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Synthesis of Highly Substituted Furans by a Cascade of Formal *anti*-Carbopalladation/Hydroxylation and Elimination

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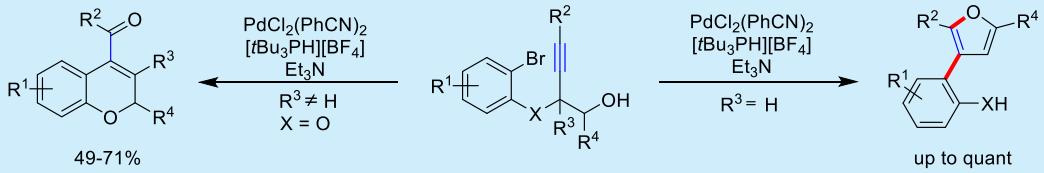
Supporting Information



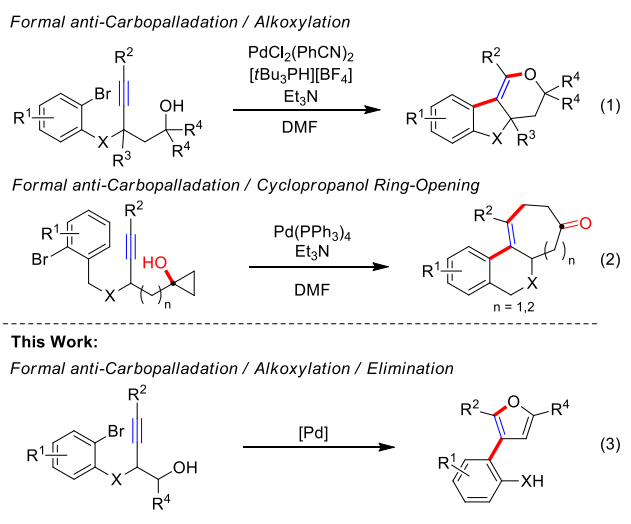
ABSTRACT: Highly substituted furans are generated by a cascade of formal *anti*-carbopalladation, attack of a nucleophilic hydroxy group, and aromatization by elimination of the emerging dihydrofuran derivative. Mono-, di-, and trisubstituted furans were obtained in good to excellent yields. When we attempted to access tetrasubstituted furan derivatives, an additional rearrangement was observed that resulted in the formation of chromenes. Follow-up chemistry shows the utility of TMS as a protecting group for the alkyne moiety.

One of the classical routes to 2,5-disubstituted furans, the well-known Paal−Knorr synthesis, consists of a condensation reaction of 1,4-dicarbonyls induced by Brønsted or Lewis acids. However, numerous other methods to access these heterocyclic compounds have been designed over the last century. Oxazoles can be employed in a Diels−Alder sequence with alkynes as dienophiles to generate 3,4-disubstituted furan derivatives;[1] metathesis of bisallyl ethers and subsequent oxidation or elimination is another possibility.[2] Gold-catalyzed transformations using allene intermediates have been used, especially to furnish highly substituted derivatives.[3,4]

Recently, we designed a cascade consisting of a formal *anti*-carbopalladation followed by an attack of a hydroxy group on the emerging *anti*-carbopalladation intermediate.[5] In this way, tetrasubstituted enol ethers incorporated into six- or seven-membered ring systems were obtained (Scheme 1, eq 1). For the nucleophilic attack, primary, secondary, and tertiary hydroxy groups were utilized. Furthermore, we showed that by a slight variation of the starting material from tertiary alcohols to cyclopropanols, ketones can be accessed in a cascade reaction (Scheme 1, eq 2).[6] Since common carbopalladation reactions lead to a *syn*-attack on the alkyne unit,[7−10] a special substrate and ligand design was required to achieve the crucial *cis*−*trans*-isomerization in the coordination sphere of Pd.[11−13] The key step was the use of a terminating substituent (e.g., thioethers, *tert*-butyl, trimethylsilyl) at the alkyne, which must be incapable of *β*-hydride elimination and a sterically encumbered phosphine ligand that facilitates the generation of a 14 VE (valence electron) complex. By computational means, the latter was shown to be the decisive intermediate for the anticipated isomerization. Unfortunately, the cascade does not work with an aryl substituent or strongly electron-withdrawing groups such as carbonyl moieties or CF_3 groups attached to the alkyne.[11] Experiments with bidentate phosphine ligands revealed that the transformation is seriously hindered, since a 14 VE intermediate is inaccessible when employing such a ligand system.[11]

With the novel procedure of enol ether formation in hand, we designed substrates that might undergo a further elimination to disubstituted furan derivatives by using an

Scheme 1. Formal *anti*-Carbopalladation of Internal Alkynes Terminated by a Hydroxy Group and Our Extension to the Synthesis of Furans



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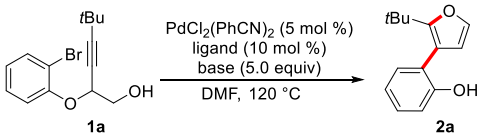
appropriate leaving group and the correct tether length to reach a five-membered heterocycle (Scheme 1, eq 3). The driving force of this process should be the gain in aromaticity.

At the outset of our studies, alkynol **1a** was chosen to explore suitable reaction conditions for the desired domino reaction. The reaction was carried out in aprotic polar solvents (DMF or DMA) at the relatively high temperature of 120 °C for 2 h (Table 1). The examination of a suitable ligand (entries 1−4) showed that the reaction works best with Fu's salt,[14] releasing the sterically demanding tris(*tert*-butyl)phosphine (entry 4). The desired product was isolated in quantitative yield. In contrast, the bidentate ligand dppe (1,2-bis(diphenylphosphino)ethane) gave only traces of the desired product, which agrees with the previous investigations of this isomerization process (see catalytic cycle, Scheme 5). By reducing the temperature to 100 °C the product was formed in 61% yield. A change of the base (K_2CO_3 and DIPEA) resulted in decreased product formation (entries 6 and 7). Other Pd(II) sources, e.g., $Pd(OAc)_2$, had only slight influence on the product formation (entry 8). By using DMA instead of DMF the yield was decreased (entry 9).

Table 1. Optimization of the Domino Reaction[a]



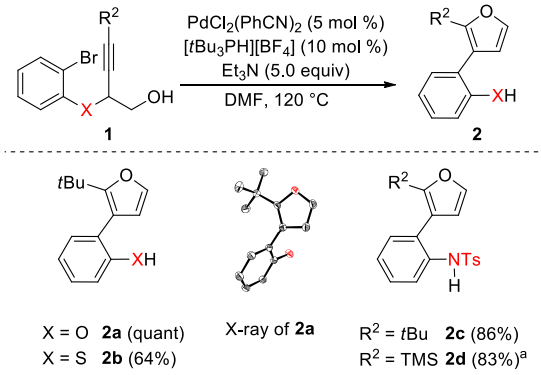
entry	ligand	base	solvent	T [°C]	yield [%]
1	PPh_3	NEt_3	DMF	120	73
2	dppe	NEt_3	DMF	120	traces
3	XPhos	NEt_3	DMF	120	42
4	**[*t*Bu$_3$PH][BF$_4$]**	**NEt$_3$**	**DMF**	**120**	**quant**
5	[*t*Bu$_3$PH][BF$_4$]	NEt_3	DMF	100	61
6	[*t*Bu$_3$PH][BF$_4$]	DIPEA	DMF	120	72
7	[*t*Bu$_3$PH][BF$_4$]	K_2CO_3	DMF	120	54
8[b]	[*t*Bu$_3$PH][BF$_4$]	NEt_3	DMF	120	85
9	XPhos	NEt_3	DMA	120	65

[a]General reaction conditions: **1** (100 μmol), solvent (3.0 mL); yields represent isolated products; DIPEA = *N*,*N*-diisopropylethylamine; DMF = dimethylformamide; DMA = dimethylacetamide; dppe = 1,2-bis(diphenylphosphino)ethane. [b]$Pd(OAc)_2$ was used instead of $PdCl_2(PhCN)_2$.

With the optimized reaction conditions in hand, the use of various leaving groups for the cascade reaction was evaluated. Besides phenol **2a**, whose structure was confirmed by X-ray crystallography,[15] a thiol (**2b**, 64%), and tosylated amides (**2c** and **2d**) were accessed in good yields (Scheme 2). Variation of substituent R^2 on the alkyne moiety showed that both the *tert*-butyl and the TMS group were tolerated (Scheme 2). One of the great advantages of the TMS group is the possibility of further functionalization (see Scheme 7).

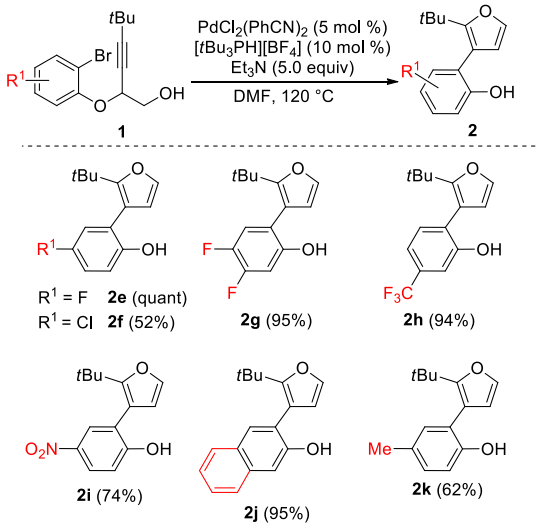
Scheme 3 depicts the scope of the cascade reaction with respect to variation of the residues at the aromatic motif. The reaction worked smoothly with electron-donating (**2e**−**2g**, **2k**) and also with electron-withdrawing groups (**2h**, **2i**) in moderate to excellent yields. In the case of the methyl-substituted derivative **2k**, the yield was slightly decreased to 62%. By using an extended π-system (**2j**), a yield of 95% was achieved. Moreover, additional halides, such as fluorine or chlorine, did not hamper the reaction. The corresponding products (**2e**−**2g**) were isolated in 52% to quantitative yields (Scheme 3).

Scheme 2. Synthesis of Furans with Various Leaving Groups[a]



[a]Large scale synthesis (1.34 mmol) afforded product **2d** in 78% yield.

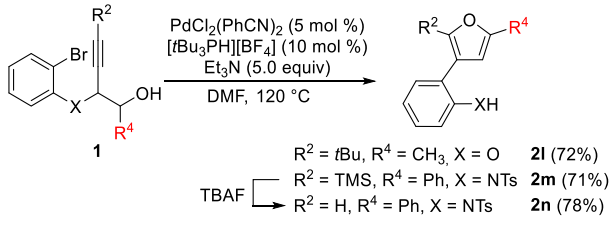
Scheme 3. Synthesis of Furans with Various Residues at the Aromatic Motif



Our next investigation focused on the synthesis of furans with a higher degree of substitution. The scope of the cascade leading to trisubstituted furan derivatives shows that both alkyl (**2l**, 72%) and aryl (**2m**, 71%) moieties in position R^4 were installed in moderate to good yields. The desilylation of **2m** with TBAF yielded the corresponding 2,4-disubstituted furan **2n** in 78% yield (Scheme 4).

The proposed catalytic cycle for the anticipated Pd-catalyzed cascade reaction is shown in Scheme 5. The starting point is the oxidative addition into the C−Br bond of **1a** forming intermediate **A**. The following *syn*-carbopalladation with the

Scheme 4. Synthesis of Furans with Various Residues R^4



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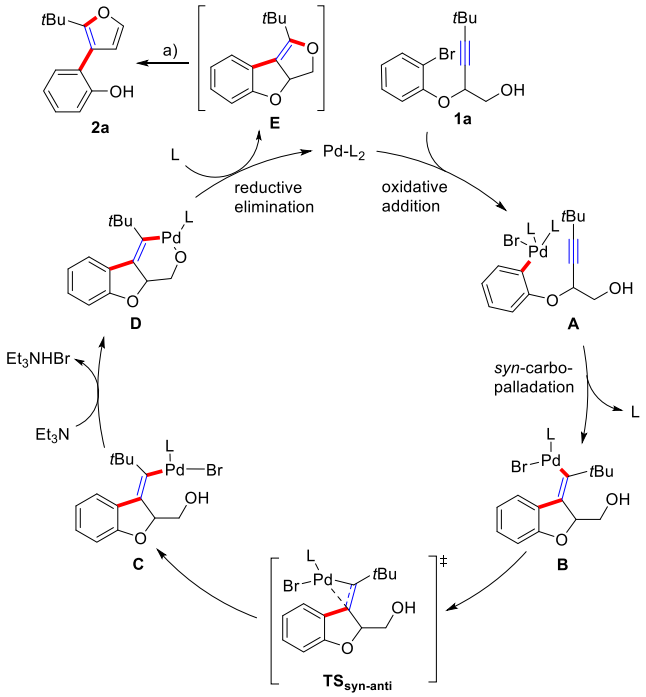
Scheme 5. Proposed Mechanism[a]



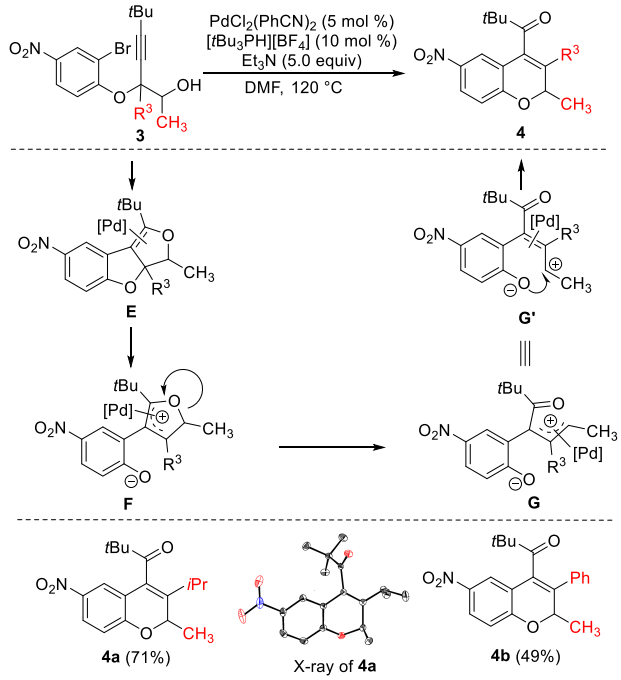
[a]Analogous to the Pd-allyl complex formed during a Tsuji-Trost-type rearrangement which we observed in previous studies,[5] the elimination process might also by supported by the Pd catalyst.

neighboring carbon−carbon triple bond affords intermediate **B**. Because of the absence of further reaction pathways, e.g., a *β*-hydride elimination, the palladium isomerizes to the opposite site of the emerging double bond via an η^2-vinyl transition state ($TS_{syn\text{-}anti}$).[11] The newly generated bonds are now located in an *anti*-configuration (see intermediate **C**). Base-mediated coordination of the hydroxy group to Pd results in intermediate **D**. By reductive elimination, the catalyst is regenerated and the intermediate **E** is formed. The dihydrofuran **E** directly isomerizes to the corresponding furan derivative **2a** by elimination of phenol (Scheme 5).

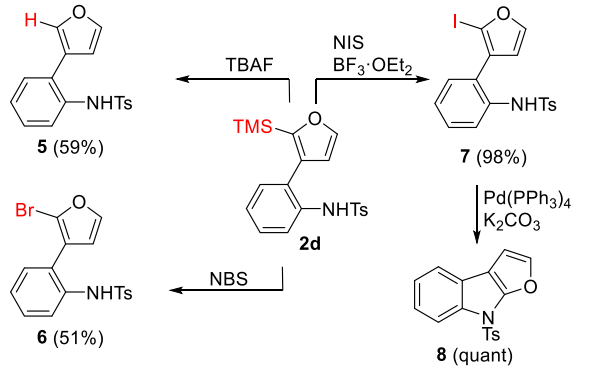
However, when we tried to address the preparation of tetrasubstituted furans by this methodology, a further Pd-catalyzed rearrangement was observed yielding chromenes of type **4** (Scheme 6). In position R^3 were installed both alkyl (**3a**) and aryl (**3b**) residues. The corresponding products **4a** and **4b** were isolated in moderate to good yields (49−71%). The structure of **4a** was unequivocally confirmed by X-ray analysis. Our mechanistic proposal is shown in Scheme 6. After the formation of dihydrofuran **E** the Pd(0) coordinates to the double bond, whereupon elimination of the highly stabilized phenolate leads to an allylic complex **F**. This allyl complex is easily converted into the more stable allyl complex **G**, whereby ring-opening and generation of a carbonyl unit are the major driving force. The attack of the phenolate in intermediate **G′** closes the six-membered ring affording chromene **4** (Scheme 6).

Finally, we demonstrated the utility of the TMS group for further functionalization (Scheme 7). Disubstituted furan **2d** was desilylated with TBAF, yielding monosubstituted derivative **5** in 59% yield. Reaction of **2d** with NBS gave brominated furan **6** in 51% yield. The corresponding iodinated derivative **7** (98% yield) was obtained by using NIS in the presence of a

Scheme 6. Synthesis of Chromenes



Scheme 7. Follow-Up Chemistry: Functionalization of the TMS Group



Lewis acid. Under Buchwald−Hartwig conditions, furyl-fused indole **8** was obtained in quantitative yield (Scheme 7).

In summary, we have demonstrated a Pd-catalyzed domino process involving a formal *anti*-carbopalladation of internal alkynes for the syntheses of highly substituted furans. Thereby, the cascade was terminated by the nucleophilic attack of a hydroxy group followed by the elimination of a good leaving group. With this method, mono-, di-, and trisubstituted furan derivatives were generated in good to excellent yields. However, when we tried to access tetrasubstituted furan derivatives, an unprecedented rearrangement to chromene derivatives was observed. By a subsequent functionalization of the TMS group, a broad variety of residues was installed in the *α*-position of the furan.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1879172 and 1879173 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) CCDC-1879172 (**2a**) and CCDC-1879173 (**4a**) contain the supplementary crystallographic data for this paper.

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