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Authors: Debendra Kumar Mohapatra

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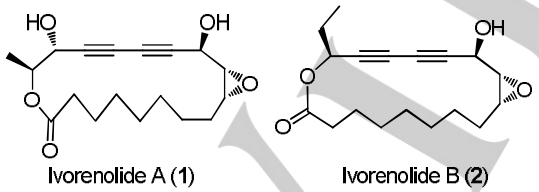
Synergistic Gold and Copper Dual Catalysis for Intramolecular Glaser-Hay Coupling: Rapid Total Synthesis of Ivorenolide B

Sudheer K. Rangaraju, Uma Maheshwar Gonela, Aala Kavita, Jhillu S. Yadav, and Debendra K. Mohapatra*

Abstract: A synergistic dual catalysis approach involving gold and copper catalysts for the synthesis of macrolactones bearing 1,3-butadiynes through an intramolecular Glaser-Hay coupling reaction in good yield is described. This dual catalytic system exhibited good selectivity, reactivity and functional group tolerance. This unique process offers a paradigm shift: the potential as well as the versatility of this novel method is not only exemplified for the synthesis of macrolactones of different ring size but also for the rapid total synthesis of ivorenolide B, a new class of macrolides endowed with conjugated 1,3-diyne motif, having impressive immunosuppressive activities.

Macrocycles are widespread structural motifs present in natural products,[1] pharmaceuticals,[2] material science compositions,[3] and have profound importance in supramolecular chemistry.[4] Among these, 1,3-butadiynes or di-acetylenic scaffolds occur widely and to date, over one thousand naturally occurring polynes were isolated and were found to display antibacterial, anti-cancer, anti-HIV, antifungal properties.[5] Further, conjugated diynes play an important role in the properties of many functional materials, such as nonlinear plastics, fibers with high density and strength, and liquid crystals.[6] A new class of 1,3-butadiyne macrolides ivorenolide A and B (Fig. 1) exhibiting immunosuppressant activities was isolated from the species *Khaya ivorenis*.[7] Immunosuppressive therapy usually has to follow surgery to ensure the success of organ transplantation[8] and also for treatment of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis, and multiple sclerosis.[9] Synthesis of conjugated diynes especially unsymmetrical diynes, depicted below is of clinical relevance.



Ivorenolide A (**1**) Ivorenolide B (**2**)

Figure 1. Structures of Ivorenolide A (**1**) and B (**2**).

[*] S. K. Rangaraju, U. M. Gonela, A. Kavita, Dr. J. S. Yadav, Dr. D. K. Mohapatra
CSIR-Indian Institute of Chemical Technology
Hyderabad-500007 (INDIA)
E-mail: Mohapatra@iict.res.in

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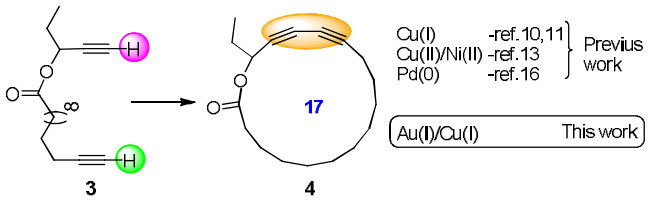
Metal mediated oxidative dimerization of terminal alkynes with stoichiometric amount of copper was developed by Glaser[10] about 150 years ago. Modified reactions such as Glaser-Hay[11] and Cadiot-Chodkiewicz[12] coupling reactions were devloped later to prepare unsymmetrical conjugated diynes. Cadiot-Chodkiewicz coupling though powerful, often suffers from poor selectivity and formation of homo-coupled byproducts. To specifically address the problems related to optimizing chemoselectivity in homo-coupling of alkynes, either of the terminal alkynes should be immobilized on a solid support or should be converted to a haloalkyne under high dilution conditions. Less is known about the Glaser-Hay coupling for macrolactonization, although recent studies by Collins et al. disclosed a novel strategy employing copper catalysis and high concentrations for the synthesis of macrocycles using a “phase separation strategy”.[13] We disclose herein, the use of gold-copper catalyst system to effect direct macrocyclization. So far very few examples are reported to achieve intermolecular Glaser-Hay coupling reaction with gold complexes.[14,15] One of the alkynes behaves as an immobilized haloalkyne to form heterodiynes in excellent yield under homogenous conditions.[14] We envisioned that gold catalyst could form complex with one of the alkynes[15] and behave like a haloalkyne or immobilized alkyne leading to improve chemoselectivity via intramolecular Glaser-Hay coupling for macrocyclization in an unprecedented manner. However, to date, gold-catalyzed intramolecular Glaser-Hay coupling was not utilized to synthesize diyne containing macrolactones.

Our investigations began with the macrocyclization of model substrate ester **3**, via intramolecular Glaser-Hay coupling of terminal alkynes. Our initial screening results concerning different metal catalysts and reagents are listed in Table 1. Treatment of ester **3** under standard intermolecular Glaser-Hay coupling reaction conditions[10,11] for macrocyclization (CuCl/TMEDA), led to low yield of the required product along with products resulting from polymerization (Table 1, entry 1). Similarly, Pd-catalyzed[16] reaction also proceeded with low yield although complete consumption of starting material (entry 3) was observed. Macrocyclization under Shi’s conditions[15b] afforded trace amount of lactone **4** accompanied with decomposition of the starting material (entry 4 and 5). When the ester was treated with the conditions reported by Corma et al., it did not afford the required product (entry 6).[14] When we employed catalytic amount of Au(I)/Cu(I) catalyst in combination for the macrocyclization a yield of 49% was realized (entry 7). To optimize these reaction conditions, different Au(I) catalysts were screened. Increase of reaction yield as well as the catalyst stability was observed with dppm$(AuBr)_2$ (entry 7). When the dppm$(AuBr)_2$ was replaced with PPh_3AuCl catalyst, gratifying increase of the yield (68%) was observed (entry 8). Next, different bases were screened.

Table 1. Optimization of catalytic system[a]



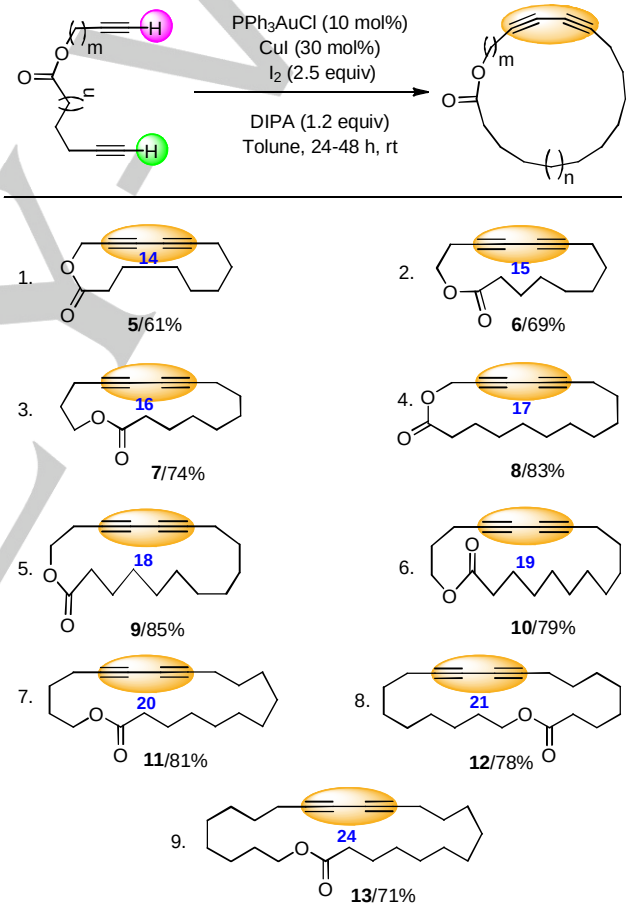
Entry	Reaction conditions	Solvent	time	Yield(%)[b]
1	CuCl, TMEDA, O_2	Toluene	2 d	19
2	CuI, I_2, DIPA	Toluene	2 d	18
3	$Pd(PPh_3)_2Cl_2$, CuI, I_2, DIPA	THF	2 d	32
4	PPh_3AuCl, BAIB, Phen	Acetonitrile	2 d	trace
5	$dppm(AuBr)_2$, BAIB, Phen	Acetonitrile	2 d	trace
6	$AuPPh_3NTf_2$, selectofluor, Na_2CO_3	Acetonitrile	1 d	0
7	$dppm(AuBr)_2$, CuI, I_2, DIPA	Acetonitrile	2 d	49
8	PPh_3AuCl, CuI, I_2, DIPA	Acetonitrile	2 d	68
9	PPh_3AuCl, CuI, I_2, Na_2CO_3	Acetonitrile	3 d	0
10	PPh_3AuCl, CuI, I_2, K_2CO_3	Acetonitrile	3 d	0
11	PPh_3AuCl, CuI, I_2, Cs_2CO_3	Acetonitrile	3 d	0
12	PPh_3AuCl, CuI, I_2, Et_3N	Acetonitrile	3 d	<20
13	PPh_3AuCl, CuI, I_2, py.	Acetonitrile	3 d	<20
14	PPh_3AuCl, CuI, I_2, TMEDA	THF	2 d	45
15	PPh_3AuCl, CuI, I_2, DIPA	THF	2 d	71
16	**PPh_3AuCl, CuI, I_2, DIPA**	**Toluene**	**2 d**	**86**
17	PPh_3AuCl, $CuCl$, I_2, DIPA	Toluene	2 d	66
18	PPh_3AuCl, $CuCl_2$, I_2, DIPA	Toluene	2 d	39
19	PPh_3AuCl, CuI, DIPA/O_2	Toluene	3 d	trace
20	PPh_3AuCl, AgOTf, I_2, DIPA	Toluene	1 d	trace
21	$AuCl_3$, CuI, I_2, DIPA	Toluene	1.5 d	trace
22[c]	PPh_3AuCl, CuI, I_2, DIPA	Toluene	2 d	79

[a] Reaction conditions: **3** (0.1 mmol), catalyst (10 mol%), cocatalyst (30 mol%), base (1.2 equiv), oxidant (2.5 equiv), and solvent (10.0 mL) at rt for 24-72 h. [b] Yield of Isolated product with 0.1 mmol scale. [c] The reaction was carried out on one gram scale.

No product was formed with inorganic bases (entry 9-11) and among organic bases (Et_3N, pyridine, TMEDA, DIPA), DIPA was found to be the best base leading too good yields (entry 12-15). An investigation of the impact of solvents showed that toluene worked best for the smooth conversion of diynes to corresponding macrolactones in the presence of 10 mol% PPh_3AuCl (10 mol%), CuI (30 mol%), I_2 (2.5 equiv.) and DIPA (1.2 equiv.), producing **4** in 86% yield (entry 16). Screening of different copper catalysts revealed low yield of the macrocyclization obtained with other co-catalysts such as CuCl, $CuCl_2$ and AgOTf. When Au(III) catalyst was used in place of Au(I) catalyst, a trace amount of **4** was observed (entry 21). The above optimized condition was also used for gram scale synthesis to afford compound **4** in 79% yield (entry 22).

In an effort to evaluate the generality of the optimized conditions, the macrocyclization of other diynes with different ring size was performed (Table 2). Change in the macrolactone ring sizes from 14- to 24-membered ring (**5**-**13**), did not significantly change the reaction yield except 14- and 15-membered ring formation were found in moderate yield along with oligomerized products in 11% and 7%, respectively (Table 2, entry 1 and 2). During the investigation of the macrocyclization of larger ring macrolactones, it was found that macrolactones having ring sizes 16-20 at high concentrations afforded the respective macrolactones in excellent yield. For 21- and 24-membered macrolactones, the yield was 78% and 71%, respectively.

Table 2. Substrate scope of Au(I)/Cu(I)- intramolecular Glaser-Hay Coupling.[a]



[a] The reaction was carried out on a 0.05 mmol scale.

While the precise reaction mechanism is not yet known, a plausible mechanism is shown in Figure 2. It is postulated that homogenous gold catalysts in situ generates organogold species which behaves like immobilized alkyne leading not only to the heterocoupling under high concentrations (0.01 M) but also enhances the yield of the macrolactone formation. The pathway is proposed as follows: The alkyne in presences of base and gold(I) catalyst forms the gold acetylide[15b] complex and simultaneously other alkyne forms copper acetylide. The

oxidative transmetalation of the organocopper species to Au^{III} in presence of molecular iodine lead to intermediate **IV**. Diisopropyl amine assisted reductive elimination of Au^{III} bis-acetylide complex yields the product with removal of Au^{I} species and continues the next catalytic cycle.

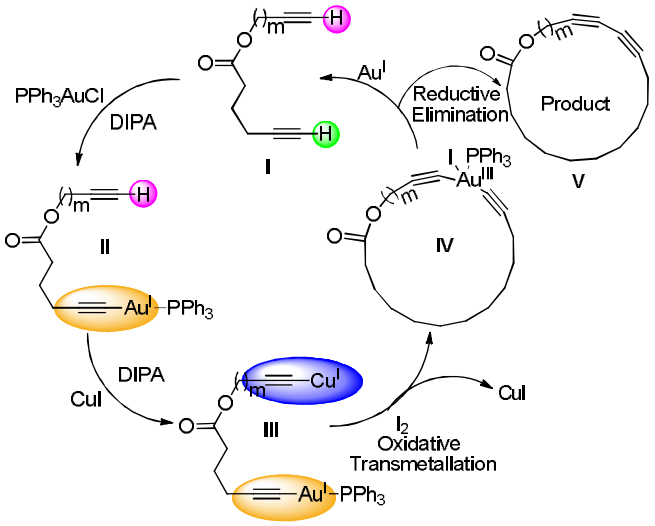
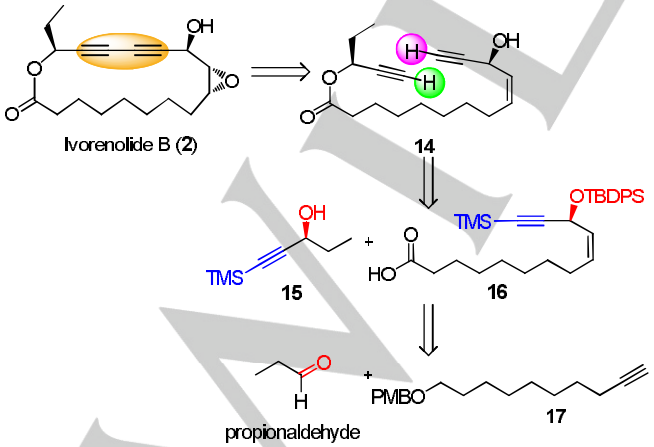


Figure 2. Possible mechanistic pathways.

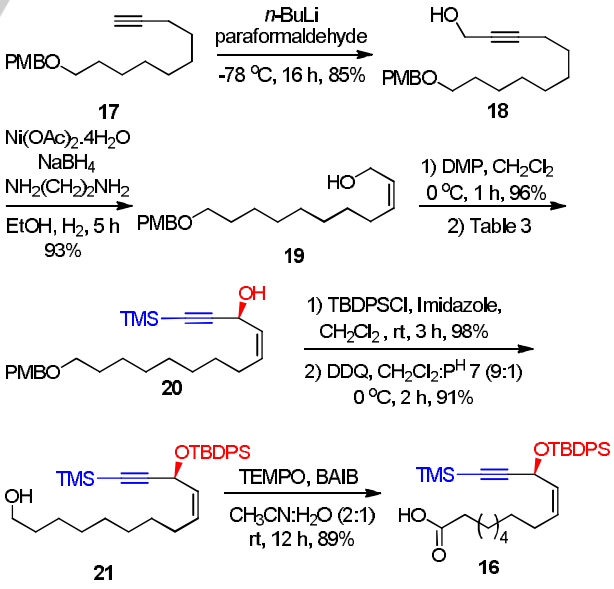
To demonstrate the utility of the novel macrocyclization, synthesis of the 17-membered macrolide ivorenolide B was undertaken. Yue et al. and our group independently achieved the total synthesis of *ent*-ivorenolide A (**1**) and ivorenolide A (**1**), respectively, utilizing alkyne-alkyne cross-coupling followed by macrolactonization.[7a,17] Collins et al. recently reported the formal total synthesis of ivorenolide A by following macrocyclization strategies under phase separation conditions using continuous flow.[13a] Further, Yue et al. reported the first total synthesis of ivorenolide B (**2**), which was achieved through esterification followed by RCM.[7b] Furstner et al. reported the second synthesis of ivorenolide B using ring-closing alkyne metathesis (RCAM) based macrocyclization, which involved highly unstable tetrayne precursors.[18]



Scheme 1. Retrosynthetic analysis of ivorenolide B.

In our current work, the development of a Au(I)/Cu(I)-catalyzed macrocyclization for the synthesis of ivorenolide B was envisaged through intramolecular Glaser-Hay coupling which disconnects the molecule framework at conjugated 1,3-diyne bond leading to terminal alkynes ester **14** as an advanced intermediate for the formation of 17-membered macrolactone. The linear ester fragment **14** could be prepared by coupling of alcohol **15** and acid **16** under Yamaguchi conditions.[19] Syntheses of both fragments were anticipated following a reliable direct catalytic asymmetric alkynylation strategy starting from PMB-protected 9-decyn-1-ol and propionaldehyde, respectively.

The synthesis of carboxylic alkynyl synthons **16** commenced from PMB-protected 9-decyn-1-ol. Hydroxymethylation[20] followed by *Z*-selective partial reduction[21] of the acetylene was performed to furnish *Z*-alcohol **19** in 79% yield over two steps. Oxidation of allylic alcohol with Dess-Martin-periodinane (DMP)[22] furnished the α,β-unsaturated aldehyde, which was subjected to zinc-ProPhenol-catalyzed alkyne addition to provide the propargyl alcohol **20** in 94% enantiomeric excess and with 91% yield.[23,24] At this juncture, in anticipation for a better result, the substrate **20** (for results, see Table 3) was prepared by BINOL-mediated alkyne addition,[25] oxidation followed by Noyori asymmetric hydrogenation[26] and enzymatic kinetic resolution.[27] The secondary hydroxyl group present in compound **20** was obtained through zinc-ProPhenol catalyzed addition, was protected as its TBDPS ether and treated with DDQ in CH_2Cl_2 (pH 7) to afford **21** in 89% yield over two steps. The primary alcohol **21** was oxidized to acid under TEMPO/BAIB in CH_3CN:H_2O (2:1) to obtain acid **16** in 89% yield.[28] With acid **16** in hand, the alkynylation of propionaldehyde was accomplished under Trost's conditions using zinc-ProPhenol as the chiral ligand and adding trimethylsilylacetylene (TMSA) slowly over 1 h at 0 °C to furnish alcohol **15** in 70% yield with 89% ee.

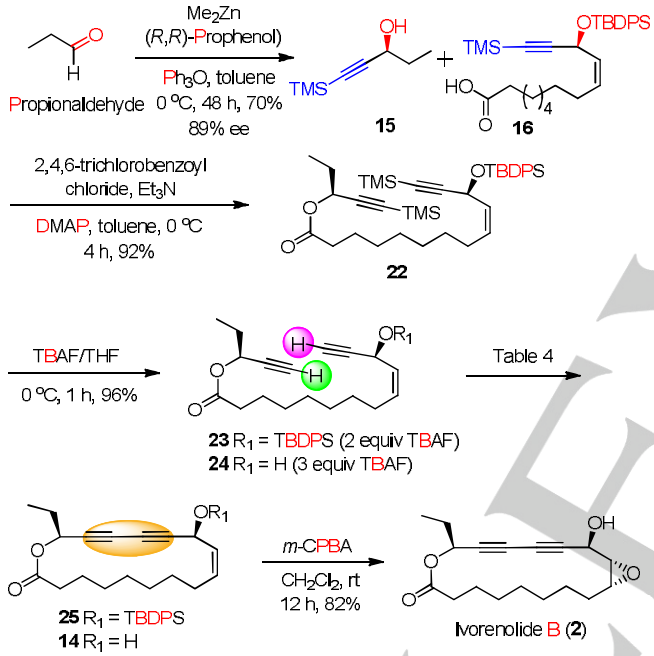


Scheme 2. Synthesis of fragment **16**.

Table 3. Optimization of reaction conditions

Entry	Reaction conditions	ee	Yield (%)
1	Me_2Zn, (*R,R*)-Prophenol, $Ph_3P{=}O$	94	91
2	Et_2Zn, (*R*)-Binol, $Ti(O{i}Pr)_4$	70	79
3	Noyori asymmetric reduction	91	82
4	Novozym Enzymatic resolution	93	39

Union of the alcohol fragment with the acid fragment was achieved smoothly under Yamaguchi conditions to furnish ester **22** in 92% yield. Deprotection of all silyl groups using TBAF in THF afforded **24** in 96% yield. The stage was set to perform the macrocyclization using Au(I)/Cu(I) in presence of iodine and DIPA in toluene. When intramolecular Glaser-Hay coupling was tried with the linear terminal alkynes with the secondary hydroxyl group protected as its TBDPS ether, macrocyclization occurred and **25** was obtained in 67% yield after two days (see Table 4).



Scheme 3. Total synthesis of Ivorenolide B.

Table 4. Optimization of reaction conditions

R_1	Reaction conditions	time (d)	Yield (%)
TBDPS	$AuCl(Ph_3P)/CuI/I_2$/DIPA	2	67
-H	$AuCl(Ph_3P)/CuI/I_2$/DIPA	1.5	81
-H	$Pd(PPh_3)_2Cl_2/CuI/I_2$/DIPA	2	36
-H	CuCl, TMEDA, O_2	2	15

Speculating that the presence of a bulky TBDPS group might be responsible for the low yield, the TBDPS ether linkage was cleaved and the macrocyclization precursor **24** was subjected to intramolecular Glaser-Hay coupling under identical conditions to afford the desired macrocycle **14** in 81% yield. The same reaction was also tried under Sonogashira type coupling and general Glaser-Hay coupling conditions which ended up with desired product in low yield (Table 4). Subsequent epoxidation with *m*-CPBA was highly regio- and stereoselective to furnish ivorenolide B (**2**) in 82% yield as a single isomer. All analytical and spectral data of the synthetic ivorenolide B (**2**) were in full agreement with those of the natural product reported in the literature.[7b,18]

In summary, we have developed a highly synergistic Au(I)/Cu(I) dual catalytic system for intramolecular Glaser-Hay coupling with linear terminal alkynes for the synthesis of macrolactones. The gold/copper conditions also can be utilized to promote macrocyclization of a wide range of macrocycles with varying ring sizes in excellent yield. The versatility of the protocol was demonstrated in the rapid asymmetric total synthesis of ivorenolide B. Further applications of this method are being researched.

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Keywords: Glaser-Hay coupling • Ivorenolide • Natural products • Macrocycle • Gold-Copper dual catalysis

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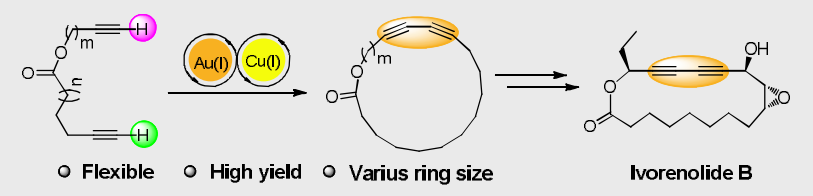

*Sudheer K. Rangaraju, Uma Maheshwar Gonela, Aala Kavita, Jhillu S. Yadav, and Debendra K. Mohapatra**

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Synergistic Gold and Copper Dual Catalysis for the Intramolecular Glaser-Hay Coupling: Rapid Total Synthesis of Ivorenolide B

Diyne macrocycles with different ring size were synthesized by developing a novel dual catalysis approach involving gold and copper catalysts through an intramolecular Glaser-Hay coupling reaction in good yield and demonstrated for a rapid total synthesis of ivorenolide B, a new class of macrolides endowed with conjugated 1,3-diyne motif, having impressive immunosuppressive activities.