C–H Activation

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Room-Temperature Au^I-Catalyzed C–C Bond Formation through a Tandem Friedel–Crafts-Type Addition/Carbocyclization Reaction**

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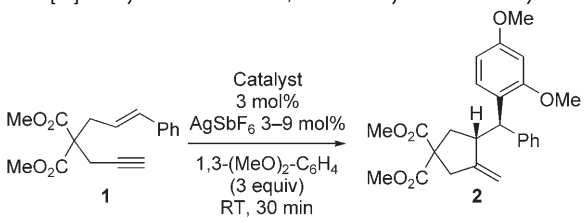
In the past ten years, significant research has been directed towards the development of catalytic reactions for the functionalization of C–H bonds.[1] These reactions represent an environmentally friendly and atom-economical concept when performed under mild conditions.[2] Several metals have been recognized as excellent candidates for the functionalization of aromatic or heteroaromatic C–H bonds.[1,3] As part of our ongoing program towards the development of catalytic tandem and atom-economical reactions,[4] we have been interested in the use of gold for such transformations. Kharash and Isbell were the first to show that Au^{III} could activate aromatic compounds at room temperature.[5] Following their seminal discovery, homogeneous gold catalysis was forsaken and interest only returned a few years ago.[6] The use of gold for C–H functionalization to create C–C bonds was recently realized in the presence of various electrophiles such as alkynes or activated alkenes.[1b,7] To our knowledge, few examples of additions to nonactivated alkenes have been described so far.[8] We anticipated that the unprecedented intermolecular addition of aromatic rings to unactivated alkenes may be feasible in the presence of a second electrophilic moiety such as an alkyne function. We describe herein our preliminary results concerning the novel and diastereoselective tandem gold-catalyzed carbocyclization reaction through Friedel–Crafts-type and cycloisomerization transformations.

Initial experiments were performed using enyne **1** and 1,3-dimethoxybenzene, and a selection of significant examples are shown in Table 1. When the reaction was attempted using

Table 1: [M]-catalyzed addition of 1,3-dimethoxybenzene to enyne **1**.[a]



Entry	Catalyst	$AgSbF_6$ [mol%]	Solvent	Conv. (Yield) [%]
1	$AuCl_3$	9	Et_2O	-
2	$PtCl_2$	6	Et_2O	-
3	AuCl	3	Et_2O	17
4[b]	$AuCl_3/PPh_3$	9	Et_2O	100
5	$[PPh_3AuCl]$	3	Et_2O	100 (73)
6	$[PPh_3AuCl]$	3	CH_3CN	<10
7	$[PPh_3AuCl]$	3	CH_2Cl_2	100[c]

[a] General conditions: 3 equiv of 1,3-$(MeO)_2C_6H_4$, solvent (2.5 mol **1** L^{-1}) [b] 3 mol% PPh_3. [c] The internal isomerized alkene was detected in 10% yield.

$AuCl_3$, AuCl, $PtCl_2$, or $Sc(OTf)_3$ as the catalyst in diethyl ether at room temperature, no conversion was observed. However, the addition of silver salts, known to be halide-sequestering agents, induced appreciable activity in the case of the Au^I catalyst precursor (Table 1, entry 3). The combination of Au^I or Au^{III} precursors, additional phosphine ligands (such as triphenylphosphine), and silver salts provided the best results (Table 1, entries 4 and 5). The use of 3 mol% of the commercially available $[PPh_3AuCl]$ with 3 mol% of $AgSbF_6$ was found to be the best reproducible system, and the functionalized alkene **2** was isolated in 73% yield (Table 1, entry 5). The choice of the solvent influenced both the activity and the selectivity of the catalytic system. Acetonitrile inhibited the reaction (Table 1, entry 6), whereas dichloromethane (Table 1, entry 7) afforded the side product resulting from the internal isomerization of the alkene. The desired cyclic derivative **2** was detected as a unique stereoisomer (Table 1, entry 5).[10] The structure of **2** was fully characterized by NMR spectroscopy, and the stereochemistry of the reaction was unambiguously established by X-ray analysis of the related derivative **12** (Figure 1 and Table 2, entry 3).

It is noteworthy that the remarkable addition of the aromatic ring to the alkene is completely chemoselective. No traces of the product resulting from addition of the aromatic ring to the alkynyl moiety[7] were detected, and the presence of the electron-rich aromatic ring completely inhibits the well-documented cycloisomerization reactions.[9]

Interestingly, in the absence of a nucleophile, enyne **1** rapidly forms the well-known cyclized products **3** and **4**, which result from a metathesis-type reaction for **3** and a 6-*endo* cyclization for **4**, both in CH_2Cl_2[9] or in diethyl ether (Scheme 1).

The compatibility of the $[PPh_3AuCl]/AgSbF_6$ system with various enyne substrates and its efficiency in the presence of other nucleophiles were then examined (Table 2). The addition of 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene to substrates in which $Z = C(CO_2Me)_2$, $C(SO_2Ph)_2$, O, or

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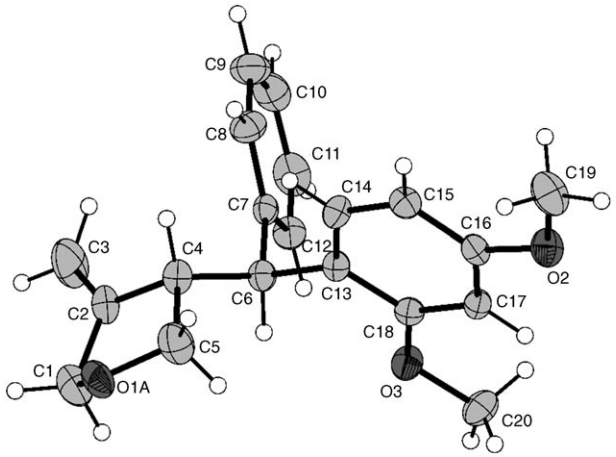


Figure 1. Molecular structure of alkene **12** with thermal ellipsoids set at the 30% probability level.

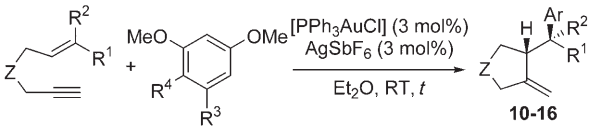
NTs (Ts = toluene-4-sulfonyl) afforded the desired alkenes **10**–**15** in good to excellent yields (Table 2, entries 1–6).

The bissulfone derivate **6** with a trisubstituted alkenyl side chain also reacted very cleanly and rapidly to give the corresponding alkene **15** in 72% yield (Table 2, entry 6). Nucleophilic aromatic halides proved to be compatible reaction partners, since the addition of 1-bromo-2,4-dimethoxybenzene to compound **7** led to the functionalized alkene **16** in 63% yield (Table 2, entry 7).

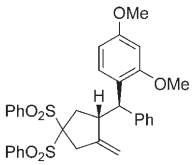
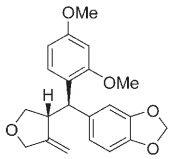
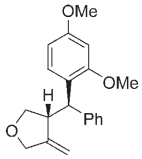
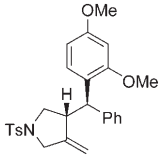
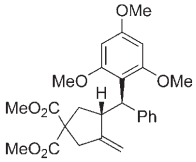
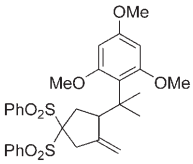
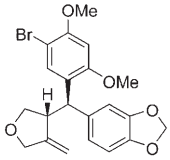
Electron-rich heteroaromatic derivatives have also been studied (Table 3). Indoles are found in many pharmaceuticals and have been described as nucleophiles in gold-catalyzed reactions to form C–C bonds.[3d,7h,r] Both methyl-substituted and nonsubstituted indoles were suitable nucleophiles for the tandem Friedel–Crafts-type addition and carbocyclization reactions. The corresponding *N*-methylindoles **17**–**20** were obtained in 47–99% yield (Table 3, entries 1–4). The addition of indoles was also possible for both carbon- and oxygen-tethered enynes, and led to the functionalized cyclic alkenes **21**–**23** in 43–99% yield (Table 3, entries 5–7). The regioselectivity in the C3 position was confirmed by comparison with other substituted derivatives.[7h,r] Pyrrole was also an excellent candidate for the tandem reaction, and the expected 2- and 3-substituted isomers **24a**,**b** and **25a**,**b** were isolated in overall yields of 58% and 90%, respectively (Table 3, entries 8 and 9).

On considering the mechanism, the first generally proposed step[6] is the formation of a cationic gold catalyst in the presence of the silver salt (Scheme 2). The complexation of the Lewis-acidic cationic gold catalyst to the alkyne function leads to intermediate **A**. The cyclization step may then occur directly through a concerted diastereoselective Friedel–Crafts-type addition/carbocyclization sequence leading to the vinylaurate intermediate **C**, or may proceed by stereoselective attack of the nucleophile on a transient carbenic species **B**, as proposed in several metal-catalyzed cycloisomerization reactions.[4e,8b,11] The final step would be the protodemetalation of the aurate intermediate. However, the actual reaction pathway cannot yet be confirmed. The process is completely stereoselective,[12] since the deuterated enyne

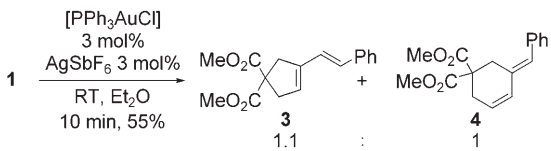
Table 2: Gold-catalyzed diastereoselective tandem addition/carbocyclization of aromatic derivatives to functionalized enynes.



1: Z = $C(CO_2Me)_2$, R^1 = Ph, R^2 = H; **5**: Z = $C(SO_2Ph)_2$, R^1 = Ph, R^2 = H
6: Z = $C(SO_2Ph)_2$, R^1 = Me, R^2 = Me; **7**: Z = O, R^1 = 3,4-$(OCH_2O)C_6H_3$, R^2 = H
8: Z = O, R^1 = Ph, R^2 = H; **9**: Z = NTs, R^1 = Ph, R^2 = H
R^3 = H, OMe, R^4 = H, Br

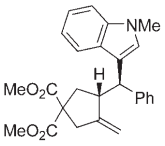
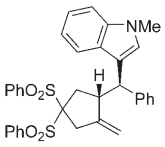
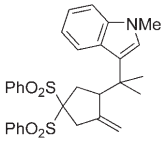
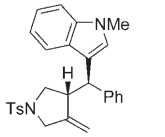
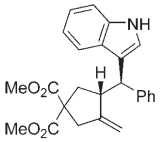
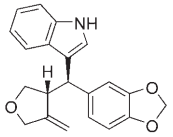
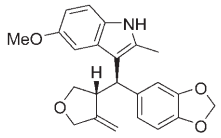
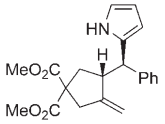
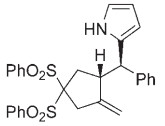
Entry	Substr.	*t* [h]	Product		Yield[a] [%]
1	**5**	2		**10**	99
2	**7**	0.5		**11**	91
3	**8**	2.5		**12**	50
4	**9**	2.5		**13**	60
5	**1**	1		**14**	68
6	**6**	1		**15**	72
7	**7**	2.5		**16**	63

[a] Yield of isolated product.



Scheme 1. Au-catalyzed cycloisomerization of enyne **1**.

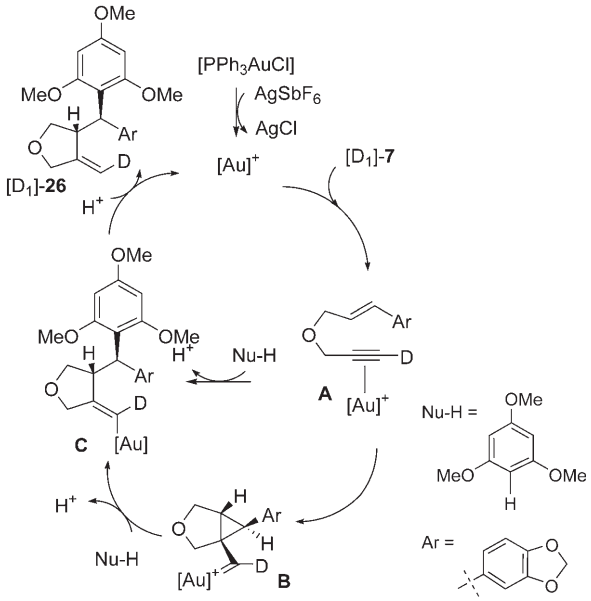
Table 3: Gold-catalyzed diastereoselective tandem addition/carbocyclization of heteroaromatic derivatives.

Entry	Substr.	*t* [h]	Product		Yield[a] [%]
1	**1**	0.5		**17**	81
2	**5**	3.5		**18**	99
3	**6**	2		**19**	82
4	**9**	6		**20**	47[b]
5	**1**	2		**21**	68
6	**7**	2.5		**22**	99
7	**7**	2.5		**23**	43
8	**1**	1		**24a**	47[c]
9	**5**	2		**25a**	80[d]

[a] Yield of isolated product. [b] 10 mol% catalyst, 40°C. [c] The 3-pyrrole derivative **24b** was also isolated in 11% yield. [d] The 3-pyrrole derivative **25b** was also isolated in 10% yield.

$[D_1]$-**7** (>95% D)[4e] underwent a clean tandem reaction in the presence of $[PPh_3AuCl]/AgSbF_6$ (3 mol%) and three equivalents of 1,3,5-trimethoxybenzene to afford the deuterated alkene $[D_1]$-**26** (Scheme 2). The alkene (with >95% D determined from the ^1H NMR spectrum of the crude product) was isolated in 54% yield.

In summary, we have developed an efficient and atom-economical method for the synthesis of cyclic and functionalized carbo- and heterocycles. The $[PPh_3AuCl]/AgSbF_6$ catalytic system promoted a novel diastereoselective tandem Friedel–Crafts-type addition of electron-rich aromatic and heteroaromatic derivatives to unactivated alkenes, followed by a C–C bond cyclization reaction. The efficiency of this system allowed the reactions to be carried out at room temperature with short reaction times. The compatibility of the reaction conditions with a bromo-substituted nucleophile would allow further metal-catalyzed cross-coupling reactions. The development of an asymmetric version of this reaction and the extension of this methodology to other nucleophiles are currently under investigation in our laboratory.



Scheme 2. Proposed mechanism and intermediates.

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