnson, W. L.; Figueroa, R.; Hsung, R. P. *Heterocycles* **2007**, *74*, 553. (h) You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, 1656. (i) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (j) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069. (k) Zhang, X.; Hsung, R. P.; Li, H. *Chem. Commun.* **2007**, *23*, 2420.

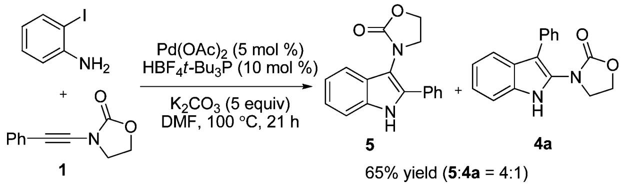
(7) (a) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630. (b) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (c) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (d) Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447. (e) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681. (f) Sagamanova, I. K.; Kurtz, K. C. M.; Hsung, R. P. *Org. Synth.* **2007**, *84*, 359. (g) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (h) Kohnen, A. L.; Dunetz, J. R.; Danheiser, R. L. *Org. Synth.* **2007**, *84*, 88. (i) For reviews on the synthesis of ynamides, see: Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

(8) Selected reviews on Au catalysis: (a) Gorin, D. J.; Toste, D. *Nature* **2007**, *446*, 395. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (d) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266.

(9) As the imine functionality of **2a** was found to be the *E*-isomer (Figure 1) and only one isomer was observed in all the reactions, the products **2b**−**k** reported were tentatively assigned this configuration.

(10) Due to the ynamides utilized being either sulfonamides or cyclic carbamates no conversion to the oxazolone products as reported by Gagosz et al. were observed (ref 5d).

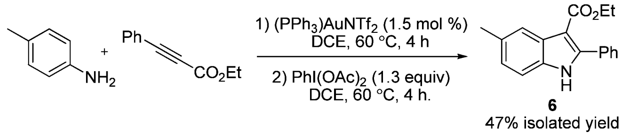
Scheme 4. One-Pot Indole Synthesis Utilizing the Larock Indole Synthesis[a]



[a] Isolated yield. Ratio determined by ^{1}H NMR.

$(OAc)_2$.[14] Utilizing their protocol in an unoptimized manner, a one-pot approach to indoles from a simple aniline was shown (Scheme 5). Interestingly, the hydroamination, yielding **3b**, which took up to 24 h using 2 mol % catalyst at room temperature, could be led to full conversion in 4 h at 60 °C with lower catalyst loading and no loss of regioselectivity.

Scheme 5. One-Pot Indole Synthesis Starting from a Simple Aniline



In conclusion, we have shown a promising method for expanding the often narrow substrate scope of intermolecular hydroaminations on internal alkynes with ynamides and propiolic acid derivatives, leading to only one of the two possible regioisomers. The simplicity, mild reaction conditions, and for the most cases short reaction times makes this an appealing strategy for accessing *N*-arylimines and enamines. Furthermore, some examples of the application toward indoles have been presented.

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Supporting Information Available: Experimental procedures and characterizataion data for all the prepared compounds as well as X-ray structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Stereochemistry was assigned according to the hydrogen bond visible in ^{1}H NMR and by comparison with the known compound. López-Alberca, M. P.; Mancheño, M. J.; Fernández, I.; Gómez-Gallengo, M.; Sierra, M. A.; Torres, R. *Org. Lett.* **2007**, *9*, 1757. The regioselectivity of **3e** was confirmed by acid hydrolysis.

(12) Several attempts to develop a one-pot protocol for the hydroamination and ensuing Pd(0)-catalyzed cyclization were unsucessful. In these cases, it was necessary to purify the intermediates in order to secure good cyclization yields.

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(14) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417.