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Gold-Catalysed Highly Chemo- and Regioselective C-H Bond Functionalization of Phenols with Haloalkynes

M.Sc. Tapas Adak,[a] M.Sc. Jürgen Schulmeister,[a] B.Sc. Martin Dietl,[a] Dr. Matthias Rudolph,[a] Dr. Frank Rominger,[a] Prof. Dr. A. Stephen K. Hashmi*.[a,b]

[a]Organisch-Chemisches Institut, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail:hashmi@hashmi.de
Homepage: http://www.hashmi.de

[b]Chemistry Department, Faculty of Science
King Abdulaziz University
Jeddah 21589 (Saudi Arabia)

Abstract: A highly chemo- and stereoselective addition of unprotected phenols to haloalkynes was developed. A ligand and counter ion controlled process enabled the highly site-selective and chemoselective C-H bond functionalization of phenol derivatives with haloalkynes in moderate to excellent yield at room temperature. The simple availability of the starting materials in combination with the preferred *para*-C-H functionalization over a competing O-H insertion makes this an attractive protocol. The stereo-selectivity of the products depends on the choice of the catalyst. From a synthetic prospective, this method offers an efficient route towards β-haloalkenes which are valuable precursor for the synthesis of pharmaceutical drugs.

Keywords: addition reactions, alkynes, diastereoselectivity, gold, vinyl halides

Introduction

The development of new synthetic strategies by employing simple and readily accessible starting materials under mild conditions (e.g. at room temperature) has great impact on organic chemistry. In this regard gold catalysis has proven to be a suitable tool for the design and development of new and valuable chemical transformations.[1] Chemo- and site-selective catalytic transformations are an interesting topic in synthetic chemistry.[2] Here we report the direct chemo- and site-selective C-H functionalization of unprotected phenols with haloalkynes by using the readily available cationic IPr-gold(I) complex at room temperature.[3]

Aryl-substituted alkenes bearing phenol substituents are versatile intermediates in organic synthesis and important structural motifs in natural products and pharmaceuticals.[4] Drugs that contain such a structural motif are for example Isocombrestatine A, Bexarotene, Panomifene, Tamoxifen and Ratanhine (Scheme 1). Moreover, Diarylethenes are present in photo-responsive molecular switch-machines and medicines.[5] Chloroalkenes as synthetic intermediates are very important synthons due to the presence of an easy transformable synthetic handle. For examples, chloroalkenes have been exploited as key building blocks for natural products such as a Pan-Bcl-2-Inhibitor (Scheme 1) and Hartellines.[6] Therefore a site-selective direct C-C coupling of phenols is of high interest.

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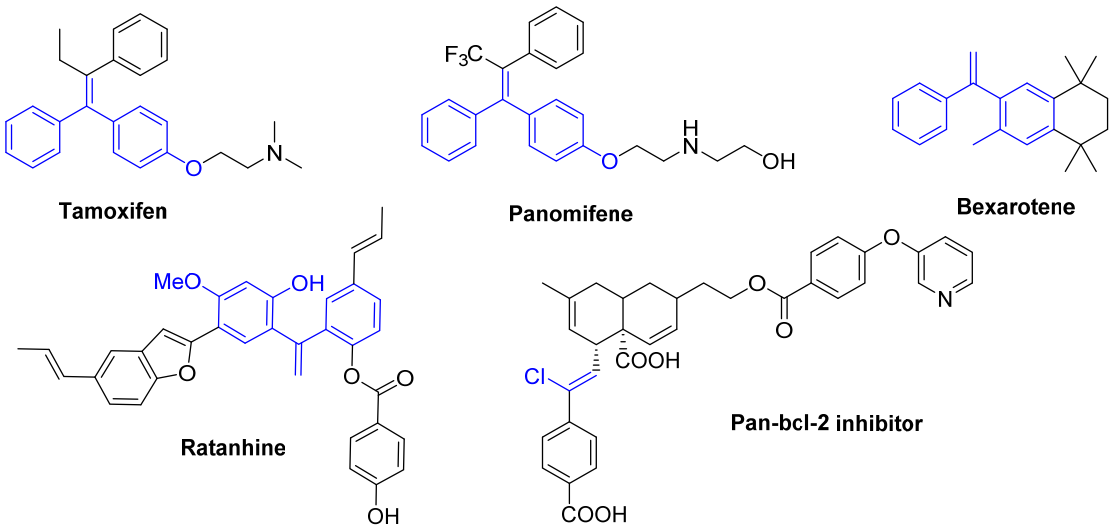

Scheme 1. Drugs and natural compounds containing aryl olefins

In the past decade, many indirect methodologies for the C-C coupling of phenols have been developed, these are based on introduction of directing groups.[7] Nevertheless, the improvement of a direct C-C coupling of unprotected phenols would significantly enhance the synthetic potential. Recently, Bedford investigated a Rh-catalysed direct *ortho*-selective C-H arylation of phenols by using catalytic amounts of phosphite as traceless directing group.[8] Dong and co-workers reported a Pd-catalysed *ortho* arylation of phenols by using carbamate as directing group.[9] Another pioneering work by Larrosa includes a palladium-catalysed *meta*-selective C-H arylation of phenols by using carbon dioxide as traceless relay directing group.[10] Zhang developed a $B(C_6F_5)_3$-catalyzed *ortho*-alkylation.[11] Very recently, Zhang's[12] and Shi's[13] groups developed a gold-catalysed site-selective C-H functionalization of phenols with highly reactive gold carbenes derived from aryl diazo-acetate precursors. The C-O coupling of chloroalkynes and phenols under basic conditions has been reported by many groups (Scheme 2a).[14] However the direct C-H arylation of phenols with an electrophile is quite challenging because of a competitive O-H bond insertion in the presence of various transition metal like Pd, Cu, Rh, Fe, Ir (Scheme 2b).[15] Recently, Nolan's group also reported a gold-catalysed C-O coupling of phenols and alkyne (Scheme 2b).[16] Herein we present the site-selective *para*-addition of phenols to chloroalkynes (Scheme 2c). Because of the carbophilic π-acidic nature[17] gold appeared promising the for a site-selective C-C coupling of haloalkynes and phenols.

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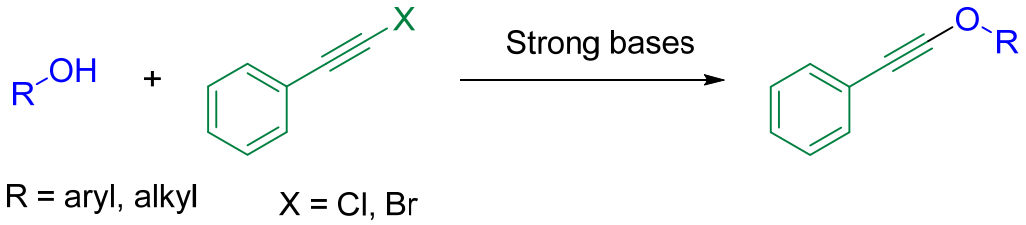
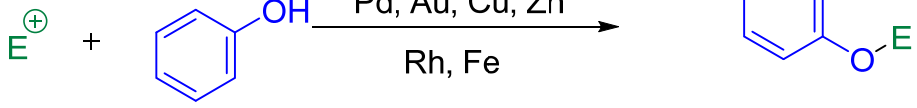
a) General reactivities for haloalkynes and phenols under basic condition



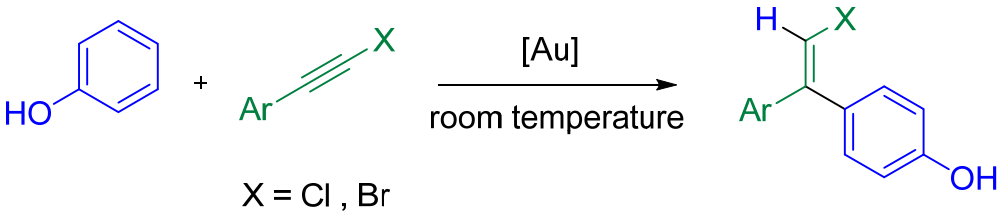
R = aryl, alkyl X = Cl, Br

b) Common regioselectivity for transition metal-catalysed reactions of phenol with carbon electrophiles



E = alkyne, diazo-ester

c) This Work: Chemo and stereo-selective addition of phenols to haloalkynes



X = Cl , Br

Scheme 2. Different reactivity modes for alkynes and phenols

Results and discussion

We started our investigation by exploring the reactivity of (chloroethynyl)benzene (**1a)** with phenol (**2a)** at room temperature as a model reaction. We were pleased to observe 46% yield of the *para*-addition product in a 3:5 (*E*:*Z*)-ratio in the presence of IPrAuCl (5 mol%) and $AgNTf_2$ (10 mol%) after 16 h in DCM (entry 1). By changing IPrAuCl to PPh_3AuCl, the yield of the reaction increased to 53% in a 9:10 (*E*:*Z*)-ratio (entry 2). A switch to bulkier ligands, improved the yield but not the (*E*:*Z*)-ratio in the case of $AgNTf_2$ as co-catalyst.[18] By changing the counter ion to $BARF^-$ in combination with IPr as ligand we were not only obtained 74% NMR yield (entry 4), but at the same time achieved a perfect diastereoselectivity at room temperature. From a brief screening of other ligands with $BARF^-$, we concluded that IPr was the best ligand for our protocol. A screening of solvent revealed that DCE (78% yield, entry 5) was more effective than DCM. Other polar solvents like acetonitrile, nitromethane (entries 7 and 8) were less effective. It is also noteworthy that in the presence of NaBARF as co-catalyst we were able to isolated a minor amount of C-O coupled product **4a** (entry 4), whereas in the presence of $AgNTf_2$ only a trace amount of C-O coupled product was observed at room temperature. We only isolated 77% acetate coupled product in presence of JohnPhosAuCl and acetic acid as solvent (entry 12) at 60 °C. Neither in the presence of NaBARF alone nor with only MsOH the reaction proceeded under these conditions (entries 13 and 14).

Table 1. Reaction Optimization

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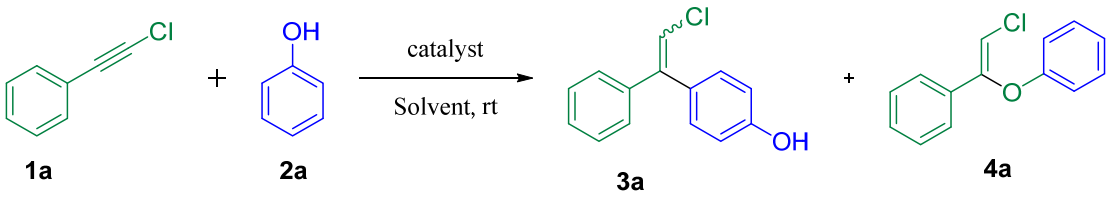

1a **2a** **3a** **4a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]	
				3a (E:Z)[b]	**4a[b]**
1	IPrAuCl (5 mol%) $AgNTf_2$ (10 mol%)	DCM	16	46 (3:5)	trace
2	PPh_3AuCl (5 mol%) $AgNTf_2$ (10 mol%)	DCM	16	53 (9:10)	trace
3	JohnPhosAuCl (10 mol%) $AgNTf_2$ (10 mol%)	DCM	16	49 (3:7)	trace
4	IPrAuCl (5 mol%) NaBARF (10 mol%)	DCM	3	74 (>99% Z)	10
5	IPrAuCl (5 mol%) NaBARF (10 mol%)	DCE	3	78 (>99% Z)	9
6[c]	IPrAuCl (2 mol%) NaBARF (3 mol%)	DCE	3	83 (79), (>99% Z)	9
7	JohnPhosAuCl (5 mol%) NaBARF (10 mol%)	DCE	24	37	ND
8	PPh_3AuCl (5 mol%) NaBARF (10 mol%)	DCE	24	trace	ND
10	IPrAuCl (5 mol%) NaBARF (10 mol%)	CH_3CN	24	-	ND
11	IPrAuCl (5 mol%) NaBARF (10 mol%)	CH_3NO_2	24	-	ND
12[d]	JohnPhosAuCl (5 mol%)	ACOH	24	-	ND
13	NaBARF (10 mol%)	DCE	24	-	ND
14	MSOH (10 mol%)	DCE		-	ND

Reaction Conditions: 0.2 mmol (**1a**), 0.24 mmol (**2a**) in 1 mL solvent at room temperature. [a]NMR yield using benzaldehyde as internal standard. Numbers in parentheses are isolated yields. [b]Calculated from the ^1H NMR of the crude reaction mixture. [c] 1.2 equiv of **1a**. [d]Reaction carried out at 60 °C

We must stress that under most of the other conditions an (*E*/*Z*)-mixture of the product was formed. This even applies to the Brettphos ligand, which in our hands provided a 1:1 mixture of diastereomers (Figure 1). Thus our results do not confirm the findings reported in the recent literature.[3]

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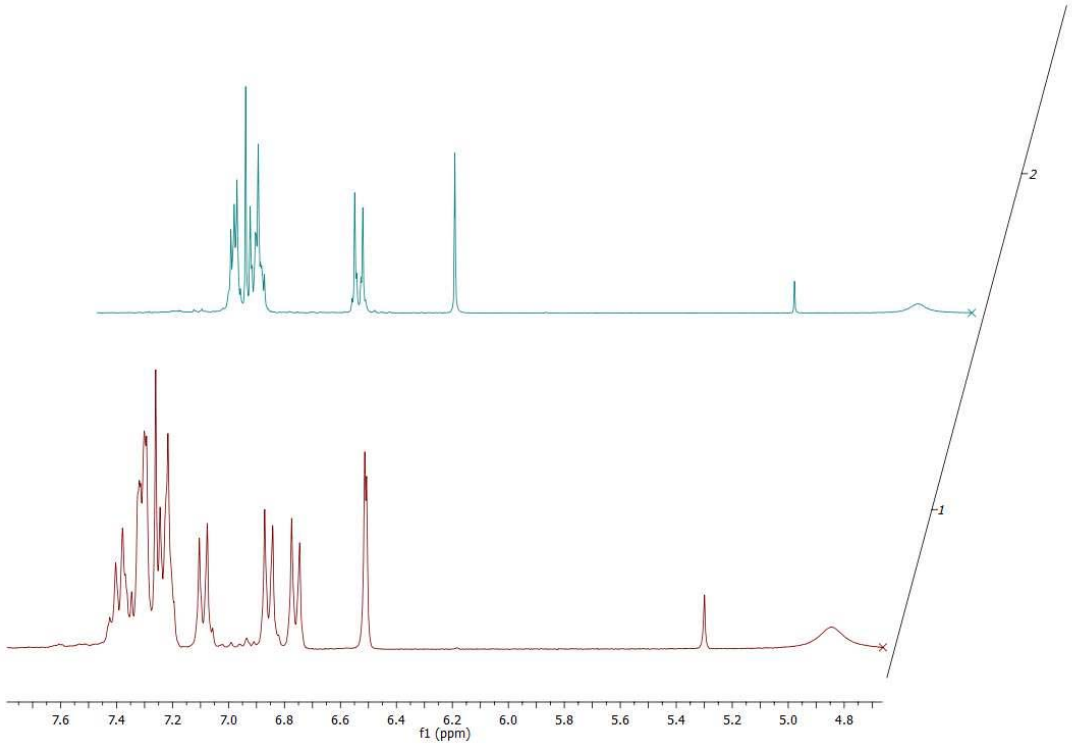

Figure 1. Comparison of the pure diasteromer (*Z*)-**3a** obtained by the optimized condition with the IPrAuBARF catalyst (top, blue) and the 1:1 mixture of the diastereomeric (*E*/*Z*)-mixture obtained with BrettPHOSAuBARF (bottom, red).

After recognizing this, we had to explore a possible subsequent but undesired rearrangement of the pure (*Z*)-**3a** obtained under our reaction conditions. Figure 2 (bottom) shows (*Z*)-**3a** at room temperature with 2 mol% of our catalyst in CD_2Cl_2, even after 12 h at room temperature (i.e. exactly the conditions for the synthesis of (*Z*)-**3a**) no isomerization to (*E*)-**3a** was observed. Finally, to be on the safe side, we heated this reaction mixture in a sealed NMR tube to 50°C for 4 h (i.e. the conditions used in the literature for the BrettPhosAuCl/NaBARF system), only traces of the (*E*)-diastereomer were detected.

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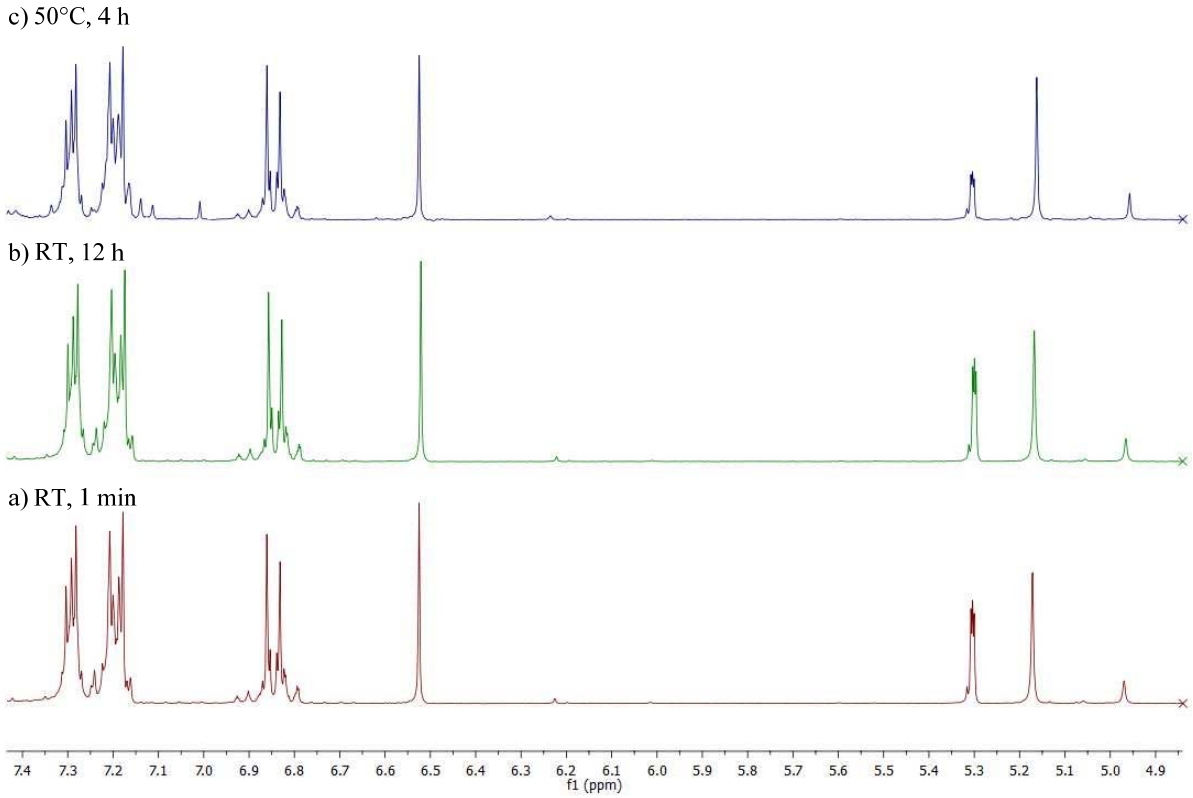

Figure 2. (*Z*)-**3a** with additional signals from 2 mol% IPrAuCl/ 4 mol% NaBARF in CD_2Cl_2 at RT: a) after 1 min (bottom); b) after 12 h (middle); c) at 50° C after 4 h.

Then we studied the reaction with the BrettPhosAuCl/NaBARF system in order to see whether also pure (*Z*)-**3a** is formed initially, but subsequently is rearranged to the observed (*Z*)/(*E*) mixture. The spectra show that even after 10 minutes when the conversion is not complete (*E*)-**3a** is already present ((*Z*)/(*E*) = 3:1). This stays the same until after 30 minutes the consumption of the starting materials is complete, then over the next hour a complete equilibration to (*Z*)/(*E*) = 1:0.93 is achieved, which does not change any more even after 2 h. This equilibrium ratio is in accord with our computations (vide infra). This experiment clearly demonstrates, that with the known BrettPhosAuCl/NaBARF system even at low conversion of the starting materials no pure diastereomers can be obtained.

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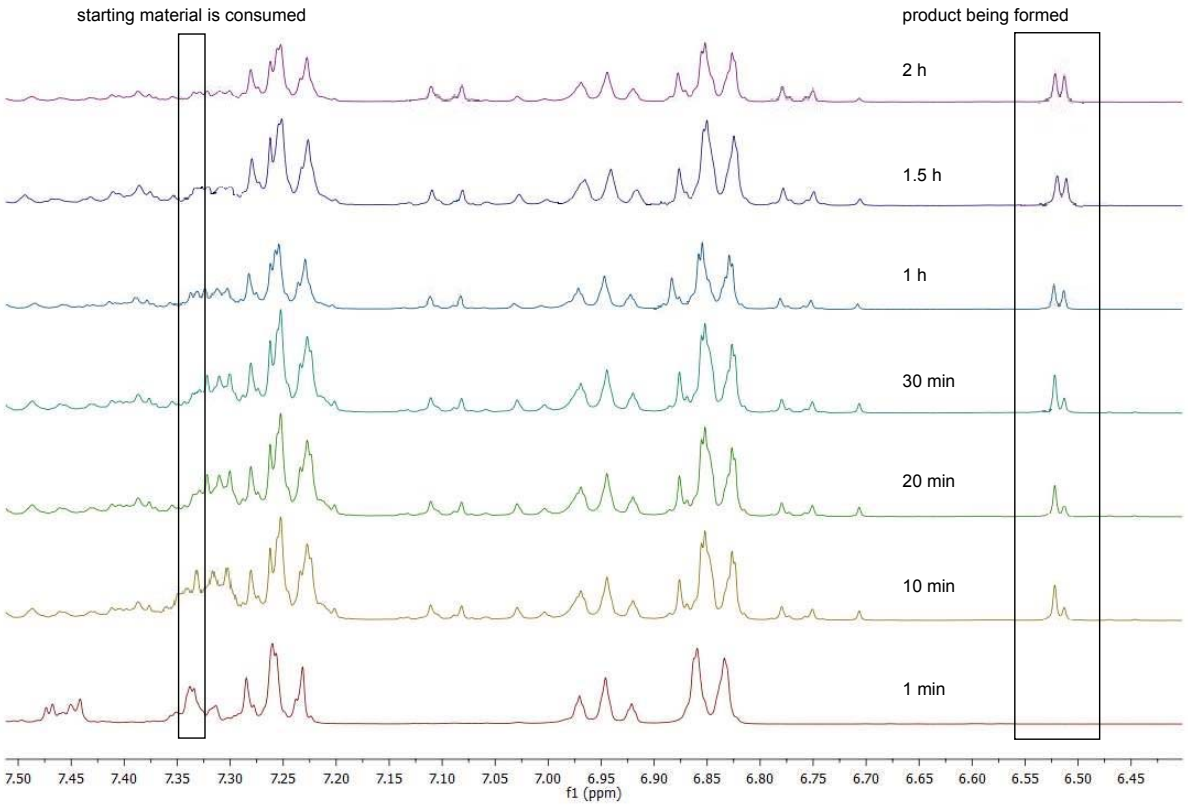

Figure 3. Conversion of (*Z*)-**3a** with 2 mol% BrettPhosAuCl / 4 mol% NaBARF in CD_2Cl_2 at 40°C followed by time from 1 min to 2 h.

With the optimal reaction conditions in hand, we investigated the scope of the gold-catalysed *ortho*/*para* selective C-H bond functionalization of chloroalkyne **1a** with varying phenols derivatives (Scheme 2). In a first series of *ortho*-substituted phenols, alkyl (**3b**, **3c**), methoxy (**3d**), allyl (**3e**) and aryl (**3f**) groups all delivered exclusively the *para*-addition products in good yields and with only one diastereomer (the one shown in Table 2). An additional substituent in *meta*-position was equally efficient (**3g**). In the case of only *meta*-substituted phenols, mixtures of *ortho*- and *para*-addition products were observed and yields were lower (**3h**, **3i**). 1,2-Dimethlyphenol delivered a better yield but also in low selectivity (**3j**). As expected a very efficient reaction (96% yield) was observed for 2,6-dimethylphenol (**3k**). Interestingly, 3,5-dimethlylphenol delivered only the *para*-addition product (**3l**). Catechol delivered an excellent yield of the *para*/*meta* product (**3m**). In a series of phenols with blocked *para*-position always *ortho*-addition at the sterically less hindered position was observed in yields ranging from 65%-98% (**3n**-**3t**).

Table 2. Scope with respect to the phenols

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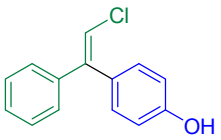
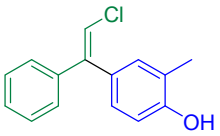
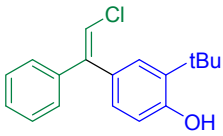


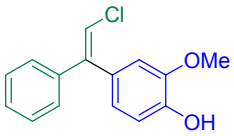
3a (79%)



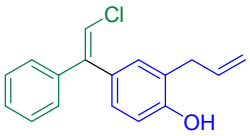
3b (84%)



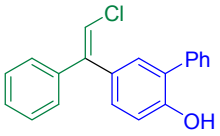
3c (86%)



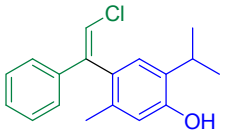
3d (93%)



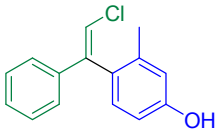
3e (68%)



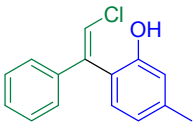
3f (77%)



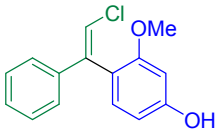
3g (73%)



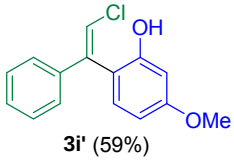
3h (51%)



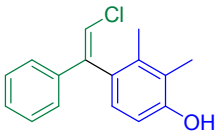
3h' (35%)



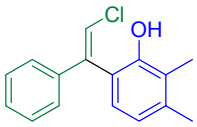
3i (32%)



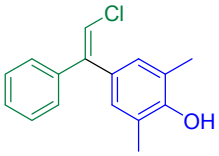
3i' (59%)



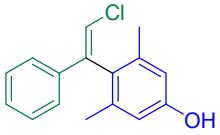
3j (60%)



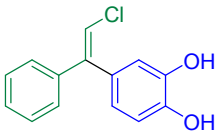
3j' (32%)



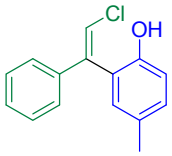
3k (96%)



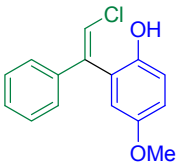
3l (78%)



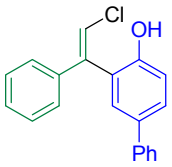
3m (98%)



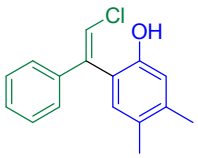
3n (73%)



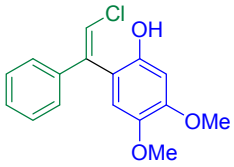
3o (80%)



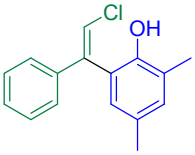
3p (77%)



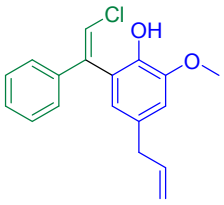
3q (89%)



3r (98%)



3s (77%)



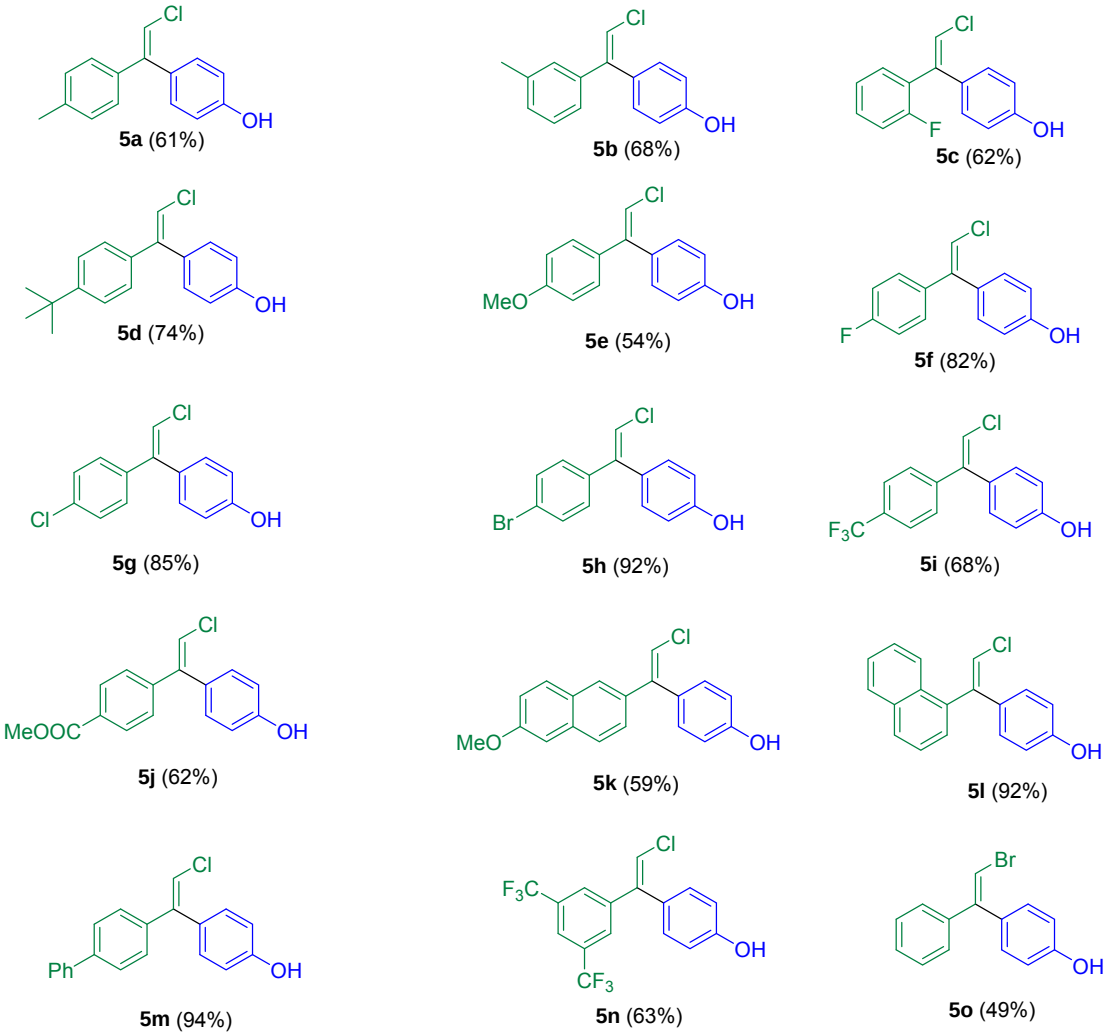
3t (65%)

General reaction conditions: **1a** (0.24 mmol), phenol (0.2 mmol), IPrAuCl (2 mol%), NaBARF (3 mol%) in 1 mL DCE at room temperature for 3-6 hours. Isolated yields are reported.

The scope with respect to the chloroalkynes was also investigated (Table 3). The substitution of the phenyl group of chloroalkyne **1a** has only a slight effect on the yield and selectivity of the reaction. Both electron-withdrawing and donating substituents at the chloroalkyne reacted smoothly with phenol (**2a**) to give the desired products (Table 3, entries **5a-o**) in good to excellent yields (49-94%). The reaction well tolerated functional groups including ester (**5j**), methoxy (**5e**), trifluoromethyl (**5i**) and halogens (**5c**, **5f**, **5g**, **5h**). Electron-deficient substituents at the phenyl ring of the chloroalkyne showed better results (**5f-i**) than electron-rich phenyl rings (**5a-b**, **5d-e**) and our protocol also well tolerates *ortho*- and *meta*-substituents at the arene ring attached to

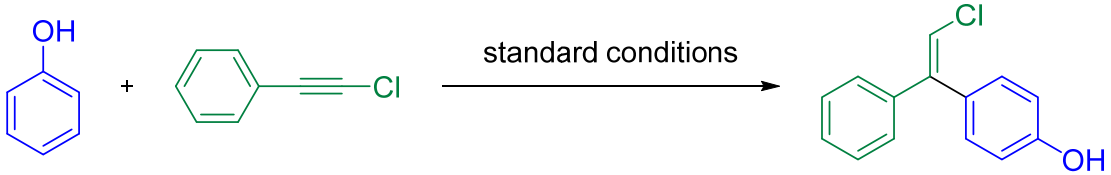
the alkyne (**5b-c, 5n**). Finally, it is noteworthy that chloroalkynes showed better reactivity than bromo alkynes (**5o**), which can be attributed to the higher electronegativity. The corresponding iodo alkyne did not react any more.

Table 3. Scope with respect to the haloalkynes



General reaction conditions: Chloroalkyne (0.24 mmol), **2a** (0.2 mmol), IPrAuCl (2 mol%), NaBARF (3 mol%) in 1 mL DCE at room temperature for 3-12 hours. Isolated yields are reported.

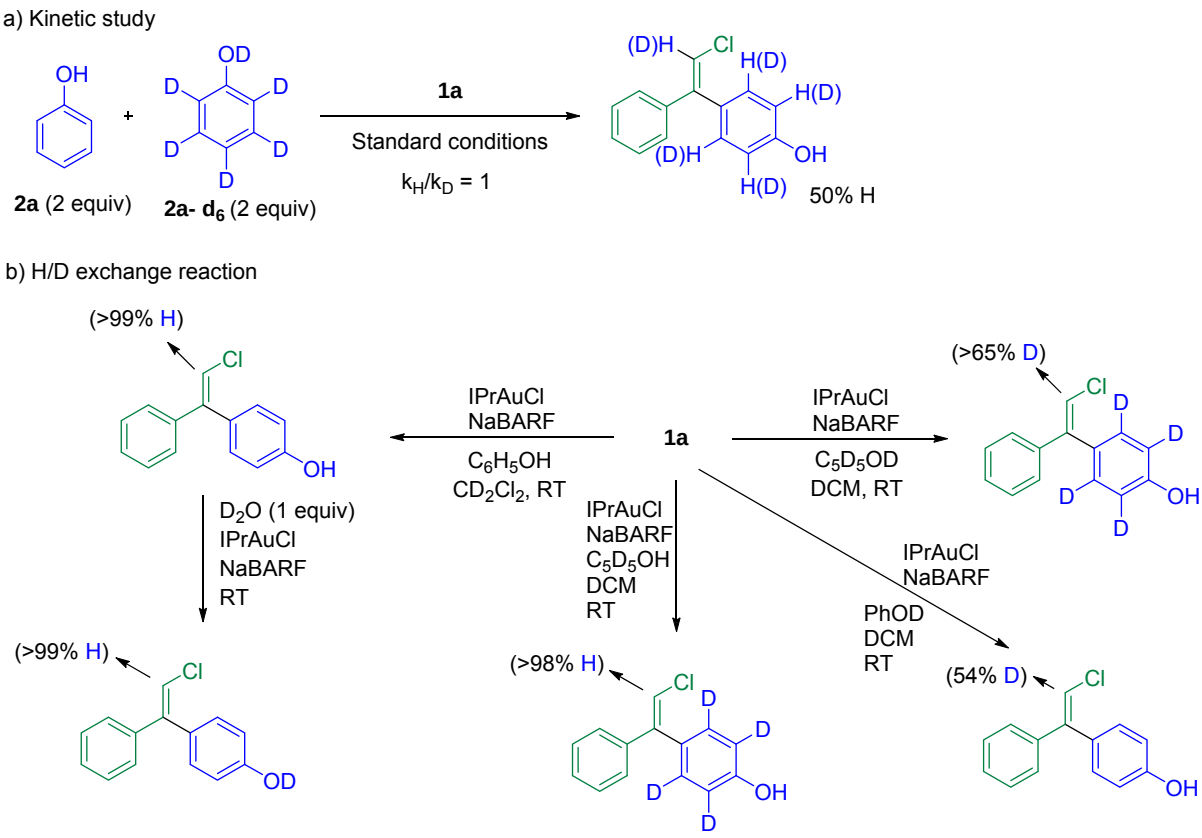
A gram-scale reaction of chlorophenyl acetylene **1a** (820 mg, 6 mmol) and phenol **2a** (471 mg, 5 mmol) was carried out with 2 mol% of gold catalyst and 3 mol% of NaBARF, furnishing 819 mg (71%) of the desired product **3a** (Scheme 3).



2a **1a** **3a** (71%)

Scheme 3. Gram-scale synthesis

Table 4. Preliminary mechanistic study



To gain mechanistic insight, several control experiments were carried out (Table 4). The observed *ortho*/*para* and (*E*/*Z*)-selectivity was confirmed by 2D NMR spectra (for details see supporting information) and by the results of the X-ray single crystal structure analysis (Figure 4).[19]

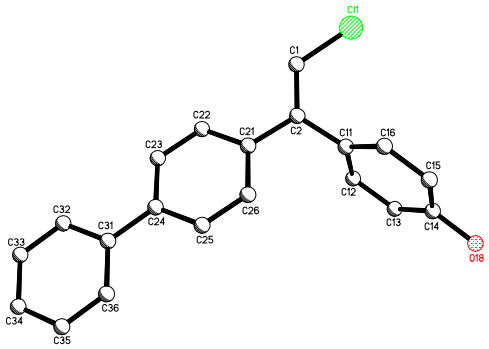


Figure 4. Solid state molecular structure of **5m**

In a preliminary competitive kinetic study no kinetic isotope effect was observed (Table 4a, for details see Supporting Information), revealing that the C-H bond cleavage of phenol is not involved in the rate determining step. Therefore a CH activation of the phenol by the gold is unlikely and the reaction should proceed via the nucleophilic addition of the phenol onto the π-activated alkyne. A series of experiments with deuterated starting materials and solvents revealed that no direct transfer of the proton released from the Wheland complex takes place instead exchange processes with either the acidic phenol group or traces of water in the reaction media take place. Based on the results we propose that the gold directly coordinates to the chloro

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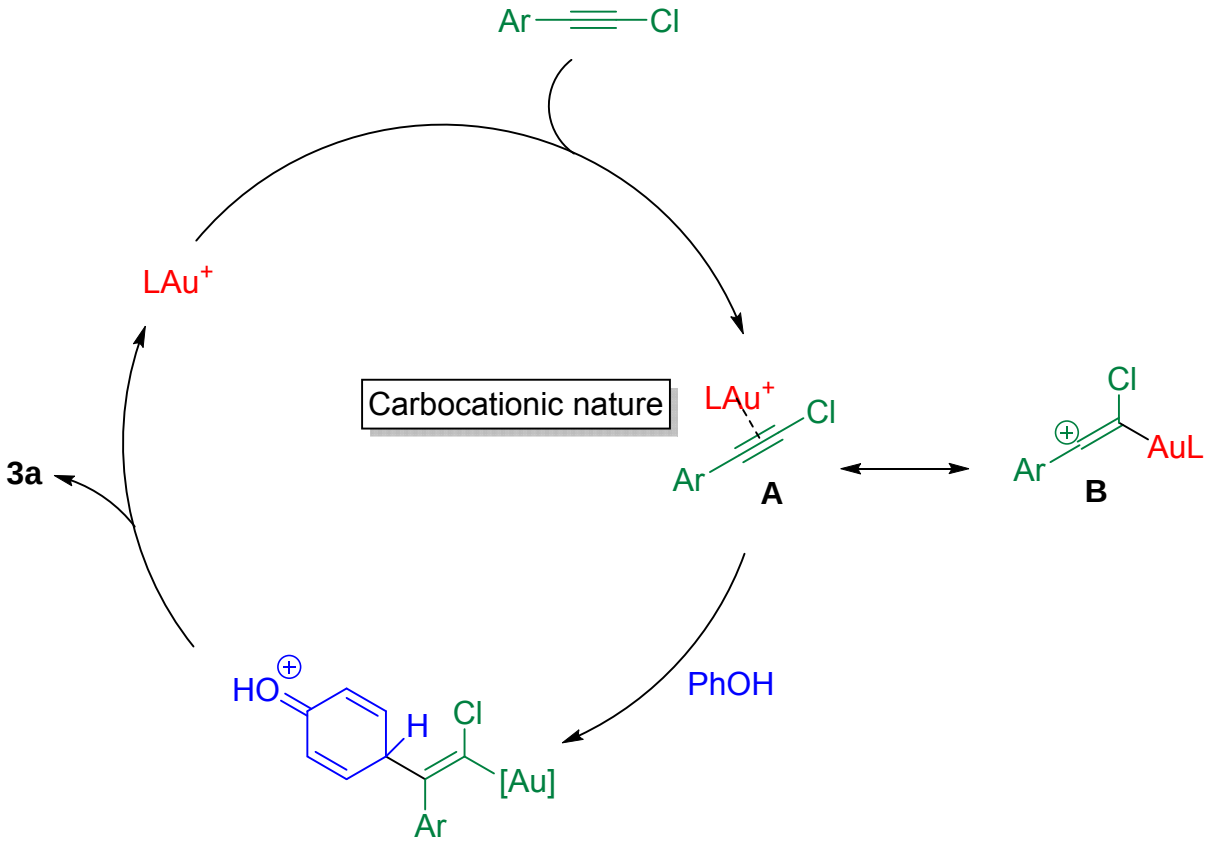
substituted alkyne carbon which leads to the more stable π-activated alkyne **A**/vinyl cation **B**. Then the phenol attacks the highly electrophilic alkyne. The addition of a neutral phenol is only possible because of the acceptor substitution of the alkyne. Other known additions with gold use phenolates which to the higher nucleophilicity of the oxygen leads to the *O*-addition products.[17] In line with that less electron-deficient bromoalkynes delivered poorer results. The observed *para*-selectivity should result from both steric and electrostatic repulsion between the polarised alkyne and the OH-moiety. Only if this favoured position is blocked selective *ortho*-coupling is feasible.



Scheme 4. Plausible reaction mechanism

Both *ortho*- and *para*-coupled products can serve as versatile intermediates towards bioactive compound or natural products. For example, the *ortho*-coupling procedure was efficiently used for the late-stage modification of estrone **5** (Scheme 5) to benzofuran **7** in 70% yield. The vinyl chloride subunit of **3a** also proved to be a useful synthetic precursor for a Suzuki coupling and coupling product **8** was obtained in excellent yield (88%). Furthermore, a variant of this method was also applicable to a one pot synthesis of 2-chlorovinyl furan derivative **10** in an excellent yield (86%) without further optimisation. In this process the intramolecular OH addition to the alkyne takes place first and then the addition of the benzofuran unit onto the chloroalkyne terminates the cascade.

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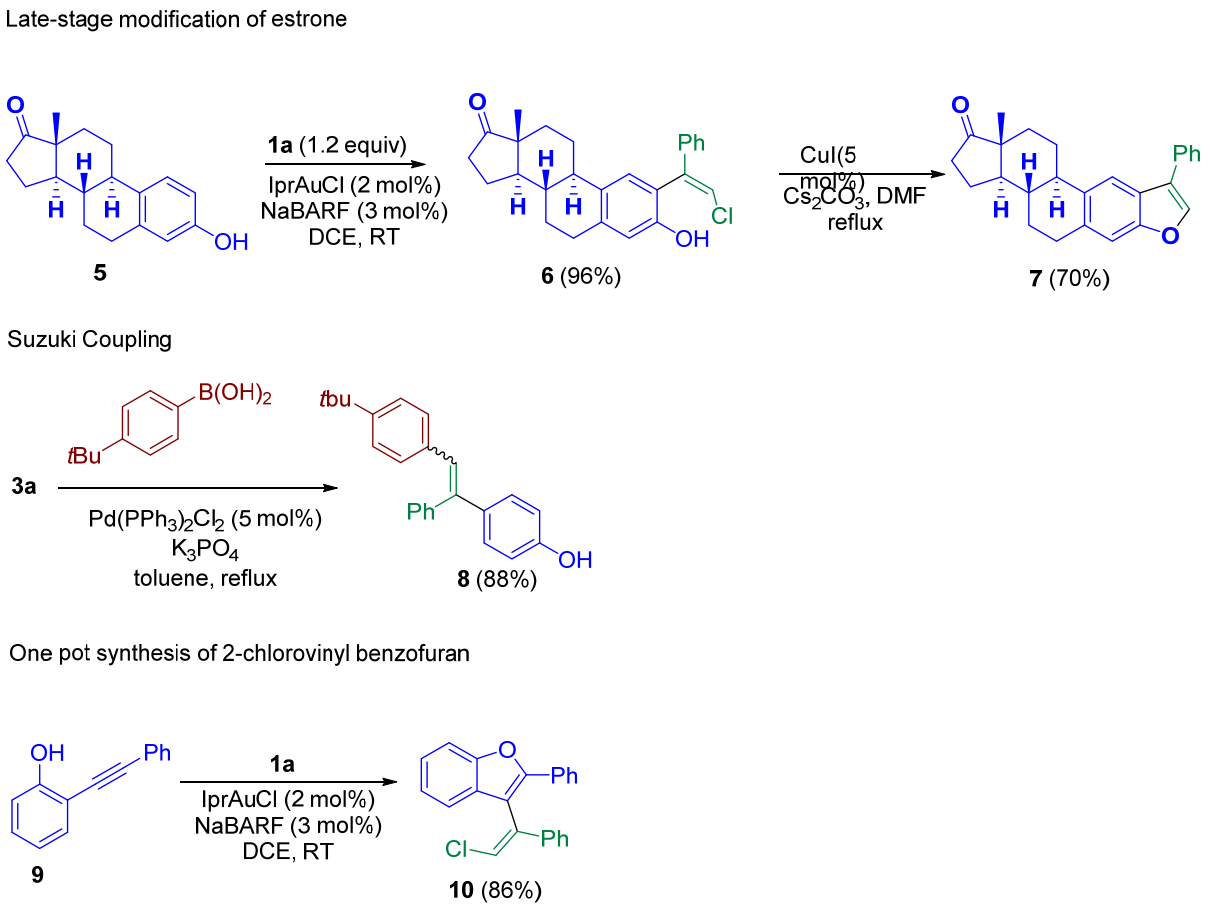

Scheme 5. Demonstrating synthetic utility

Overall four isomers of the addition product could be formed, namely the two diastereomers of the C-C coupling ((*Z*)-**3a** and (*E*)-**3a**) and the two diastereomers of the C-O coupling ((*Z*)-**4a** and (*E*)-**4a**, constitutional isomers of the diastereomers of **3a**). We conducted a small computational study of the relative energies of these four species (Figure 5). The results clearly indicate that the C-C coupling provides the more stable products; (*Z*)-**3a** and (*E*)-**3a** are about 34 kcal/mol lower in energy than (*Z*)-**4a** and even about 44 kJ/mol lower than (*E*)-**4a**. Between the two diastereoisomers (*Z*)-**4a** and (*E*)-**4a** the unvavorable interaction of two π-donor substituents located *trans* at the double bond is most pronounced, leading to an energy difference of 10 kJ/mol. In the diastereomeric pair (*Z*)-**3a** and (*E*)-**3a** the much larger distance of the donor atoms leads to a smaller difference in energy for this pair of diastereomers. The small energy difference of only 0.4 kJ/mol for (*Z*)-**3a** and (*E*)-**3a** is smaller than the error of the computation, based on this data the two diastereomers of **3a** energetically are equivalent, which fully confirms the equilibration to a 1:0.93 mixture discussed for Figure 3. The computations also make clear that an attack at the *ortho*-position with respect to the phenolic hydroxyl group, which would lead to (*Z*)-**11a** and (*Z*)-**11a**, expectedly would provide products 7-10 kJ/mol higher in energy than the observed products.

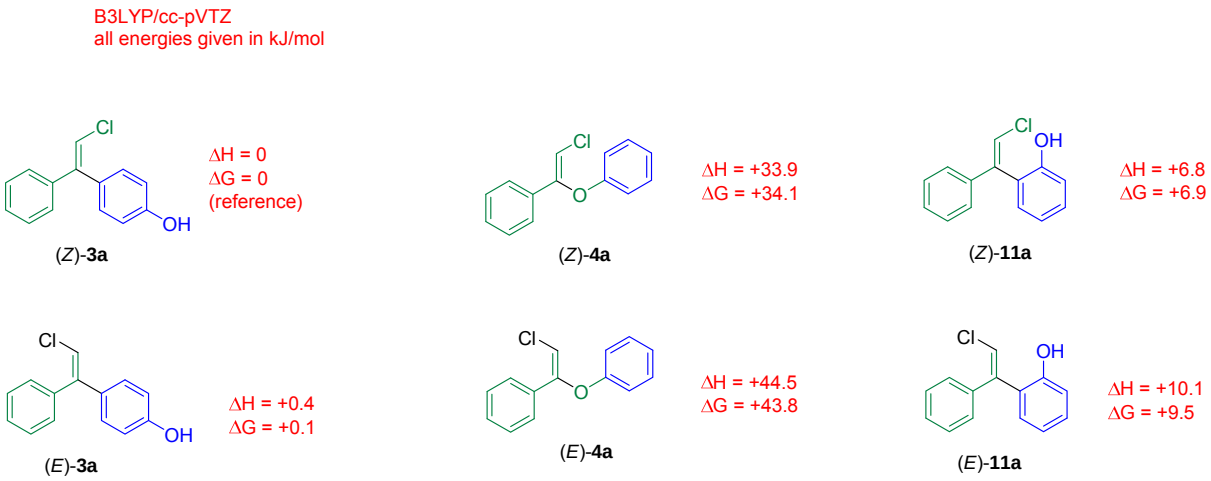

Figure 5. Relative energies of the four isomers which can be expected (B3LYP/cc-pVTZ; all energies given in kJ/mol)

Conclusion

In summary we developed a straightforward gold-catalysed intermolecular *C*-addition of phenols to haloalkynes in good to excellent regio-selectivity and diastereoselectivity. Noteworthy, no competing OH-additions were observed which can be attributed to the base-free conditions that are enabled by the high electrophilicity of the applied alkynes. The features of this reaction include mild conditions, good substrate scope and easy available starting materials. The obtained products are of high value as synthetic intermediates for organic chemists. As demonstrated even late stage modifications of bio-active molecules are feasible.

Experimental Section

General procedure for the gold-catalysed synthesis of chlorovinyl derivatives

In a dried schlenk tube IPrAuCl (2 mol %), NaBARF (3 mol %) was stirred for 5 min. in DCE (0.2 mL) and chloroalkyne (0.24 mmol, 1.2 equiv) was added under a nitrogen atmosphere at room temperature. Finally, phenol (0.2 mmol, 1.0 equiv) was added to reaction mixture and stirred for 3 hours at room temperature. After completion, the mixture was passed through a short silica gel and then concentrated under reduced pressure reaction mixture and the residue was purified by silica gel flash column chromatography using petroleum ether and ethyl acetate as eluent to give the desired product.

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[19] CCDC 1895479 (**5m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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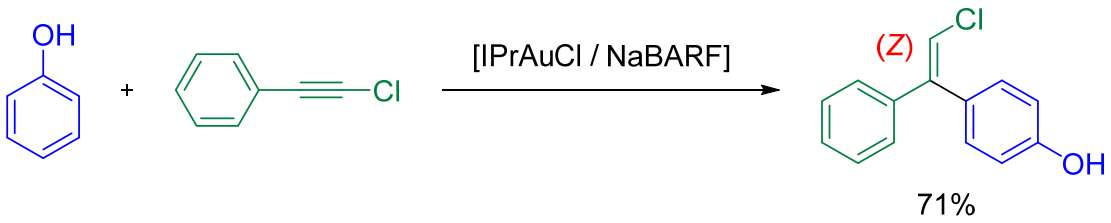
TOC Entry



TOC Text

Two simple building blocks in an easy-to-conduct gold catalysed reaction provide diastereomerically pure trisubstituted alkenes.

Key Topic

Selective gold catalysis