An Au/Zn-catalyzed Synthesis of N-Protected Indoles via Annulation of N-Aylhydroxamic Acids and Alkynes

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Procedure (Note 1)

A. Chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold (I) (3). A one-necked (B14, diameter: 4.5 cm) 25 mL round-bottomed flask is open to air, equipped with a 3 x 10 mm egg shaped magnetic stirring bar, and charged with tris(2,4-di-tert-butylphenyl)phosphite (1) (0.647 g, 1.00 mmol) and
chloro(dimethyl sulfide)gold (2) (0.295 g, 1.00 mmol, 1.0 equiv) (Note 2). Dichloromethane (5 mL) is added via syringe (Note 3) and the flask is fitted with a glass stopper.

The resulting colorless solution (Figure 1) is stirred (800 rpm) at 23 °C for 1 h. The volatiles are removed by rotatory evaporation (300 mmHg, 30 °C bath temperature) and then, under a higher vacuum (1 mmHg) for 24 h to afford gold(I) chloride complex 3 (0.879 g, quantitative yield) as a white solid (Note 4) (Figure 2).

Figure 1. Colorless solution  Figure 2. White solid

B. 1-(2-Butyl-1H-indol-1-yl)ethanone (6). A two-necked (B24, diameter: 8 cm) 250 mL round-bottomed flask is open to air, equipped with an egg shaped magnetic stirring bar (2.5 x 1.0 cm) and a thermometer (–10 °C – 250 °C), and charged with toluene (80 mL) (Note 5). N-Hydroxy-N-phenylacetamide (4) (6.046 g, 40.0 mmol), 1-hexyne (5) (6.50 mL, 4.60 g, 56.0 mmol, 1.4 equiv), zinc trifluoromethanesulfonate (0.731 g, 2.0 mmol, 0.05 equiv), chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold (I) (3) (176 mg, 0.2 mmol, 0.005 equiv), and silver bis(trifluoromethanesulfonyl)imide (78 mg, 0.2 mmol, 0.005 equiv) are successively added (Note 6). The color of the solution changes from colorless to yellow upon the addition of silver bis(trifluoromethanesulfonyl)imide into the solution, while white silver chloride precipitation is observed. (Figure 3)
Both necks of the flask are fitted with septa. The reaction mixture is heated in a 60 °C oil bath and stirred for 24 h. During its course, the reaction turns progressively from yellow to orange and finally to black (Figure 4).

A 150 mL Büchner funnel with fritted disc (diameter: 7 cm) is mounted on the top of a 250 mL one-necked round-bottomed flask and charged with 10.5 g celite (Note 7). While the funnel is connected to a vacuum source (375 mmHg), THF (10 mL) (Note 8) is poured into the funnel, followed by the reaction mixture, and THF (2 x 10 mL) (Note 8). The filtrate is washed with 50 mL saturated sodium bicarbonate solution (Note 9), and the aqueous solution is extracted with dichloromethane (3 x 10 mL) (Note 10). The combined organic layers are dried for 20 min over Na₂SO₄ (15 g) (Note 11). The volatiles are removed by rotatory evaporation (30 mmHg, 40 °C bath temperature), and then under a higher vacuum for 4 h (1 mmHg) (Note 12). The resulting solid is dissolved in dichloromethane (20 mL) (Note 10), and 10 g silica gel (Note 13) is added into the solution. After removing the solvent by rotatory evaporation (300 mmHg, 30 °C bath temperature), the
silica gel with adsorbed crude material is charged on a silica gel (Note 13) column (5 cm diameter x 15 cm height). The column is packed with hexanes (800 mL) and eluted with hexanes/ethyl acetate (20/1, 1.3 L) using compressed air (2 atm) (Notes 14 and 15). Fractions 42-58 (Note 16) containing the pure product are concentrated by rotary evaporation (45 mmHg, 30 °C bath temperature). The resultant solid is dried under high vacuum (1.0 mmHg) for 10 h to afford indole 6 (7.77 g, 90% yield) as a white solid (Note 17) (Figure 5).

![Figure 5. White solid produced in Step B](image)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical](https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at
In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with tris(2,4-di-tert-butylphenyl)phosphite, chloro(dimethyl sulfide)gold, dichloromethane, toluene, N-hydroxy-N-phenylacetamide, 1-hexyne, zinc trifluoromethanesulfonate, chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold (I), silver bis(trifluoromethanesulfonyl)-imide, celite, tetrahydrofuran, sodium bicarbonate, silica gel, hexanes, ethyl acetate, and sodium sulfate.

2. Tris(2,4-di-tert-butylphenyl)phosphite (98%) was purchased from Sigma-Aldrich and used as received. Chloro(dimethyl sulfide)gold (I) was purchased from Strem Chemicals and used as received.

3. Dichloromethane (unstabilized HPLC grade, \( \geq 99.9\% \)) was purchased from Fisher Scientific and passed over columns of activated alumina prior to use.

4. A second run on the same scale provided 0.878 g (quantitative yield) of the same products. The physical and spectroscopic properties of gold(I) chloride complex (3) are as follows: mp = 237–238 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 1.29 (s, 9H), 1.44 (s, 9H), 7.13 (dd, \(J = 8.5, 2.4\) Hz, 1H), 7.38–7.44 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 30.7, 31.52, 34.8, 35.2, 119.25, 119.32, 124.3, 125.5, 139.2, 139.3, 147.35, 147.40, 148.2. \(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 100.65. IR (film): 2960, 2907, 2870, 1490, 1176, 1075, 928 cm\(^{-1}\). HRMS–APCI (m/z) calculated for [C\(_{42}\)H\(_{63}\)AuO\(_3\)P]: 843.41749, found: 843.41350. The purity was determined to be \(>99\%\) wt. by quantitative \(^1\)H NMR spectroscopy in CDCl\(_3\) using 20.2 mg of the compound and 5.1 mg of HMB(hexamethylbenzene) as an internal standard.

5. Toluene (Certified ACS grade, \( \geq 99.5\% \)) was purchased from Fisher Scientific and passed over columns of activated alumina prior to use.

6. N-Hydroxy-N-phenylacetamide was prepared according to literature procedure.\(^3\) 1-Hexyne (98%) was purchased from GFS Chemicals (Ref. 3193). Zinc trifluoromethanesulfonate (98%) was purchased from Acros Organics. Both were used as received. Silver bis(trifluoromethanesulfonyl)imide was purchased from Sigma-Aldrich and used as received.

7. Celite (545, Filter agent) was purchased from Sigma-Aldrich and used as received.
8. Tetrahydrofuran (Certified) was purchased from Fisher Scientific and used as received.
9. A gray solid is formed upon washing.
10. Dichloromethane (Certified ACS grade, \( \geq 99.5 \% \)) was purchased from Fisher Scientific and used as received.
11. Sodium sulfate anhydrous (Low nitrogen grade) was purchased from EMD Millipore and used as received.
12. The crude product solidifies under vacuum after 30 min.
13. Silica gel (SiliaFlash P60, pore size 60Å, 230-400 mesh particle size, 40-63 µm particle size) was purchased from SiliCycle Inc.
14. Hexanes (Certified ACS grade), ethyl acetate (Certified ACS grade) were purchased from Fisher Scientific and used as received.
15. Column fractions were checked by TLC analysis on silica gel 60 F254 TLC plate (SiliaPlate™ TLC Plates), using hexanes/ethyl acetate (20/1) as eluent. Visualization is accomplished with 254 nm UV light. The starting material \( \text{N}-\text{hydroxy-}\text{N}-\text{phenylacetamide (4)} \) stays at base line whereas the indole product (6) has \( R_f = 0.30 \).

**Figure 6. TLC analysis of the reaction mixture**

16. Fractions were collected by test tubes (diameter: 1.8 cm, height: 15 cm). When indole product (6) starts to elute from the column, a white solid will form on the edge of test tubes due to evaporation of solvent.
17. A second run on the same scale provided 7.50 g (87\%) of the same products. The physical and spectroscopic properties of indole (6) are as follows: mp = 56–57 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 0.98 (t, \( J = 7.4 \) Hz, 3H), 1.48 (sextet, \( J = 7.4 \) Hz, 2H), 1.71 (quintet, \( J = 7.7 \) Hz, 2H), 2.76 (s, 3H), 3.01 (t, \( J = 7.5 \) Hz, 2H), 6.42 (m, 1H), 7.19–7.28 (m, 2H), 7.48 (m, 1H), 7.84 (m, 1H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 14.1, 22.7, 27.8,
30.4, 31.2, 108.3, 114.9, 120.3, 123.10, 123.52, 130.1, 136.5, 143.1, 170.5. IR (film): 2956, 2869, 1703, 1454, 11369, 1302, 1197, 748 cm$^{-1}$. HRMS–APCI ($m/z$) calculated for C$_{14}$H$_{18}$NO [M + H]$^+$ 216.13829, found 216.13802. The purity was determined to be >99% wt. by quantitative $^1$H NMR spectroscopy in CDCl$_3$ using 99.1 mg of the compound and 16.1 mg of HMB (hexamethylbenzene) as an internal standard.

**Working with Hazardous Chemicals**

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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Discussion

The annulation between an arylhydrazine and a ketone to construct an indole, also called the Fischer indole synthesis, is one of the most important reactions in organic synthesis. This method has been used extensively in the construction of various indole alkaloids since the first report by Fischer in 1883. While it has been subjected to various modifications/improvements over the years, there are still notable drawbacks including the poor regioselectivities with non-symmetric ketones and strong acidic reaction conditions. Furthermore, 2-alkenylindoles cannot be prepared via this method except for a few special cases.

In this context, we developed a gold-catalyzed addition of N-arylhydroxylamine to aliphatic terminal alkynes to access 2-alkylindoles with regioselectivity. As shown in Scheme 1, the reaction mechanism likely entails the addition of the OH group of an N-arylhydroxylamine onto a terminal aliphatic alkyne in the presence of a gold catalyst, followed by one-pot sequential 3,3-rearrangement and dehydrative cyclization reaction. Despite the exceptionally mild reaction conditions (ambient temperature), the utility of this chemistry is largely limited by the moderate thermostability of the N-arylhydroxylamines, which prohibits the extension of this chemistry beyond kinetically facile terminal aliphatic alkyne reaction partners due to the inability to perform the reaction at elevated temperatures.

Scheme 1: Regiospecific formation of 2-alkylindole from aliphatic terminal alkyne via gold-catalyzed O-addition of hydroxylamine to C-C triple bond
To substantially improve this indole synthesis, we opted to use thermally much more stable hydroxamic acids or N-hydroxycarbamates in place of N-hydroxylamines. However, this modification is at the expense of the nucleophilicity of the N-hydroxyl group and hence the reaction rates are substantially reduced. Although increasing the reaction temperature could compensate the rate loss, reaction optimizations along this line led to little success.

Scheme 2 Enhancing the nucleophilicity of 7 by a metal salt

Inspired by the role of metal ions in enhancing nucleophilicity of H\textsubscript{2}O by forming metal hydroxides in metalloenzyme catalysis (Scheme 2A),\textsuperscript{10} we reason that the nucleophilicity of hydroxamic acid or N-hydroxycarbamate would be enhanced in a similar manner. As shown in Scheme 2B, 7 could react with a metal ion to form metal chelate 7-M and proton reversibly. As in metalloenzyme catalysis, 7-M should be more nucleophilic than 7 due to the increased negative charge on the deprotonated oxygen. After screening various metal salts, we identified Zn(OTf)\textsubscript{2} as the most effective. Even with only 5 mol\% of this salt, the desired annulation of 7 with alkynes can be achieved at 60 °C in toluene in the presence of a gold catalyst (5 mol\%), affording N-protected indoles in generally good yields. Scheme 3 shows a general reaction with the proposed mechanism, which entails cooperative catalysis by Zn(OTf)\textsubscript{2} and LAu\textsuperscript{+}.

Some representative cases from the scope study\textsuperscript{11} are shown in Table 1. With terminal alkynes as substrates, LAuNTf\textsubscript{2} with L = 1 is the preferred gold catalyst due to its higher acidity/electrophilicity, and the reactions finish in 4-8 h. On the other hand, IPrAuOTf is a better catalyst when less reactive internal alkynes are employed, owing to its higher thermostability, and the reactions require 18-30 h to go to completion. Compared with the N-hydroxylamine-based indole synthesis, this modified strategy dramatically expands the scope of alkynes to include internal alkynes and enynes as well as the scope of the N-aryl group.
For the scaled-up procedure reported here, in order to minimize the reaction cost, we were able to lower down the loading of the gold catalyst from 5 mol% used in our original report to 0.5 mol% without affecting the reaction yield. Moreover, the active catalyst LAuNTf₂ (L = 1) can be generated in situ from its chloride salt 3 upon the treatment of it with an equivalent of AgNTf₂.
Table 1. Representative N-protected indoles synthesized in the reported scope study

![Chemical structures of indoles](image1)

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<thead>
<tr>
<th>Structure</th>
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<th>Yield (%)</th>
<th>Regioselectivity</th>
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<td>80%</td>
<td>&gt;20:1</td>
</tr>
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</table>

References

1. Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States. E-mail: zhang@chem.ucsb.edu. We thank NSF CHE-1301343 for financial support and for NIH shared instrument grant S10OD012077 for the purchase of a 400 MHz NMR spectrometer.


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**Appendix**

**Chemical Abstracts Nomenclature (Registry Number)**

Tris(2,4-di-tert-buty1phenyl)phosphite: Phenol, 2,4-bis(1,1-dimethylethyl)-, 1,1',1''-phosphite; (31570-04-4)

Chloro(dimethylsulfide)gold(I): Gold, chloro[thiobis[methane]]-; (29892-37-3)

Chloro[tris(2,4-di-tert-buty1phenyl)phosphite]gold(I): Gold, chloro[tris[2,4-bis(1,1-dimethylethyl)phenyl] phosphite-κP]-; (915299-24-0)

N-Hydroxy-N-phenylacetamide: Acetamide, N-Hydroxy-N-phenyl-; (1795-83-1)

1-Hexyne: 1-Hexyne; (693-02-7)

1-(2-Butyl-1H-indol-1-yl)ethanone: Ethanone, 1-(2-butyl-1H-indol-1-yl)-; (116491-55-5)
Xinpeng Cheng was born in Nanchang (China) in 1994. He graduated with a B.S. degree in Chemistry from Zhejiang University in 2016. In the same year, he joined the group of Prof. Liming Zhang at the University of California, Santa Barbara (UCSB) to perform his Ph.D. studies.

Liming Zhang was born in Pingxiang, China in 1972. He received his B.S. degree in chemistry from Nanchang University in 1993, his first M.S. degree in organometallic chemistry with Professor Zhengzhi Zhang from Nankai University in 1996, and his second M.S. degree in organic chemistry with Professor Michael P. Cava from the University of Alabama in 1998. He obtained his Ph.D. degree with Professor Masato Koreeda from the medicinal chemistry program at the University of Michigan in 2003 and then carried out a post-doctoral study with Professor Sergey A. Kozmin at the University of Chicago. He started his independent academic career at the University of Nevada, Reno in 2005 and moved to the University of California, Santa Barbara in 2009. He is currently a Professor in Organic Chemistry. His research interests include late transition metal-catalyzed reactions, natural product synthesis and medicinal chemistry.
Lucas Morrill received his B.A. in Chemistry from Carleton College in Northfield, MN, where he performed undergraduate research with Professors David Alberg and Gretchen Hofmeister. He is currently a fourth-year graduate student in Professor Neil K. Garg’s laboratory at the University of California, Los Angeles. His graduate studies are focused on the total synthesis of complex natural products.

Junyong Kim was born in Seoul, South Korea in 1988. He received his B.S. in Chemistry from Seoul National University, where he performed undergraduate research with Professor David Y.-K. Chen on the total synthesis of dendrobine. In the summer of 2013, he began his graduate studies at the University of California, Los Angeles. He is currently a fourth-year graduate student in the laboratory of Professor Neil K. Garg, pursuing the total synthesis of tubingensin natural products.
Chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold(I)

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Chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold(I)
Chloro[tris(2,4-di-tert-butylphenyl)phosphite]gold (I)
1-(2-Butyl-1H-indol-1-yl)ethanone

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