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Gold-Catalyzed Intramolecular Indole/Alkyne Cyclization Cascades through a Heterolytic Fragmentation: 1,5-Indole Migration and Allenylation

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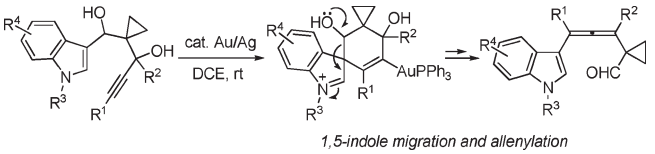
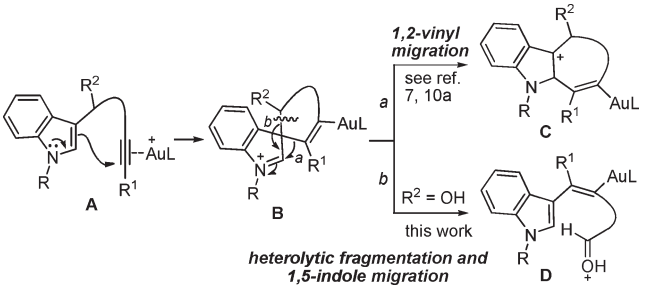
Received March 20, 2010



Gold-catalyzed intramolecular reactions of 3-alkynyl-bearing indoles with diol groups lead to the formation of highly functionalized 3-allenylindoles with high efficiency. The reaction likely proceeds by a new gold-catalyzed cascade cyclization/heterolytic fragmentation/elimination reactions, which results in 1,5-indole migration and C-3 allenylation of indole moiety.

Transition-metal-catalyzed cascade reactions that enable multiple bond-forming and -cleaving events in one sequence occupy an important place in organic synthesis.[1] In this regard, gold complexes and its salts are emerging as powerful catalysts due to their unique ability to activate alkynes, allenes, and alkenes toward nucleophilic attack.[2] Indoles can be viewed as excellent nucleophiles to induce cascade reactions since both of its C-2 and C-3 positions may react with activated intermediates. These include [4 + 2] annulations,[3] 3,3-rearrangement/

SCHEME 1



[2 + 2] cycloadditions of propargylic esters,[4] 1,2-indole migrations,[5] *N*-acyliminium cyclizations,[6] etc. Particularly interesting are the intramolecular indole/alkyne cyclizations due to the versatile reaction modes occurring in the system.[7−9] For example, Echavarren et al. have reported that intramolecular cyclization of indoles with alkynes proceeded either by an *endo*- or *exo-dig* process which is highly dependent on the oxidation state of the gold catalyst.[7a−c] Moreover, an unusual allenylation of the indole nucleus at C-2 derived by fragmentation reaction has been disclosed in certain cases.[7a,b] Recently, we have also developed a domino process for the efficient construction of indole-fused carbocycles[10a] through a Friedel−Crafts/hydroarylation sequence. These annulation reactions are suggested to proceed by first formation of a C−C bond at C-3 leading to a spirocyclic iminium cation **B** followed by 1,2-migration to generate fused indoles as depicted in path a of Scheme 1 (exemplified by *endo*-cyclization).[7a,b,10a] We envisioned that a special R^2 group such as a hydroxyl group α to the indole ring might induce the C−C bond cleavage of bond b in a similar manner of heterolytic fragmentation[11] fiollowed by the new transformations (Scheme 1, path b). In this paper, we report a new cyclization of 3-alkynyl-bearing indoles with

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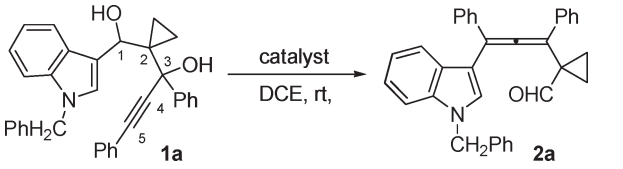
Published on Web 04/21/2010 DOI: 10.1021/jo1005125

TABLE 1. Optimzation of the Reaction Conditions



entry	catalyst	time (h)	yield[a] (%)
1[b]	5% $Ph_3PAuNTf_2$	2	75
2[b]	2% $[(Ph_3PAu)_3O]BF_4$	2	73
3[b]	5% $AuCl_3$	5	20
4[b]	5% Ph_3PAuCl	3	NR[c]
5[b]	5% $AgBF_4$	2	[d]
6[e]	5% $AgSbF_6$	4	[f]
7[b]	7.5% Ph_3PAuCl/5% $AgBF_4$	1	73
8[e]	7.5% Ph_3PAuCl/5% $AgSbF_6$	1	79
9[e]	5% Ph_3PAuCl/5% $AgSbF_6$	1	68
10[e,g]	5% $PtCl_2$	15	58
11[e]	10% TfOH	4.5	[h]

[a]Isolated yield. [b]One of the diastereomers was used. [c]No reaction. [d]There were three products, but no **2a**. [e]Another diastereomer was used. [f]Starting material remained as a major component, and several products were observed. [g]The reaction was carried out at 60 °C. [h]Complicated reaction mixture.

hydroxyl groups through a heterolytic fragmentation, which resulted in a 1,5-indole migration and allenylation at C-3 of indole nucleus. As far as we know, the 1,5-indole migration has not been reported and herein we present the first example in this context.

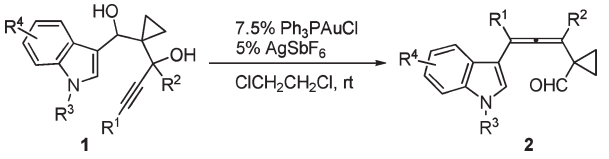
To test the hypothesis, the newly designed indoles **1** with diol groups were synthesized in two or three steps from the readily available indole-3-carbaldehydes. It was found that the reaction of diol **1a** with $Ph_3PAuNTf_2$ as catalyst in DCE at room temperature gave the allenic aldehyde **2a** cleanly in 75% yield (Table 1, entry 1). A competitive cyclization derived by addition of an oxygen nucleophile to the alkyne moiety was not observed. The gold−oxo complex $[(Ph_3PAu)_3O]BF_4$ also afforded **2a** in 73% yield (entry 2). In contrast, $AuCl_3$ only led to low yield (entry 3). The best catalyst was proven to be $PPh_3AuCl/AgSbF_6$ with a slight excess of gold catalyst, which allowed the formation of **2a** in 79% yield (entry 8). It is interesting to note that in this new transformation, allene **2a** was obtained as a result of an overall intramolecular allenylation at C-3 of the indole nucleus, and most strikingly, a 1,5-indole migration occurred in the catalytic process.

With this result in hand, we next examined the substrate scope with a range of 3-alkynyl-bearing indoles **1**[12,13] (Table 2). The substrates containing electron-rich or electron-deficient aryl groups afforded good yields of the desired 3-allenyl indoles (entries 2−4). A thienyl group was also compatible under the reaction conditions (entry 5). However, an alkyl group as R^1 led to only 37% yield of **2f** by using 10 mol % of $Ph_3PAuNTf_2$ (entry 6). This result indicated that the nature of the substituent on the alkyne terminus played an important role in this reaction. Regarding the indole moiety, *N*-methyl- or *N*-allyl-protected indoles were all suitable for this reaction (entries 7−13). The functionality of 5-MeO, 5-Br, or 6-Me on indole

(12) The indoles **1** used in this study were a mixture of two diastereomers or single diastereomers. We noted that, in some cases, an isomerization between the two diastereomers occurred during the reaction.

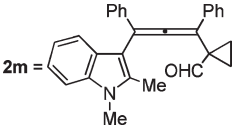
(13) The cyclopropane moiety in the substrates may not be necessary for this reaction. However, we failed to synthesize substrates without the cyclopropane ring so far.

TABLE 2. Gold-Catalyzed 1,5-Migration of Indoles from the Indolyl Alkynes 1

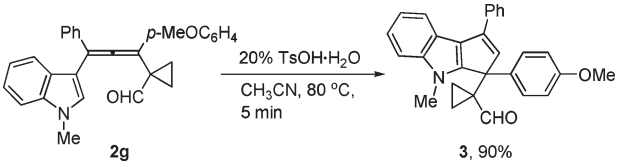


entry	sub.	R^1	R^2	R^3	R^4	time	product	yield(%)[a]
1	**1a**	Ph	Ph	CH_2Ph	H	1 h	**2a**	79
2	**1b**	*p*-$MeOC_6H_4$	Ph	CH_2Ph	H	1 h	**2b**	75
3	**1c**	*p*-BrC_6H_4	Ph	CH_2Ph	H	1 h	**2c**	72
4	**1d**	*p*-EtO_2C-C_6H_4	Ph	CH_2Ph	H	1 h	**2d**	73[b]
5	**1e**	2-thienyl	Ph	CH_2Ph	H	1 h	**2e**	79[b]
6	**1f**	n-Bu	Ph	CH_2Ph	H	2 h	**2f**	37[b]
7	**1g**	Ph	*p*-$MeOC_6H_4$	Me	H	0.5 h	**2g**	73
8	**1h**	Ph	Ph	Me	H	1 h	**2h**	75
9	**1i**	Ph	Ph		H	1 h	**2i**	83
10	**1j**	Ph	Ph	Me	5-MeO	1.5 h	**2j**	61[b]
11	**1k**	Ph	Ph	Me	5-Br	0.5 h	**2k**	81
12	**1l**	Ph	Ph	Me	6-Me	1.5 h	**2l**	54[b]
13	**1m**	Ph	Ph	Me	2-Me	1.5 h	**2m**	63[c]

[a]Isolated yield. [b]10% $Ph_3PAuNTf_2$ was used. [c]30% $Ph_3PAuNTf_2$ was used.



SCHEME 2



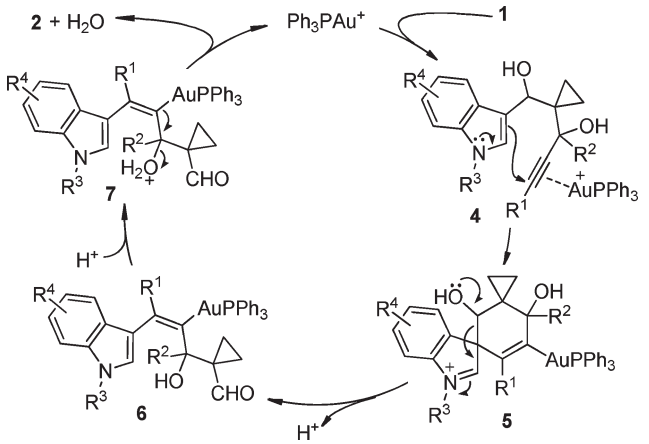
ring can be incorporated well into the reaction (entries 10−12). Interestingly, the C-2 methyl-substituted **1m** on indole ring underwent the similar indole-migration reaction to yield the allene **2m** in 63% yield, although with higher catalyst loading (entry 13). These results indicated that the initial C−C bond formation likely takes place at C-3 of the indole ring rather than at C-2. The structures of **2a** and **2b** were unambiguously confirmed by X-ray crystallographic analysis.[14]

To further highlight the synthetic potential of the allenylindoles, treatment of **2g** with 20% $TsOH \cdot H_2O$ at 80 °C in CH_3CN was carried out, and dihydrocyclopenta[*b*]indole **3** was efficiently synthesized in 90% yield (Scheme 2).

A possible reaction mechanism based on a cyclization-induced rearrangement is outlined in Scheme 3. The reaction is initiated through activation of the C−C triple bond in 3-alkynylindole **1** by cationic Ph_3PAu^+ generated through

(14) See the Supporting Information.

SCHEME 3



chloride abstraction by silver salts. A 6-*endo-dig* addition of the indole C-3 position onto gold(I)−alkyne complex **4** results in the formation of a spirocyclic intermediate **5**. Then a heterolytic fragmentation of **5** rather than normal 1,2-migration takes place, which results in a 1,5-indole migration to afford the alkenyl gold species **6**.[15] This is followed by elimination to yield the allenyl aldehyde **2** and regenerate the cationic Au(I) catalyst. The final step may also occur through a cationic intermediate formed by elimination of H_2O.

In conclusion, we have demonstrated that gold-catalyzed intramolecular reactions of 3-alkynyl-bearing indoles with diol groups lead to the formation of highly functionalized 3-allenylindoles with high efficiency. The reaction likely proceeds by a new gold-catalyzed cascade cyclization/heterolytic fragmentation/elimination reactions, which results in 1,5-indole migration and C-3 allenylation of indole moiety.

Experimental Section

Typical Procedure for Au(I)-Catalyzed Intramolecular Cascade Reactions of 3-Alkynyl-Bearing Indoles 1. To a solution of Ph_3PAuCl (0.015 mmol, 7.4 mg) in $ClCH_2CH_2Cl$ (2 mL) was added $AgSbF_6$ (0.010 mmol, 200 μL, used as a 0.05 M solution in CH_3CN), and the reaction mixture was allowed to stir at room temperature for 10 min. 1,3-Diol **1** (0.20 mmol) and $ClCH_2CH_2Cl$ (2 mL) were added, and the resulting solution continued to stir at room temperature until the reaction was complete as monitored by thin-layer chromatography. Four drops of Et_3N were added to quench the reaction. The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (the silica gel in the column must be pretreated first by a solution of petroleum ether/Et_3N = 100:1; eluent: petroleum ether/Et_3N = 100:1, petroleum ether/ethyl acetate/Et_3N = 100:10:1) to afford the desired product **2**. (It should be noted that these allenic aldehydes usually were not stable upon separation by normal silica gel; however, we found that the pure products could be obtained smoothly using the silica gel pretreated with the eluent containing 1% Et_3N.)

1-(3-(1-Benzyl-1*H*-indol-3-yl)-1,3-diphenylpropa-1,2-dienyl)-cyclopropanecarbaldehyde (2a). The title product was synthesized from **1a** (the more polar isomer was used). It was isolated in 79% yield as a light yellow solid: mp 147−148 °C; ^{1}H NMR ($CDCl_3$, Me_4Si, 400 MHz) δ 1.31−1.34 (m, 1H), 1.37−1.40 (m, 1H), 1.61−1.67 (m, 2H), 5.26 (s, 2H), 7.02−7.11 (m, 4H), 7.17 (t, J = 8.4 Hz, 1H), 7.20−7.34 (m, 10H), 7.51 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H) 7.64 (d, J = 8.0 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si, 100 MHz) δ 17.7, 18.1, 33.7, 50.2, 107.1, 107.7, 110.0, 120.2, 120.4, 122.4, 126.6, 126.7, 126.8, 127.3, 127.6, 128.2, 128.3, 128.5, 128.7, 128.8, 135.6, 136.8, 137.0, 137.1, 201.3, 208.3; IR (KBr) 3058, 3028, 2926, 2821, 2723, 2245, 1709, 1596, 1537, 1492, 1466, 1453, 1445, 1391, 1354, 1335, 1239, 1179, 1075, 1030, 1003, 908, 762, 737, 696 cm^{-1}; HRMS (EI) for $C_{34}H_{27}NO$ calcd 465.2093, found 465.2096.

Typical Procedure for the Synthesis of Dihydrocyclopenta-[*b*]indole 3. To a solution of **2g** (60 mg, 0.143 mmol) in CH_3CN (2.8 mL) was added $TsOH\cdot H_2O$ (5.4 mg, 0.0286 mmol), and the reaction mixture was stirred at 80 °C for 5 min. The mixture was cooled to room temperature. The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1. The silica gel in the column must be pretreated first by a solution of petroleum ether/Et_3N = 100:1) to afford the product **1-(3-(4-methoxyphenyl)-4-methyl-1-phenyl-3,4-dihydrocyclopenta[*b*]indol-3-yl)cyclopropanecarbaldehyde** (**3**) as a light yellow sticky liquid in 90% yield: ^{1}H NMR ($CDCl_3$, Me_4Si, 300 MHz) δ 0.84−0.91 (m, 1H), 1.05−1.12 (m, 1H), 1.23−1.30 (m, 1H), 1.53−1.59 (m, 1H), 3.56 (s, 3H), 3.76 (s, 3H), 6.50 (s, 1H), 6.81 (d, J = 9.0 Hz, 2H), 7.12−7.31 (m, 5H), 7.36−7.40 (m, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.76 (d, J = 7.2 Hz, 1H), 7.80−7.83 (m, 2H), 9.44 (s, 1H); ^{13}C NMR ($CDCl_3$, Me_4Si, 75 MHz) δ 13.6, 14.7, 31.8, 34.0, 55.2, 56.2, 110.1, 114.1, 119.9, 120.1, 120.7, 121.0, 121.2, 127.3, 127.9, 128.5, 128.6, 129.0, 132.4, 135.9, 141.6, 141.9, 152.5, 158.6, 201.9; IR (KBr) 3055, 3033, 3004, 2953, 2932, 2836, 2749, 1709, 1608, 1580, 1510, 1462, 1413, 1333, 1295, 1250, 1179, 1116, 1036, 984, 951, 909, 833, 744, 699 cm^{-1}; HRMS (EI) for $C_{29}H_{25}NO_2$ calcd 419.1885, found 419.1884.

Acknowledgment. We thank the National Natural Science Foundation of China (Grant Nos. 20872163, 20732008, 20821002), Chinese Academy of Science, Science and Technology Commission of Shanghai (Grant No. 08QH14030), and the Major State Basic Research Development Program (Grant No. 2006CB806105) for financial support.

Supporting Information Available: Experimental details, spectroscopic characterization of all new compounds, and crystallographic data of compounds **2a** and **2b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(15) This step also can be described as a retro-aldol-type fragmentation as suggested by one reviewer.