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Au-Catalyzed Synthesis of 2-Alkylindoles from *N*-Arylhydroxylamines and Terminal Alkynes

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Abstract

The first gold-catalyzed addition of *N*-arylhydroxylamines to aliphatic terminal alkynes is developed to access *O*-alkenyl-*N*-arylhydroxylamines, which undergo facile *in situ* sequential 3,3-rearrangements and cyclodehydrations to afford 2-alkylindoles with regiospecificity and under exceptionally mild reaction conditions.

The Fischer indole synthesis[1] is perhaps the most versatile method for the construction of indole rings[2] and has been applied extensively in the synthesis of various indole alkaloids[3] since the original report by Fischer[4] more than one hundred years ago. This annulation between an arylhydrazine and a ketone relies on a key 3,3-sigmatropic rearrangement of an *N*-alkenyl-*N*'-arylhydrazine intermediate. While it has been subjected to various modifications/improvements,[5] there are still notable deficiencies including the often difficulty in achieving excellent regioselectivities with non-symmetric ketones and demanding reaction conditions such as strong acidities and/or elevated reaction temperatures.

Similarly, 3, 3-rearrangements of *O*-vinyl-*N*-arylhydroxylamines or their derivatives[6] can lead to indole synthesis upon subsequent cyclodehydration. A notable example is the Bartoli indole synthesis.[7] While this rearrangement typically proceeds at much lower temperatures than in the case of the Fischer indole synthesis, there is a lack of general and straigthforward methods[6] for the generation of *O*-alkenyl-*N*-arylhydroxyamines. We envisioned that these intermediates could be formed via metal-promoted additions of the HO groups of *N*-arylhydroxylamines onto C-C triple bonds (Scheme 1). By using alkynes as substrates, this indole synthesis may provide solutions to some of the deficiencies in the Fischer indole synthesis. Surprisingly, this strategy has not been realized although related ones using propiolates and hydroxamic acids in the presence of bases have been reported.[8]

Efficient additions of various nucleophiles (NuH) to C-C triple bonds have been realized in gold catalysis;[9] however, hydroxyamine have not been used as nucleophiles.[10] In continuation of our research on gold catalysis, we anticipated that gold complexes could be employed in Scheme 1 to promote the formation of *O*-alkenyl-*N*-arylhydroxylamine **1** via activation of alkynes toward nucleophilic attack. Herein, we disclose a regiospecific synthesis of 2-alkylindoles via the annulation of *N*-arylhydroxylamines and terminal alkynes under mild reaction conditions.

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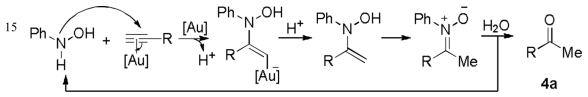
† Electronic Supplementary Information (ESI) available: experimental procedure, ^{1}H and ^{13}C NMR spectra, and the X-ray structure of compound **6a**. See DOI: 10.1039/b000000x/

We started by using *N*-phenylhydroxylamine and 1-dodecyne (2 equiv) as substrates and $Ph_3PAuNTf_2$ as the catalyst. To our delight, 2-*n*-decylindole **3a**[11] was indeed formed after reacting at room temperature for 18 h (Table 1, entry 1), and methyl ketone **4a** was the major side product. Due to the disproportionation of the hydroxylamine substrate, some aniline and trace amount of diazene *N*-oxide **5a** were observed. We attributed the formation of ketone **4a** partly to the competitive N-H addition of the hydroxylamine to **2a** followed by subsequent hydrolysis (Eq. 1) and partly to direct gold-catalyzed hydration. H_2O consumed in these processes should mostly come from the cyclodehydrative indole formation. Screening different gold catalysts (entries 2-7) revealed that phosphite-based cationic gold(I) complex, $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl), gave the best result (entry 4). Somewhat to our surprise, DCE was a better solvent than DCM, and the yield was up to 94% (entry 8). Additional solvents (entries 10-14) were examined, and both diethyl ether (entry 10) and toluene (entry 13) were excellent choices as well. The reaction yield decreases as the amount of the alkyne decreases (entries 15 and 16). With 1.8 equivalents of 1-dodecyne (entry 15), the reaction yield was still very good, and the isolated yield was 84%.



(1)

As shown in Table 2, this indole synthesis worked well with various cycloalkylacetylenes (entries 1-3) including cyclopropylacetylene (entry 3). Linear aliphatic terminal alkynes containing various functional groups also reacted well. These functional groups include phenyl (entry 4), protected HO groups (entries 5 and 6), chloro (entry 7), carboxylic acid (entry 8) and a protected amino group (entry 9). Of particular note is the tolerance of the acid labile THP group, confirming the exceptionally mild nature of this indole synthesis; in contrast, the Fischer indole synthesis is typically performed under highly acidic environment. These mild reaction conditions also permit the preparation of chloroindole **3h** without affecting with the chloro moiety. A methyl (entry 10) or electron-withdrawing substituents (entries 11-15) at the benzene ring *para* or *meta* to the hydroxylamine moiety permitted good to efficient reactions; however, an *ortho*-Me led to little indole product (<10%), and *N*-(4-methoxyphenyl)hydroxylamine[12] was not stable to try this chemistry. Attempts to extend this chemistry to aliphatic internal alkynes and arylacetylenes, however, yielded little products.

An important feature of all the above cases is the exclusive selectivity toward 2-alkylindoles, and no 3-alkylindoles were observed. This regioselectivity stems from the Markovnikov additions of hydroxamic acids to the gold-activated terminal alkynes. In contrast, with corresponding methyl ketones as substrates in the Fischer indole synthesis, strongly acidic mediums (e.g., 5 % P_2O_5/neat MsOH[13] or neat PPA[14]) are necessary to favor 2-alkylindoles with low to moderate regioselectivities.

Conclusions

We have developed a novel access to *O*-alkenyl-*N*-arylhydroxylamines via the first gold-catalyzed addition of *N*-arylhydroxylamines to aliphatic terminal alkynes. This mild gold catalysis is coupled in situ with sequential facile 3,3-rearrangement and cyclodehydration, affording 2-alkylindoles regiospecifically in typically good yields and under exceptionally mild reaction conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. The regiochemistry is supported by the chemical shift at 6.24 ppm at its ^{1}H NMR spectrum, and the observed nOe between the 3- and 4-protons in the NOESY1D spectrum of product 3**n**.
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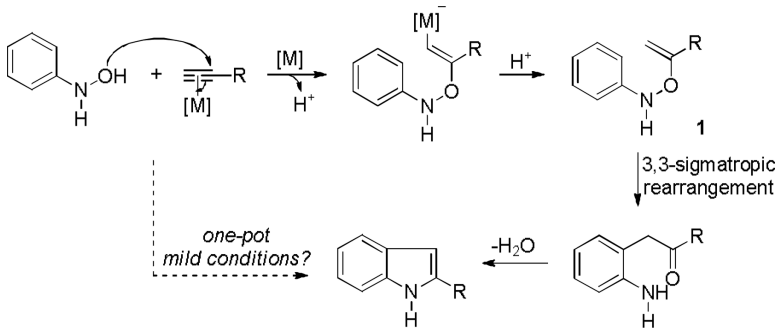
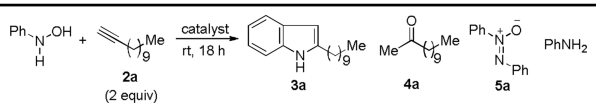


Scheme 1.

Formation of *O*-alkenyl-*N*-phenylhydroxylamines via HO addition to alkynes en route to indoles

Table 1

Screening gold catalysts and reaction conditions.[a]



entry	catalyst	solvent	yield[b]			
			3a	4a	5a	6a
1	$Ph_3PAuNTf_2$	DCM	57%	62%	trace	9%
2	$(4\text{-}CF_3Ph)_3PAuNTf_2$	DCM	74%	72%	trace	6%
3	$IPrAuNTf_2$	DCM	63%	55%	trace	8%
4	$(ArO)_3PAuNTf_2$[c]	DCM	83%	74%	1%	3%
5	$Et_3PAuNTf_2$	DCM	46%	61%	trace	11%
6	$BrettphosAuNTf_2$	DCM	21%	67%	-	10%
7	$(F_5C_6)_3PAuNTf_2$	DCM	4%	8%	9%	7%
8	$(ArO)_3PAuNTf_2$[c]	DCE	94%	71%	2%	4%
9	$(ArO)_3PAuOTf$[c]	DCE	55%	64%	3%	4%
10	$(ArO)_3PAuNTf_2$[c]	Et_2O	94%	80%	3%	1%
11	$(ArO)_3PAuNTf_2$[c]	THF	41%	80%	6%	2%
12	$(ArO)_3PAuNTf_2$[c]	CH_3CN	38%	24%	4%	5%
13	$(ArO)_3PAuNTf_2$[c]	toluene	93%	65%	1%	2%
14	$(ArO)_3PAuNTf_2$[c]	hexanes	28%	66%	1%	4%
15[d]	**$(ArO)_3PAuNTf_2$[c]**	**DCE**	**86%**[e]	**75%**	**1%**	**2%**
16[f]	$(ArO)_3PAuNTf_2$[c]	DCE	76%	63%	2%	4%

[a] Anhydrous solvents were used; [*N*-phenylhydroxylamine] = 0.1 M; under nitrogen.

[b] Estimated by ^{1}H NMR using diethyl phthalate as an internal reference; the yield for methyl ketone **4a** is calculated based on *N*-phenylhydroxylamine for comparison purpose although it was formally formed via hydration of **2a**.

[c] Ar = 2,4-di-*tert*-butylphenyl.

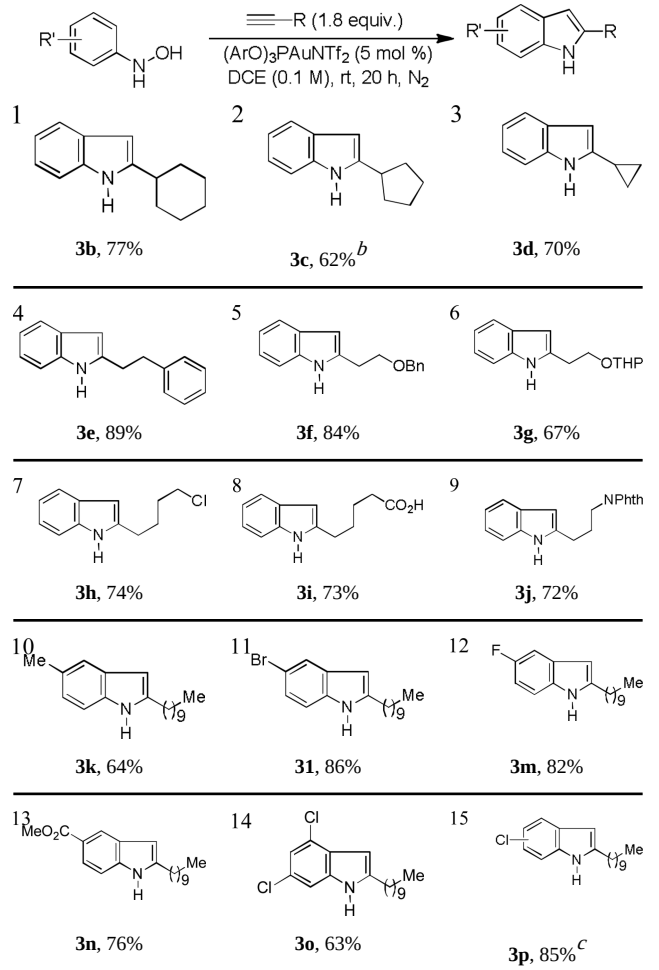
[d] 1.8 Equiv of 1-dodecyne.

[e] 84% isolated yield.

[f] 1.6 Equiv of 1-dodecyne.

Table 2

Reaction scope studies[a]



3b, 77% **3c**, 62%[b] **3d**, 70%

3e, 89% **3f**, 84% **3g**, 67%

3h, 74% **3i**, 73% **3j**, 72%

3k, 64% **3l**, 86% **3m**, 82%

3n, 76% **3o**, 63% **3p**, 85%[c]

[a] [hydroxylamine] = 0.1 M; Ar = 2,4-di-*tert*-butyl

[b] Toluene as solvent.

[c] 4-Cl/6-Cl = 1/1.3.