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Gold(I)-Catalyzed Functionalization of Benzhydryl C(sp^3)–H Bonds

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Abstract: The selective activation/functionalization of benzhydryl C(sp^3)–H bonds is documented. The gold complex $XPhosAuNTf_2$ turned out to be an efficient catalyst (5 mol%) to transform readily available propargylic esters into di- or trisubstituted naphthalenes in high yield. A 1,5-hydride shift is postulated as the key step of the cascade reaction sequence.

Keywords: C–H functionalization; gold catalysis; 1,5-hydride shift; naphthalenes

The selective functionalization of unactivated C(sp^3)–H bonds is currently a hot topic in modern organic synthesis.[1] Step, atom and redox economies are positively affected by introducing the direct manipulation of unfunctionalized C(sp^3)–H bonds with implications also for the total synthesis of structurally complex molecular architectures.[2]

1,5-Hydride transfer (HT) is a well-consolidated methodology to accomplish regioselective C–H modifications *via* LA (Lewis acid), BA (Brønsted acid) or amino-catalyzed intramolecular migration of hydride species to pre-installed electrophilic centers.[3] Generally, the so formed highly reactive cationic intermediate can be trapped by the newly generated organic or organometallic nucleophiles. When π-systems are utilized as hydride acceptors, carbophilic late-transition metal (LTM) species are conventionally employed in order to ensure an adequate electrophilic activation of the unsaturated hydrocarbon moiety.[4]

In this research segment, cationic gold(I) complexes[5] have already proven competence in triggering 1,5-hydrogen sigmatropic shifts of -OR and -NR_2 *stabilized* C(sp^3)–H bonds onto alkynes or allenes.[6,7] Moreover, a complementary approach based on a structurally "facilitated" strategy has been recently reported by Barluenga and co-workers.[8] On the contrary, [Au]-catalyzed hydride transfer from benzyl or benzhydryl C–H bonds has been considerably less investigated.[9]

As part of our ongoing interest toward the development of gold-catalyzed manipulations of propargylic derivatives,[10] we decided to investigate the suitability of synthetically flexible propargylic esters as valuable hydride acceptors under gold assistance.[11] As a matter of fact, the well-recognized and predictable gold promoted 1,3-OXO migration of propargylic esters would lead to the corresponding allenoates that can undergo further manipulations *via* nucleophilic attack (Figure 1).[12,13]

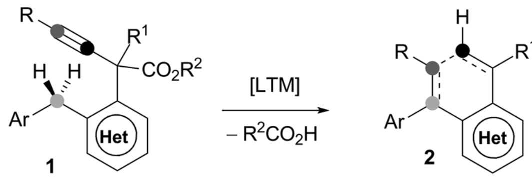


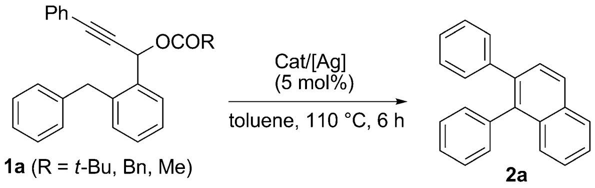
Figure 1. Planning a new synthetic tool for the regioselective functionalization of small acenes.

Accordingly, we envisioned that the readily accessible benzhydrylic substrates **1** could open new synthetic enterprises towards small acenes **2**, *via* metal-catalyzed C(sp^3)–H bond activation/functionalization reactions.

In this regard, it should be emphasized that naphthalenes and hetero-substituted analogues continue to play a major role both in catalysis[14] and molecular organic electronics.[15] Therefore, the current request for effective and site-selective synthetic routes to condensed arenes is not surprising.[16]

At the outset of the catalyst optimization, a range of σ- as well as π-acids was screened with the model compound **1a** (R = *t*-Bu) and the resulting outcomes are listed in Table 1.

Table 1. Optimization of reaction conditions.[a]



Run	Catalyst	[Ag]	**1a** (R)	Yield of **2a** [%][b]
1	$FeCl_3$	–	**1a** (*t*-Bu)	15
2	$In(OTf)_3$	–	**1a** (*t*-Bu)	Nr
3	$PdCl_2$	–	**1a** (*t*-Bu)	27
4	AgOTf	–	**1a** (*t*-Bu)	nr
5	TfOH	–	**1a** (*t*-Bu)	decomp.
6	$HNTf_2$	–	**1a** (*t*-Bu)	–[c]
7	$PtCl_2$	–	**1a** (*t*-Bu)	66
8	$PtCl_2$	AgOTf	**1a** (*t*-Bu)	–[d]
9	$AuCl_3$	–	**1a** (*t*-Bu)	56
10	PPh_3AuCl	AgOTf	**1a** (*t*-Bu)	18
11	PPh_3AuCl	$AgPF_6$	**a** (*t*-Bu)	34
12	PPh_3AuNTf_2	–	**1a** (*t*-Bu)	61
13	$(pCF_3C_6H_4)_3PAuCl$	$AgNTf_2$	**1a** (*t*-Bu)	36
14	IPrAuCl	$AgNTf_2$	**1a** (*t*-Bu)	77
15	$JhonPhosAuNTf_2$	–	**1a** (*t*-Bu)	54
16	***$XPhosAuNTf_2$***	**–**	***1a (t-Bu)***	***91***
17	$XPhosAuNTf_2$	–	**1a** (Me)	57
18	$XPhosAuNTf_2$	–	**1a** (Bn)	50
19[e]	$XPhosAuNTf_2$	–	**1a** (*t*-Bu)	traces
20[f]	$XPhosAuNTf_2$	–	**1a** (*t*-Bu)	45

[a] All the reactions were carried in anhydrous toluene, under a nitrogen atmosphere unless otherwise specified.
[b] Isolated yield after flash chromatography.
[c] Room temperature.
[d] A complex mixture of unknown products was obtained.
[e] Reaction temperature: 60 °C.
[f] Reaction time: 1 h. Decomp. = decomposition, Nr = no reaction, JhonPhos = (2-biphenyl)di-*tert*-butylphosphine, XPhos = dicyclohexyl{2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]phosphine}, IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

Notably, while Brønsted acids (i.e., TfOH, $HNTf_2$) and common σ-Lewis acids [i.e., $FeCl_3$, $In(OTf)_3$] did not provide 1,2-diphenylnaphthalene **2a** in synthetically acceptable isolated yields, late-transition metal species furnished promising results with particular regard to [Pt(II)], [Pd(II)], [Au(III)] and [Au(I)] salts (entries 3, 7, 9, and 12). Among them, $PtCl_2$ and PPh_3AuNTf_2 furnished the higher yields of **2a** in refluxing toluene (66%, 61%, respectively).

Delightfully, optimization of the [Au(I)] source led to commercially available well-defined silver-free $XPhosAuNTf_2$[17] as the optimal catalyst providing **2a** in nearly quantitative yield (91%, entry 16), although satisfying results were obtained also with cationic carbene-based gold species *i*-PrAuCl/$AgNTf_2$ (yield = 77%, entry 14).[6c,18] Different ester derivatives such as phenylacetate (**1a**, R = Bn) and acetate (**1a**, R = Me) were also tested, but naphthalene **2a** was always isolated in lower yields (entries 17 and 18). Finally, attempts to perform the reaction at lower temperature (60 °C, entry 19) or shorten the reaction time (1 h, entry 20) resulted into unsatisfactory outcomes.[19,20]

Interestingly, the high chemoselectivity towards naphthalene synthesis guaranteed by $XPhosAuNTf_2$ should be emphasized, showing a net preference of the 1,5-hydride transfer event *vs.* alternative hydroarylation processes as elegantly described by Nolan and co-workers for similar substrates.[21]

Having established the catalytic system, the generality of the protocol was then assessed by subjecting a range of benzhydryl derivatives (**1b–1p**) to the ring-closing process. A collection of results is summarized in Figure 2.

Propargylic esters derived from secondary alcohols (**1b–1k**) were firstly examined. Interestingly, a range of EWG and EDG substituents were adequately tolerated in different positions of the benzhydrylic unit and acetylene terminals.[22]

Also *ortho*-substituted aromatic rings proved suitable in the model protocol (i.e., **2f**, yield = 82%; **2j**, yield = 89%).

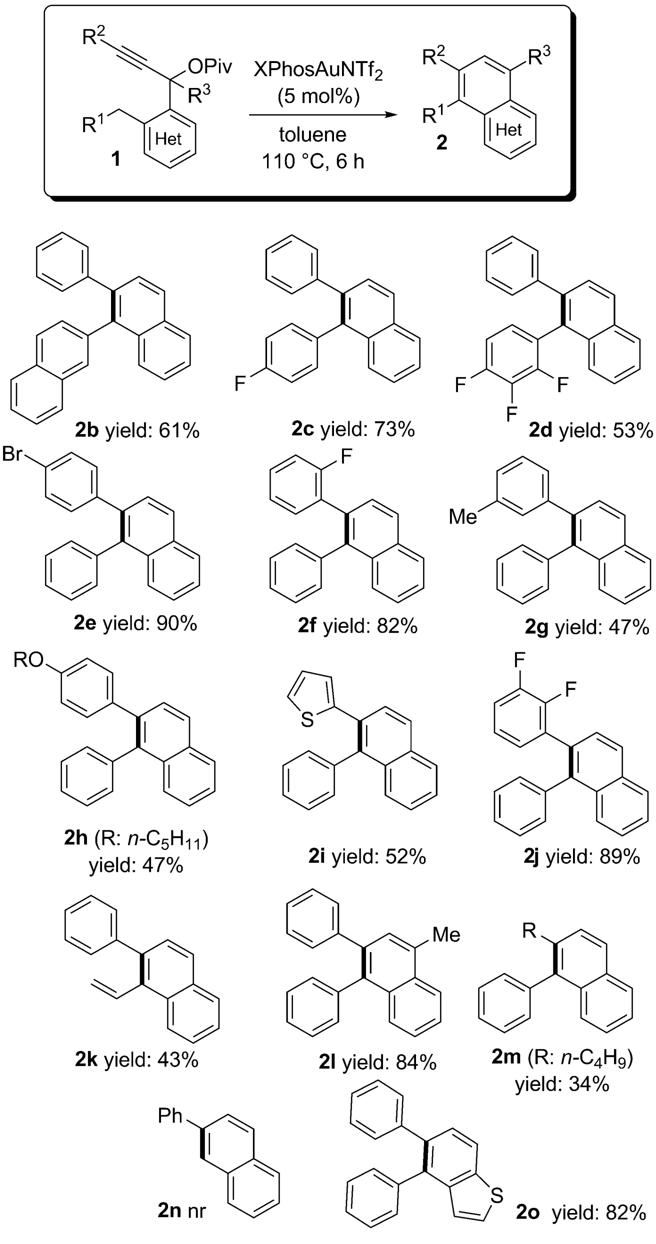


Figure 2. Proving the scope of the reaction. [In bold the interatomic connections formed during the cascade process. Nr: no reaction].

Interestingly, 1,2,4-trisubstituted naphthalene **2l** was also readily accessible in regioselective manner and acceptable yield (84%).

It is worth noting that the 1,5[H]-transfer reaction worked satisfactorily not only with benzhydryl frameworks but also in the presence of the allylbenzene derivative **1k**, delivering 2-phenyl-1-vinylnaphthalene **2k** in 43% yield. Contrarily, *ortho*-tolyl motifs did not undergo activation of the corresponding benzylic C(sp^3)–H bonds (**2n**: no reaction). Finally, the suitability of the present protocol toward the realization of substituted heteroarenes was ascertained with the synthesis of 4,5-diphenylbenzo[*b*]thiophene **2o** in 82% isolated yield.

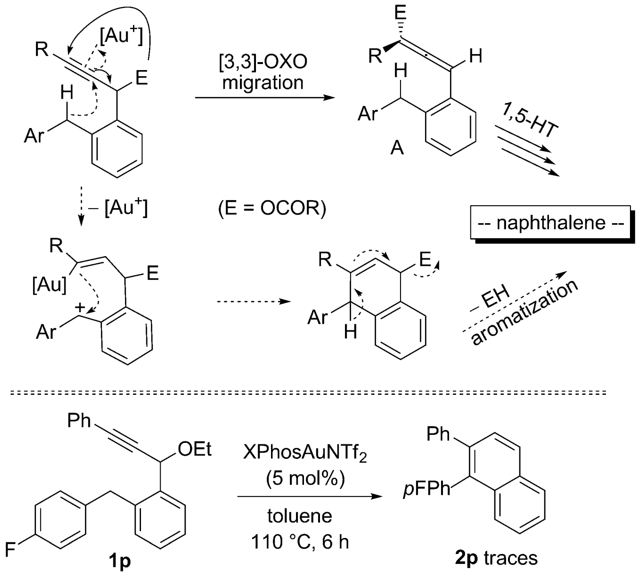


Figure 3. Possible reaction pathways for the initial hydride transfer event.

Mechanistically, two distinct reaction pathways can be envisioned. Specifically, the gold-triggered 1,5-hydride migration could directly involve the electrophilically activated alkynes (dashed lines) or the allenoate **A** originated from [Au(I)]-assisted [3,3]-sigmatropic rearrangement of the internal propargylic ester (plain lines, Figure 3).[12]

Although a conclusive mechanistic rationale is still not available, the inertness of the propargylic ethyl ether **1p** towards the transformation employing the best conditions (Figure 3) led us to hypothesize the initial formation of the allenoate as the more likely.[23] Additionally, the disappointing outcomes recorded with Brønsted acids (entries 5 and 6, Table 1) might rule out the initial formation of a propargylic cationic species.[24]

Accordingly, we can speculate that the 1,5-hydride migration would involve the C-2 position of the allenyl unit,[25] leading to either alkyl-[Au(I)] species (**B**) that could intercept intramolecularly the stabilized benzhydrylic carbocation intermediate (dashed lines, Figure 4) or the formal "triene" **C** followed by a [4+2] cycloaddition process (plain lines, Figure 4).[13,26]

In order to get more insight into the reaction profile, some deuterium-labelling experiments were carried out. In particular by subjecting [D_2]-**1a** to the gold-catalyzed cascade process we unambiguously demonstrated the intramolecular 1,5-hydride sigmatropic shift of one hydride atom from the benzhydryl position to the 3(β′)-position of the naphthalene ring (formally the C-2 of the allenoate intermediate **A**).

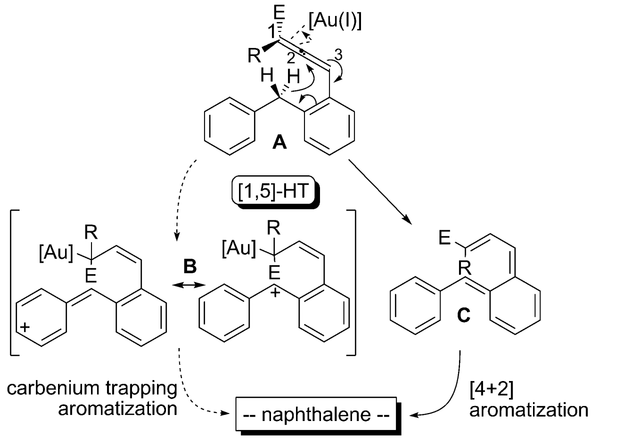
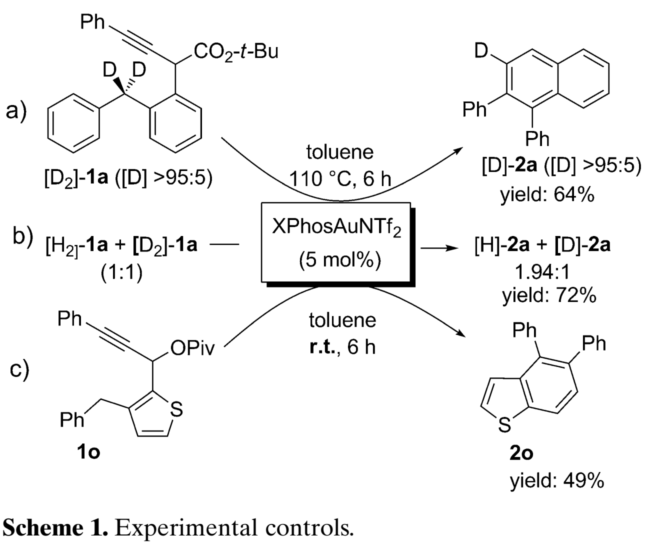


Figure 4. Possible reaction machineries for the C-C forming ring-closing event.

Moreover, the full deuterium incorporation at the C-3 position of **2a** allowed us to measure a kinetic isotopic effect (k_H/k_D), by monitoring the reaction course of a 1:1 mixture of $[H_2]$- and $[D_2]$-labelled **1a**. Interestingly a primary isotopic effect $k_H/k_D = 1.94$[27] was recorded supporting the C–H cleavage as the rate-determining event of the whole process (Scheme 1b). This evidence is also in agreement with the moderate reactivity of the thienyl-substrate **1o** at room temperature (Scheme 1c, yield = 49%), that could be rationalized in terms of increased stabilization of the transient electrophilic species **B** or triene **C**.

In conclusion, we have documented an unprecedented synthesis of substituted bicyclic fused aromatic systems *via* a gold(I)-catalyzed 1,5-HT reaction. The methodology impacts the current synthetic scenario of modular preparation of substituted di- and trisubstituted arene and heteroarene derivatives in high yields. Further mechanistic studies and applications of this gold-catalyzed $C(sp^3)$–H bond functionalization towards the preparation of different heterocyclic scaffolds are currently underway in our laboratory.



Scheme 1. Experimental controls.

Experimental Section

General Procedure

The reaction was carried out under anhydrous conditions. The flask was charged with 1 mL of dry toluene, 0.1 mmol of the desired propargylic ester **1** and XPhosAuNTf$_2$ (5 mol%). The reaction flask was placed in a pre-warmed oil-bath at 110 °C and the reaction mixture stirred at the same temperature until complete consumption of the starting material was ascertained by TLC. The crude reaction mixture was then charged onto a plug of silica for chromatographic purification (see the Supporting Information for details).

Acknowledgements

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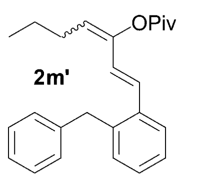

2m′

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