CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201003363

Gold(I)-Catalyzed, Highly Diastereoselective, Tandem Heterocyclizations/[3+2] Cycloadditions: Synthesis of Highly Substituted Cyclopenta[*c*]furans

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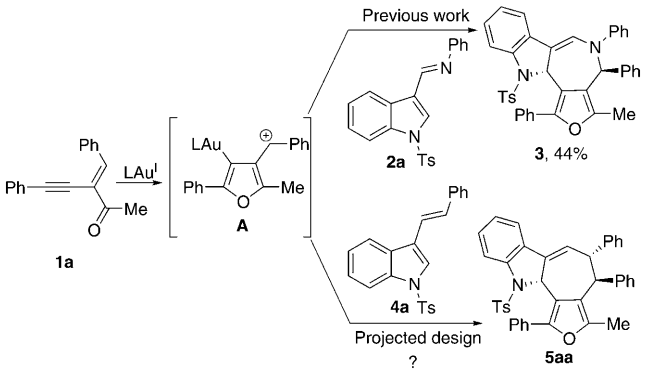
Carbo- and heterocyclic compounds play an irreplaceable role as lead candidates in drug discovery. Thus, highly efficient design and synthesis of these compounds are highly desirable in synthetic chemistry. Transition-metal-catalyzed cycloaddition reactions provide efficient tools for the chemo-, regio-, and diastereoselective construction of highly substituted medium-sized ring systems from simple acyclic starting materials.[1] In particular, transition-metal-catalyzed [3+2] cycloadditions provide access to five-membered rings,[2] which are difficult to achieve by alternative approaches, such as intramolecular substitution reactions. Herein, we report a novel approach to highly substituted cyclopenta[*c*]-furans by a gold(I)-catalyzed, highly regio- and diastereoselective, tandem heterocyclization/[3+2] cycloaddition reaction.[3]

Because of the recent attention given to cascade reactions,[4] an increasing number of studies have highlighted the utility of 2-(1-alkynyl)-2-alken-1-ones,[5] which were first reported by Larock in 2004,[5a] as substrates in transition-metal-catalyzed carbon–carbon or carbon–hetero atom bond-formation reactions. For example, we have recently reported an efficient and convenient synthetic route to fused heterobicyclic furo[3,4-*c*]azepines by a gold-catalyzed, highly diastereoselective, tandem, double heterocyclizations and 1,2-alkyl migrations.[6,7] During the course of this investigation, we found that the $Ph_3PAuOTf$-catalyzed (OTf = triflate) reaction of 2-(1-alkynyl)-2-alken-1-ones (**1a**) with heteroaryl imine **2a** underwent the formal [4+3] cycloaddition without 1,2-alkyl migration.[6h] As part of an ongoing program to develop this type of synthetic approaches to polyheterocyclic compounds, we reasoned that readily available (*E*)-1-tosyl-3-styryl-1*H*-indole (**4a**), an analogue of heteroaryl imine **2a**, might also undergo a similar tandem heterocyclization and formal [4+3] cycloaddition reaction through intermediate **A** to give cyclohepta[*c*]furan (Scheme 1).



Scheme 1. Previous work and projected reaction pattern of ketones **1a** with 3-styrylindole **4a** (Ts = tosyl).

With this hypothesis in mind, we began our study by examining the reaction of **1a** and **4a** catalyzed by various metal complexes. Unfortunately, the reaction products always contained impurities and failed to give any major products under the different reaction conditions investigated. We reasoned that this may result from the weak nucleophilicity of **4a** due to the electron-withdrawing Ts group. The more electron-rich (*E*)-1-methyl-3-styryl-1*H*-indole (**4b**) was then proposed and tested as a substrate. Luckily, the reaction proceeded smoothly at RT in 1,2-dichlorethane (DCE) catalyzed by 5 mol% $Ph_3PAuOTf$ (generated from the 1:1 ratio of Ph_3PAuCl/AgOTf, Table 1, entry 1). However, to our surprise, the product is the 5,5-fused cyclopenta[*c*]furan **6ab** with a high diastereo-selectivity rather than the expected 5,7-fused cyclohepta[*c*]furan **5ab**. The structure of **6ab** was confirmed by single-crystal X-ray diffraction.[8] With AgOTf or $In(OTf)_3$ as catalysts the yield and diastereoselectivity decreased drastically(Table 1, entries 2 and 3). There was no improvement in yield or diastereoselectivity, when $Cu(OTf)_2$ or $Fe(OTf)_3$ were employed as catalysts (Table 1, entries 4 and 5). $PtCl_2$ and $Sc(OTf)_3$ were inefficient catalysts for this transformation (Table 1, entries 6 and 7). Finally, we were pleased to find that Cy_3PAuCl/AgOTf was the best catalyst system and the reaction gave **6ab** in

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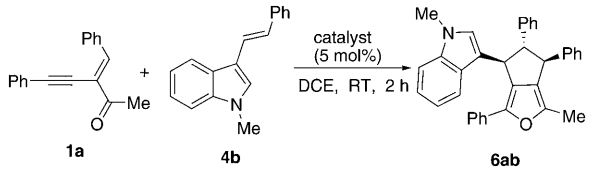
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003363.

Table 1. Optimization of the reaction conditions for the [3+2] tandem cycloaddition between **1a** and **4b**.[a]



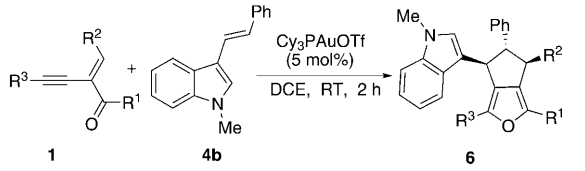
Entry	Catalyst	**6ab** Yield [%][b]	d.r.[c]
1	$Ph_3PAuCl/AgOTf$	88	8.3:1
2	AgOTf	38	1:1.4
3	$In(OTf)_3$	28	1:1.8
4	$Cu(OTf)_2$	45	1:1
5	$Fe(OTf)_3$	52	1:1.2
6	$PtCl_2$	trace	-
7	$Sc(OTf)_3$	trace	-
8	Cy_3PAuCl[d]/AgOTf	93	>20:1

[a] **1a** (0.3 mmol), **4b** (0.36 mmol), and DCE (3 mL) were employed at RT. [b] Yield of the isolated product. [c] d.r. = diastereomeric ratio, determined by ^{1}H NMR analysis of the crude product. [d] Cy = cyclohexyl.

93% yield and excellent diastereoselectivity (>20:1, Table 1, entry 8).

With the optimal conditions in hand, we turned our attention to the reaction scope of this gold-catalyzed tandem transformation by varying the 2-(1-alkynyl)-2-alken-1-one (Table 2). In general, various substituents (R^1, R^2, and R^3) at all three positions of ketone **1** are well-tolerated. Substituent R^1, which can be either an aliphatic or aromatic group, has little impact on the yield, but remarkable impact on the diastereoselectivity (Table 2, entries 1 vs. 12, entries 6 vs. 13). The R^1 alkyl-substituted substrates can achieve

Table 2. Diastereoselective synthesis of highly substituted cyclopenta[*c*]-furans through variation of ketone **1**.[a]



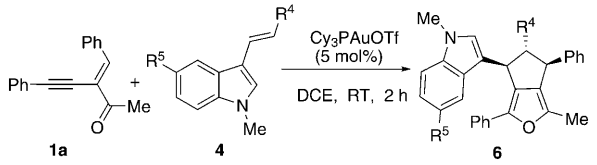
Entry	$R^1/R^2/R^3$	**6** Yield [%][b]	d.r.[c]
1	Me/Ph/Ph (**1a**)	**6ab**: 93	>20:1
2	Me/Ph/4-$MeOC_6H_4$ (**1b**)	**6bb**: 82	>20:1
3	Me/Ph/4-MeC_6H_4 (**1c**)	**6cb**: 87	>20:1
4	Me/Ph/1-Cyclohexenyl (**1d**)	**6db**: 67	>20:1
5	Me/Ph/1-Cyclopropyl (**1e**)	**6eb**: 68	>20:1
6	Me/Ph/*n*Bu (**1f**)	**6fb**: 72	>20:1
7	Me/Ph/4-$NO_2C_6H_4$ (**1g**)	**6gb**: 87	>20:1
8	Me/Ph/1-Naphthyl (**1h**)	**6hb**: 94	10:1
9	Me/4-$MeOC_6H_4$/Ph (**1i**)	**6ib**: 81	>20:1
10	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1j**)	**6jb**: 85	>20:1
11	Me/4-$MeOC_6H_4$/1-Naphthyl (**1k**)	**6kb**: 92	>20:1
12	Ph/Ph/Ph (**1l**)	**6lb**: 89	3.7:1
13	Ph/Ph/*n*Bu (**1m**)	**6mb**:80	3.4:1
14	Ph/4-ClC_6H_4/Ph (**1n**)	**6nb**: 83	4.5:1

[a] All reactions were carried out with **1** (0.3 mmol) under standard conditions. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude product.

better diastereoselectivity than aromatic-substituted ones (Table 2, entries 1–11 vs. entries 12–14). Not only electron-rich and electron-deficient aromatic substituents, but also cyclic and acyclic aliphatic substituents can be introduced as R^3 (Table 2, entries 2,3,7,8, and 4–6, respectively). Both a cyclopropyl group as R^3 and a halogen atom on the aromatic ring of R^2 are compatible with this catalytic system (Table 2, entries 5 and 14).

To expand the generality of this process, other substituted 3-styrylindoles were tested and the results are summarized in Table 3. To our delight, a diverse array of highly substitut-

Table 3. Diastereoselective synthesis of highly substituted cyclopenta[*c*]-furan through variation of 3-styrylindole **4**.[a]

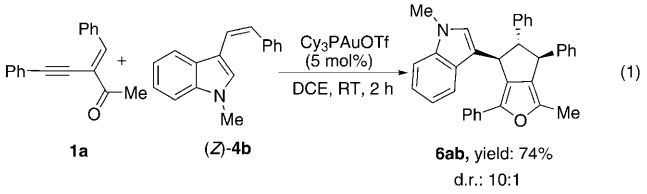


Entry	R^4/R^5	**6** Yield [%][b]	d.r.[c]
1	4-MeC_6H_4/H (**4c**)	**6ac**: 89	>20:1
2	4-$MeOC_6H_4$/H (**4d**)	**6ad**: 87	>20:1
3	4-CNC_6H_4/H (**4e**)	**6ae**: 87	>20:1
4	4-$NO_2C_6H_4$/H (**4f**)	**6af**: 89	>20:1
5	4-ClC_6H_4/H (**4g**)	**6ag**: 84	>20:1
6	4-BrC_6H_4/H (**4h**)	**6ah**: 92	>20:1
7	Ph/OMe (**4i**)	**6ai**: 96	>20:1
8	Ph/Me (**4j**)	**6aj**: 96	>20:1
9	Ph/Br (**4k**)	**6ak**: 93	>20:1

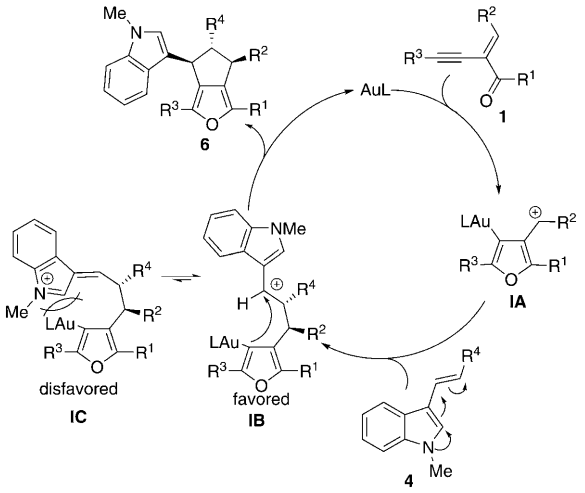
[a] All reactions were carried out with **1a** (0.3 mmol) under standard conditions. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude product.

ed cyclopenta[*c*]furans was easily constructed in good to excellent yields with excellent diastereoselectivities. Two points are noteworthy: 1) not only electron-rich, but also electron-deficient aromatic substituents can be introduced at R^4; this has little impact on the yield and diastereoselectivity (Table 3, entries 1–6), and 2) a halogen substituent on either of the two aromatic rings is tolerated (Table 3, entries 3, 5, 6, and 9).

To gain insight into the mechanism and check whether the stereochemistry of the dipolarophile **4** affects the stereochemistry of the product, the *Z* isomer of **4b** (**(*Z*)-4b**) was subjected to the reaction under the standard conditions, the same product as for the *E* isomer (**6ab**) was isolated in 74% yield with 10:1 diasteroselectivity after 2 h at room temperature, indicating that the reaction proceeds through a stepwise, formal [3+2] cycloaddition reaction pathway [Eq. (1)].



A proposed stepwise mechanism that accounts for this gold(I)-catalyzed [3+2] tandem bicyclizations is depicted in Scheme 2. The furanyl gold intermediate **IA** would be afforded by the gold(I)-mediated heterocyclization of ketone **1**. The nucleophilic attack of alkene **4** on the carbocation of intermediate **IA** through a diastereo- and regioselective fashion would afford two convertible intermediates, **IB** and **IC**. The stability of the aromatic indole and the steric interaction of **IC** should lead to **IB** as the favored intermediate. Intermediate **IB** would further undergo diastereoselective intramolecular 1,5-cyclization leading to the final formal [3+2] cycloaddition-product **6** and regenerate the gold catalyst.



Scheme 2. Plausible mechanism.

In conclusion, we have demonstrated that highly substituted cyclopenta[c]furans can be efficiently constructed from readily available 2-(1-alkynyl)-2-alken-1-ones and 3-styrylindoles in a one-pot manner by employing a gold-catalyzed tandem cyclization. Mild reaction conditions, ease of operation, high yields, high diastereoselectivities, and a wide functional-group tolerance are several merits of this highly efficient protocol. Further investigations to extend the scope of this reaction, asymmetric catalysis, as well as biological evaluation of these compounds are currently underway in our group.

Experimental Section

Synthesis of 6ab: AgOTf (3.8 mg, 0.015 mmol) was added to a solution of Cy_3PAuCl (7.8 mg, 0.015 mmol) in DCE (1 mL) under an Ar atmosphere. The mixture was stirred for 10 min at room temperature. Then the solution of ketone **1a** (73.8 mg, 0.3 mmol) and **4b** (83.9 mg, 0.36 mmol) in DCE (2 mL) was added to this mixture. After stirring for 2 h at room temperature, ketone **1a** was consumed completely according to TLC analysis. The mixture was passed through a short silica-gel column and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the pure product **6ab** (133.2 mg) in 93% yield as a white solid. M.p. 212–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.0$ Hz, 2H), 7.22–7.06 (m, 13H), 7.05–7.00 (m, 2H), 6.97–6.90 (m, 1H), 6.85 (t, $J = 7.2$ Hz, 1H), 6.65 (s, 1H), 4.78 (d, $J = 8.4$ Hz, 1H), 4.32 (d, $J = 8.4$ Hz, 1H), 3.83 (t, $J = 8.4$ Hz, 1H), 3.48 (s, 3H), 2.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 143.1, 142.7, 142.3, 142.1, 137.3, 131.0, 130.4, 128.31, 128.25, 127.99, 127.95, 127.7, 126.93, 126.87, 126.5, 126.3, 125.6, 124.3, 121.1, 119.8, 118.4, 115.0, 108.9, 73.3, 51.7, 44.8, 32.5, 12.5 ppm; MS (EI): m/z (%): 479 [M^+] (2.90), 84 (100); HRMS: calcd for $C_{35}H_{29}NO$: 479.2249, found: 479.2248. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

Acknowledgements

Financial support from the 973 program (2009CB825300), NSFC (20972054), Ministry of Education of PRC, Science and Technology Commission of Shanghai Municipality (08dj1400100) and the PhD Program Scholarship Fund of ECNU (2010032) are greatly appreciated.

Keywords: cycloaddition · cyclopenta[*c*]furans · diastereoselectivity · domino reactions · gold

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[8] CCDC-801595 (**6ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: November 22, 2010
Published online: February 3, 2011

