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Gold-Catalyzed Cyclization of Alkynylaziridines as an Efficient Approach toward Functionalized *N*-Phth Pyrroles

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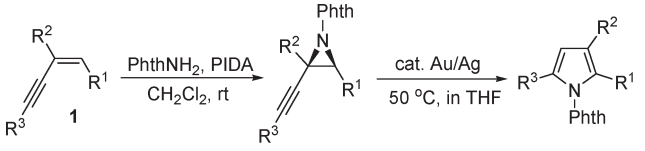

An efficient access to *N*-phth pyrrroles via gold-catalyzed cycloisomerization of *N*-phth alkynylaziridines has been described. Functionalized pyrroles including pyrrole-2-carboxylates or 2-pyrrolyl ketone are easily constructed in generally good yields by this method. The resulting pyrroles can be further converted to *N*-amino pyrrole or 2-acyl pyrrole, which are important synthetic intermediates for amplification of molecular complexity.

Pyrroles are one of the most important classes of heterocyclic compounds as they widely occur as key structural subunits in numerous natural products which exhibit interesting biological activities,[1] and can find a variety of applications in pharmaceutical use[2] and material science.[3] Furthermore, substituted pyrroles are of significant interest since they are useful and versatile synthetic intermediates for further structural elaboration.[4] As a consequence, much attention has been paid to the synthesis of pyrrole derivatives either by classic methods such as the Paal−Knorr[5] and Hantzsch syntheses[6] or by transition metal-catalyzed reactions.[7] In particular, protocols relying on intramolecular cyclization of alkynes bearing proximate nucleophiles utilizing gold as catalyst have received considerable attention.[8] In a recent example, Hashmi et al. had reported an elegant application for the transformation of alkynyl epoxides to furans catalyzed by $AuCl_3$.[9] We have also developed several gold-catalyzed processes for the efficient construction of furans, pyrroles, indole-fused carbocycles, etc. from enynols.[10] We envisioned that if the double bond of these enyne substrates is further elaborated to the aziridine moiety, it may afford functionalized pyrroles. During our ongoing work, several groups have reported gold-catalyzed cyclization of alkynylaziridines to *N*-Ts[11a,b] or *N*-Bn[11c] pyrroles. In their reports, the functional groups have rarely been introduced, and only disubstituted pyrroles were prepared. Therefore, increasing the functional group tolerance and structure scope of the current procedures is still highly attractive. Herein we'd like to report a gold-catalyzed cyclization of

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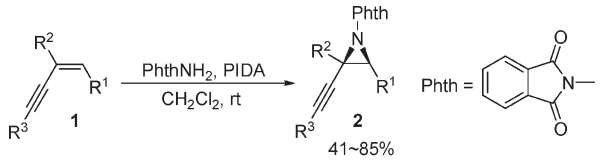
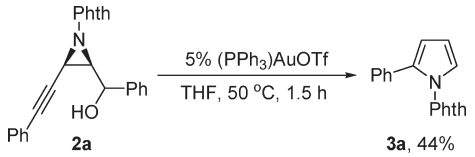
SCHEME 1



SCHEME 2



alkynyl *N*-phth-aziridines, in which various substituted pyrroles with functional groups can be generated efficiently.

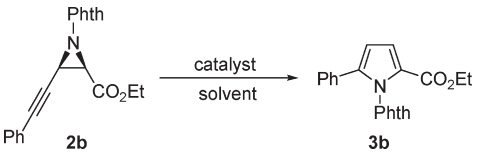
The alkynylaziridine substrates **2** were synthesized according to Che and Yudin's procedure with use of the *N*-aminophthalimide/phenyliodine(III) diacetate (PIDA) system.[12] This method was reported to be versatile with regard to the electronic nature of olefin, and also with high diastereoselectivity. A series of *cis*-aziridine **2** compounds with −CH(OH)R, $-CO_2R$, and −COR functionalities were conveniently prepared in 41−85% yield from *cis*-enynes by this method (Scheme 1). In several cases, the aziridine **2** exists as a mixture of invertomers as determined by ^{1}H NMR.

In an initial experiment, we investigated the reaction of aziridine **2a** under our previous gold-catalyzed cycloisomerization conditions.[10a] To our surprise, monophenyl-substituted pyrrole **3a** was obtained in 44% yield (Scheme 2) (containing 7% of inseparable byproduct[13]). It is obvious that a C−C bond cleavage occurred during the process.

Since the functional group was easily lost using alcoholic substrate **2a**, we turned our attention to the use of aziridine-2-carboxylate **2b**. Satisfyingly, the reaction proceeded smoothly, and the desired pyrrole-2-carboxylate **3b** was obtained in 97% yield at 50 °C in THF for 1 h with use of 5 mol % of $(PPh_3)AuCl$ and 5 mol % of AgOTf as catalysts (Table 1, entry 1). The reaction could also be performed in DCE or MeOH, although lower yields (83−90%) were observed (entries 2 and 3). AgOTf alone did not promote any transformations (entry 6). $PtCl_2$ gave a reduced yield of 61% and a longer reaction time (21 h, entry 7).

We chose the reaction conditions shown in Table 1, entry 1, to examine the scope of this reaction. The method is applicable to a wide range of suitably substituted *cis*-aziridines as illustrated in Table 2. We first investigated the electronic effects of the arene substitutent on alkyne terminus R^3. While a −Cl substituent afforded **3c** in 93% yield, the electron-donating group −OMe afforded a lower yield of 72% (entries 2 and 3). When R^3 is an alkyl group, the reaction proceeded smoothly to produce **3e** in 87% yield (entry 4). When **2f** containing a siloxymethyl group on R^3 was used, a partial desilylation occurred within 1 h. Extension

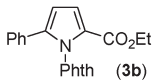
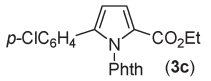
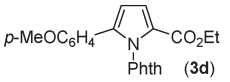
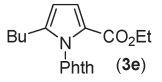
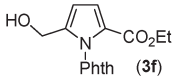
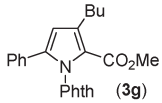
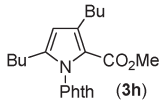
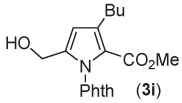
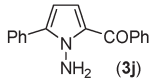
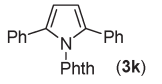
TABLE 1. Optimization Studies for the Formation of Pyrrole-2-carboxylate



entry	catalyst	solvent	temp (°C)	time (h)	yield (%) of **3b**[a]
1	5% Ph_3PAuCl/AgOTf	THF	50	1	97
2	5% Ph_3PAuCl/AgOTf	DCE	50	1.5	83
3	5% Ph_3PAuCl/AgOTf	MeOH	50	1	90
4	2% Ph_3PAuCl/AgOTf	THF	50	3	90
5	5% Ph_3PAuCl/AgOTf	THF	rt	6	96
6	5% AgOTf	THF	50	13	NR[b]
7	10% $PtCl_2$	toluene	80	21	61

[a]Isolated yield. [b]NR = no reaction.

TABLE 2. Synthesis of Pyrroles through Gold(I)-Catalyzed Cyclization of Alkynylaziridines

entry		R^1	R^2	R^3	time (h)	product	yield[a]
1	**2b**	CO_2Et	H	Ph	1	 (**3b**)	97
2	**2c**	CO_2Et	H	*p*-ClC_6H_4	1.5	 (**3c**)	93
3	**2d**	CO_2Et	H	*p*-$MeOC_6H_4$	0.5	 (**3d**)	72
4	**2e**	CO_2Et	H	Bu	1	 (**3e**)	87
5	**2f**	CO_2Et	H	CH_2OTBS	10	 (**3f**)	55[b]
6	**2g**	CO_2Me	Bu	Ph	1	 (**3g**)	83
7	**2h**	CO_2Me	Bu	Bu	1	 (**3h**)	92
8	**2i**	CO_2Me	Bu	CH_2OTBS	10	 (**3i**)	59[b]
9	**2j**	COPh	H	Ph	2	 (**3j**)	39[c]
10	**2k**	Ph	H	Ph	4	 (**3k**)	75[d]

[a]Isolated yield. [b]The desilytion product was obtained. [c]After deprotection of the phthaloyl group with hydrazine monohydrate. [d]The reaction was carried out in MeOH.

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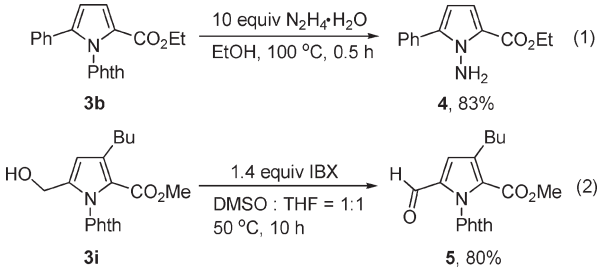
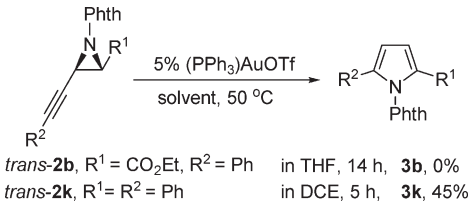
(13) The byproduct was assigned to be the imine of 2-(benzylideneamino)-isoindoline-1,3-dione by comparison of the ^{1}H NMR spectra of the mixture to ^{1}H NMR spectra of the authentic sample.

SCHEME 3



SCHEME 4

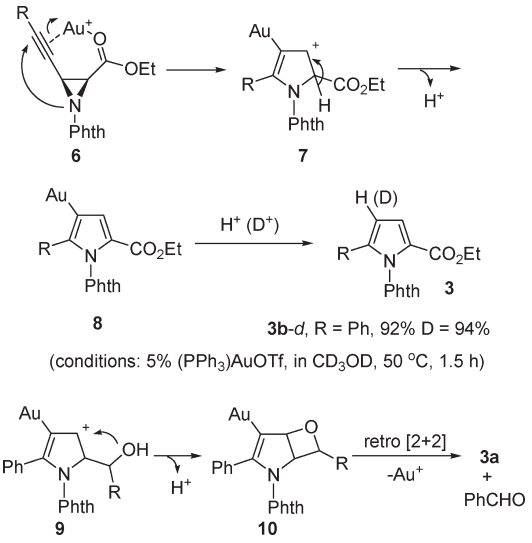


of the reaction time to 10 h resulted in complete desilylation, leading to the primary alcohol **3f** in 55% yield (entry 5). Trisubstituted aziridines **2g**−**i** were also compatible under the cyclization conditions, yielding 3,5-disubstituted pyrrole-2-carboxylates **3g**−**i** in 59−92% yields (entries 6−8). However, with a ketone present in the aziridine **2j**, the yield dropped to 39% after deprotection of the phthalyl group. In this case, the desired *N*-phth pyrrole could not be separated from the byproducts upon isolation by column chromatography (entry 9). It is noted that when the phenyl group was placed on the aziridine ring instead of the ester group, the corresponding pyrrole **3k** was formed in a lower yield of 45% in THF; however, the yield could be improved to 75% by switching the solvent to MeOH (entry 10).

Removal of a phthalyl protecting group from pyrroles **3** to $-NH_2$-substituted pyrroles can be accomplished with use of $N_2H_4 \cdot H_2O$ in EtOH, as already exemplified in product **3j** (Table 2, entry 9). In an additional case, amino-pyrrole **4** was obtained in 83% yield from the corresponding *N*-protected pyrrole **3b** (Scheme 3, eq 1). This type of substrate is known to be the key intermediate for the synthesis of biologically active substances such as protein kinase inhibitors.[14] Oxidation of **3i** by IBX in DMSO/THF afforded 5-formyl-1-pyrrole-2-carboxylate **5** in 80% yield, which has the potential to access further synthetic applications (Scheme 3, eq 2).

When *trans*-aziridines were used, however, we observed different results. The *trans*-**2b** (invertomer ratio is 2.3:1) led to no formation of pyrrole (Scheme 4), and most of the starting materials was recovered, which may be due to the competed coordination of the *trans*-ester group and the phthalyl carbonyl group or nitrogen lone pair in different invertomers versus the alkynyl group with gold catalyst, thus the π-bond could not be activated efficiently. In the *cis*-aziridines, however, the ester and the alkynyl group are located in the same direction, thus the triple bond could be sufficiently activated. When *trans*-**2k** was used, the corresponding **3k** was isolated in a lower yield of 45%.

SCHEME 5



We propose the following mechanism for these cyclizations as depicted in Scheme 5, which involves coordination of the triple bond by gold, nucleophilic attack of the aziridine nitrogen on the alkyne, followed by ring-opening to afford **7**, then deprotonation to give the aromatized gold species **8**, which further undergoes deauration to afford pyrrole **3**. The formation of aryl-gold intermediate **8** has been supported in a deuteration experiment; a high deuterium incorporation of 94% was observed when the reaction was carried out in CD_3OD. To account for the formation of monosubstituted pyrrole **3a** from alcoholic substrate **2a**, a nucleophlic attack of the adjacent OH group to the cationic center in **9** to form oxabutane **10** followed by ring-opening is proposed.[15]

In summary, we have developed an Au/Ag-catalyzed cyclization of alkynylaziridines to *N*-phth pyrroles under mild reaction conditions. The method is particularly attractive for assembling multisubstituted pyrrole-2-carboxylates with high diversity and in a regioselective manner. These compounds are potentially useful in pharmaceutical and material science.

Experimental Section

A Typical Procedure for Gold-Catalyzed Cycloisomerization of Alkynylaziridine 2b. To a solution of (2*R**,3*R**)-ethyl-1-(1,3-dioxoisoindolin-2-yl)-3-(phenyl-ethynyl)aziridine-2-carboxylate **2b** (72.1 mg, 0.2 mmol) in 2.0 mL of THF was added 5 mol % of $(PPh_3)AuCl$ followed by AgOTf (5 mol %, used as a 0.05 M solution in THF) at room temperature. The resulting solution was stirred at 50 °C for 1 h until the reaction was complete as monitored by thin-layer chromatography. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to afford the pyrrole derivative **3b** as a pale yellow solid in 97% yield. **Ethyl 1-(1,3-dioxoisoindolin-2-yl)-5-phenyl-1*H*-pyrrole-2-carboxylate (3b):** mp 166−168 °C; ^1H NMR ($CDCl_3$, Me_4Si, 300 MHz)

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δ 1.16 (t, J = 7.2 Hz, 3H), 4.14 (q, J = 7.2 Hz, 2H), 6.45 (d, J = 4.2 Hz, 1H), 7.19 (d, J = 4.5 Hz, 1H), 7.28−7.32 (m, 3H), 7.42−7.45 (m, 2H), 7.75−7.78 (m, 2H), 7.89−7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, Me_4Si, 100.6 MHz) δ 14.0, 60.2, 108.6, 118.0, 122.2, 124.3, 128.2, 128.6, 128.7, 129.6, 129.9, 134.8, 141.8, 159.5, 165.1; IR (neat) 2991, 1746, 1468, 1073, 880, 751 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{16}N_2O_4$ 360.1110, found 360.1114.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.