

C–H Activation

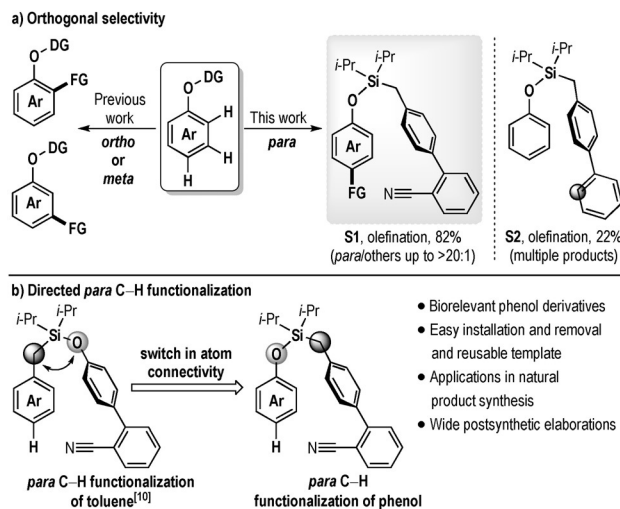
Deutsche Ausgabe: DOI: 10.1002/ange.201601999
Internationale Ausgabe: DOI: 10.1002/anie.201601999Palladium-Catalyzed Directed *para* C–H Functionalization of Phenols

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Abstract: Various practical methods for the selective C–H functionalization of the *ortho* and recently also of the *meta* position of an arene have already been developed. Following our recent development of the directing-group-assisted *para* C–H functionalization of toluene derivatives, we herein report the first remote *para* C–H functionalization of phenol derivatives by using a recyclable silicon-containing biphenyl-based template. The effectiveness of this strategy was illustrated with different synthetic elaborations and by the synthesis of various phenol-based natural products.

Recent years have witnessed the emergence of C–H activation as an effective method for the synthesis of complex molecules.^[1] As evident from several examples in nature, chemical transformations that involve the functionalization of C–H bonds are coined to be efficient when they proceed with a commendable degree of selectivity.^[2–5] One strategy for ensuring a highly selective functionalization entails the use of a directing group.^[6] This approach has been significantly exploited in the last two decades to selectively activate the *ortho*^[7] and more recently the *meta* C–H bonds^[8,9] of arenes containing multiple C–H bonds with very similar intrinsic reactivity. However, the effective employment of such a strategy for the selective activation of a *para* C–H bond has remained extremely difficult. This was attributed to the problems associated with forming a large cyclophane-like metallacycle, which is required for the functionalization of a C–H bond situated far away from the coordinating functional group. The need for an optimum chain length poses a further impediment towards devising a template that would enable the facilitated delivery of the electrophile through a weakly coordinating donor group. Overcoming these challenges, our group recently reported the first template-directed *para* C–H functionalization of toluene derivatives.^[10]

To date, C–H activation reactions with phenol derivatives have predominantly occurred at the *ortho* and *meta* position in the presence of a suitable template,^[11,12] or selectivity was based exclusively on steric and electronic bias.^[5,13] The directing-group-assisted *para*-selective functionalization of such a molecule would effectively overrule its vulnerability towards electrophilic attack at both the 2- and 4-position (Scheme 1a).

Scheme 1. Directed *para* C–H functionalization of phenols.

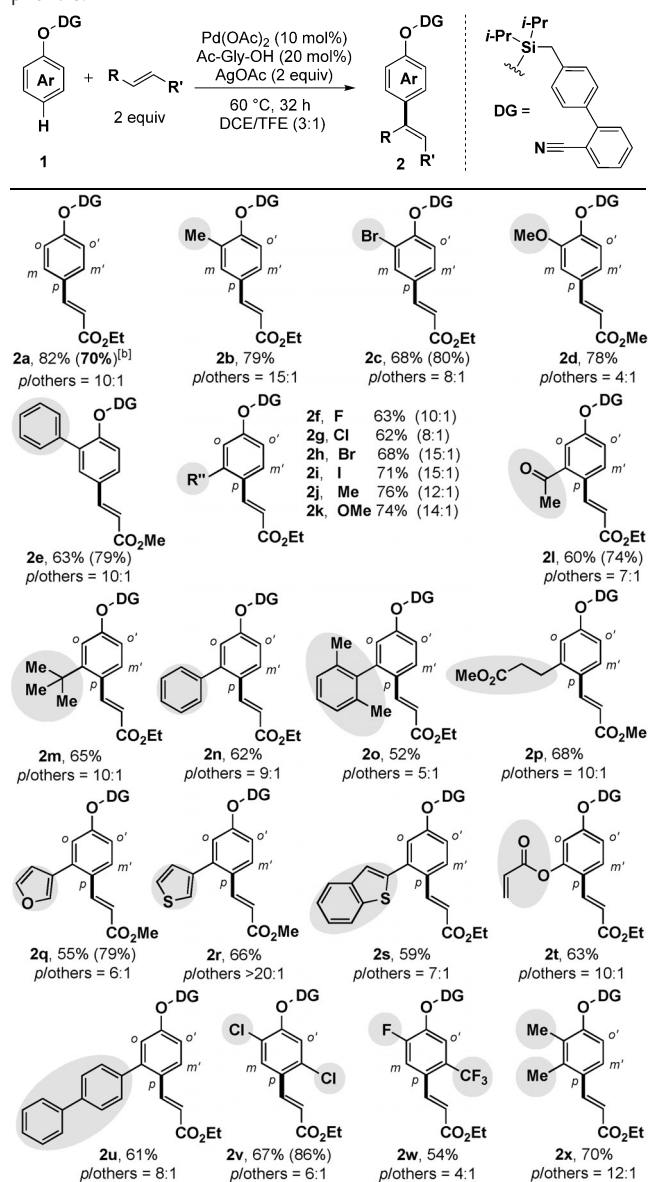
Following our previous report^[10] and in order to optimize the template design, a biphenyl moiety was employed as part of the template chain along with a silicon center with two bulky isopropyl groups as the ligation center (Scheme 1b, **S1**).^[14] Switching the connecting carbon and oxygen atoms in our previous template led to a modified system for the *para* C–H functionalization of phenol.^[15] This modification ensures that the donor nitrile group will be placed at a position suitable for the formation of the desired metallacycle in the transition state. The end-on coordination by the directing moiety leads to a suitable placement of the weakly held electrophile through the cyclophane 17-membered transition state.

With template **S1** in hand, we attempted the palladium-catalyzed olefination of phenol in the presence of AgOAc as the oxidant. Consistent with our expectations, the *para* C–H olefination product was formed in 84% yield (isolated in 82%) with 10:1 selectivity in the presence of *N*-acetylglycine as the ligand. The crucial role of the template morphology was corroborated by the complete loss of selectivity for the olefination of anisole, *tert*-butyldimethyl(phenoxysilane), and simple phenol.^[16] Importantly, the requirement for a suitably located donor to activate the *para* C–H bond was further confirmed by the poor yield achieved with template **S2**.

Proceeding further with our investigation, the *para* C–H functionalization of various substituted phenol derivatives with both electron-donating and electron-withdrawing groups was explored (**2a–2x**, Table 1). Mono-*ortho*-substituted derivatives were found to be suitable substrates (**2b–2e**). To confirm the role of the directing template in overruling the probable electronic bias, electron-withdrawing groups were

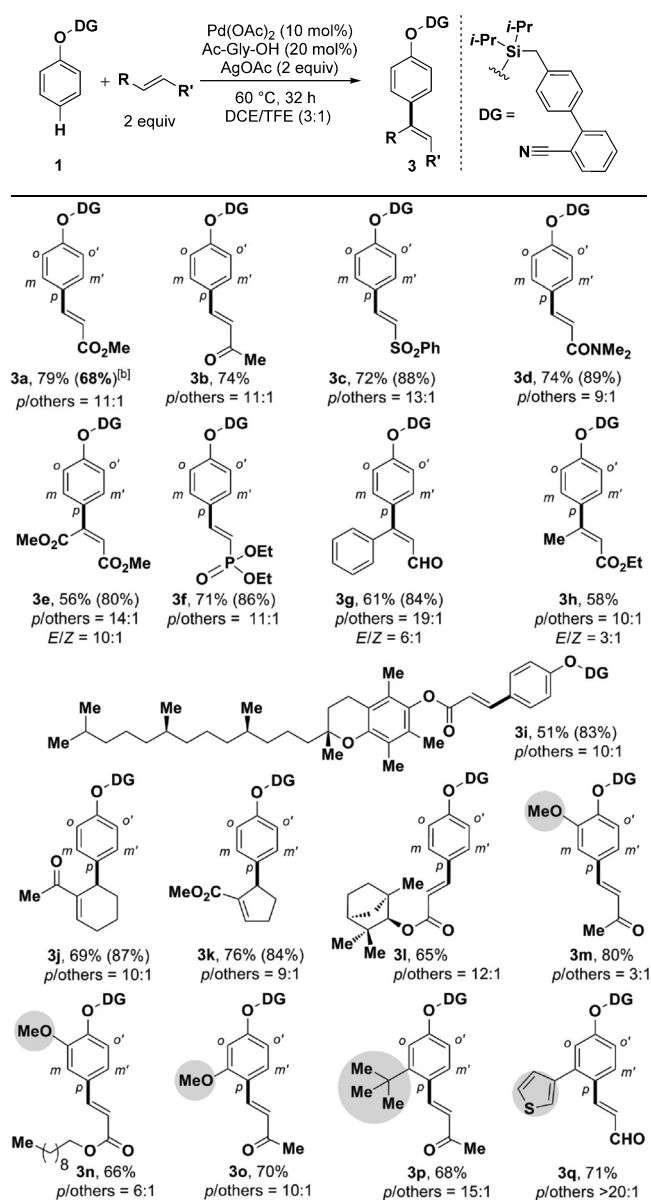
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Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201601999>.

Table 1: Arene scope of the template-assisted *para* C–H olefination of phenols.^[a]

[a] Phenol (0.2 mmol), olefin (0.4 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.4 mmol), DCE/TFE (1.2/0.4 mL), 60 °C, 32 h. [b] Yields in parentheses correspond to reactions on 2.5 mmol scale. TFE = 2,2,2-trifluoroethanol.

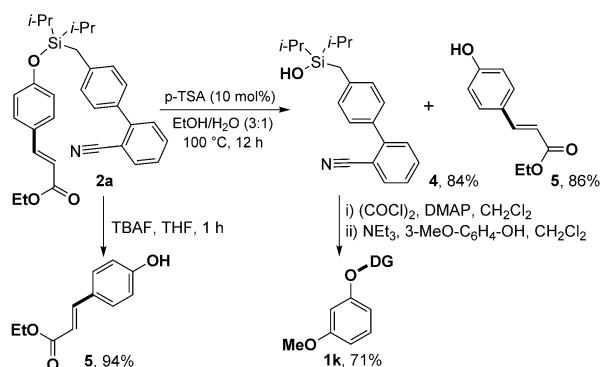
installed at the *meta* position with respect to the hydroxy group (2f, 2g, 2l, and 2t). The successful olefination of these substrates established the pivotal role of the directing template. Sterically demanding substituents were also tolerated, as demonstrated in particular by 2m–2x where the *para* selectivity remained unaffected. The efficacy of the directing group was further confirmed by the fact that no effect on the selectivity was observed in the presence of molecules with multiple vulnerable C–H bonds (2e, 2n, and 2u). The presence of oxygen- and sulfur-based heterocycles did not affect the reactivity and selectivity (2q–2s).

Table 2: Olefin scope of the *para* C–H olefination of phenols.^[a]

[a] Phenol (0.2 mmol), olefin (0.4 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.4 mmol), DCE/TFE (1.2/0.4 mL), 60 °C, 32 h. [b] Yields in parentheses correspond to reactions on 2.5 mmol scale.

Following this, we investigated the olefination of directing-template-modified phenol with a wide range of olefins (Table 2). A diverse set of functional groups, including esters, amides, aldehydes, ketones, sulfonyls, and phosphonates, were found to be compatible with the reaction conditions (3a–3g, 3q). Olefins with long-chain alkyl substituents as well as internal and cyclic olefins were also tolerated (3h–3n).

After *para* functionalization, the silanol template 4 was recovered using catalytic amounts of *para*-toluenesulfonic acid. Silanol 4 could be then reinstalled in good yield (71 %, Scheme 2). Alternatively, the template could be removed in situ with TBAF after *para* functionalization to provide 5 in excellent yield (Scheme 2).



Scheme 2. Template removal and reinstallation.^[16] DMAP = 4-dimethylaminopyridine, p-TSA = *para*-toluenesulfonic acid, TBAF = tetrabutylammonium fluoride.

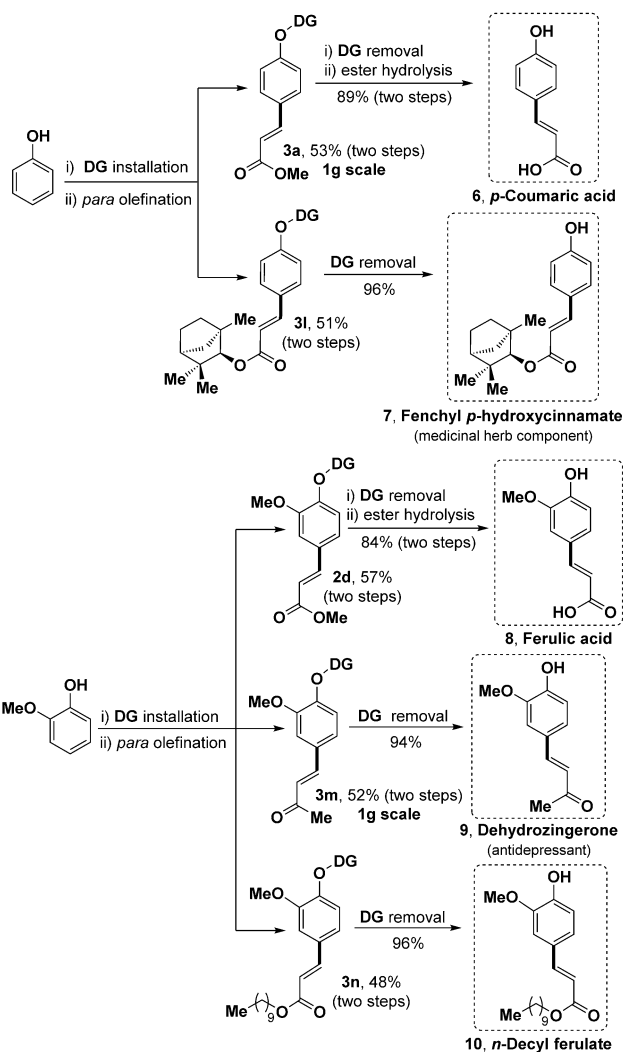
This *para*-functionalization strategy was then applied to several phenol-based natural products (Scheme 3 and Scheme 4). For example, phenol can thus be employed as the starting material of the synthesis of *para*-coumaric acid (**6**; 4 steps, 47%), which is an inhibitor of stomach cancer aside from being a potent antioxidant.^[17] Terpene derivative **7**, found in petroleum extracts of the roots of *Seseli sibiricum*, was also synthesized from phenol (3 steps, 49%).^[18] The phenolic phytochemical ferulic acid (**8**)^[19] was also synthesized using the present approach (4 steps, 47%). Intriguingly, the potent growth inhibitor factor **9** was prepared by this template-directed *para*-functionalization approach (3 steps, 48%).^[20] Aside from **10** (3 steps, 46%), anti-inflammatory artemillin C (**11**; 5 steps, 23%), antimicrobial plicatin B (**12**; 4 steps, 34%), and drupanin (**13**; 5 steps, 29%) were also synthesized (Scheme 4).^[21,22]

The importance of this *para*-olefination method was further established by postsynthetic modifications of both the phenol and olefin core. By making use of the phenolic hydroxy group, **5** was converted into benzofuran **14** and coumarin **23** (Scheme 5).^[23] A C–O coupling yielded derivative **15**.^[16] Alternatively, the phenolic hydroxy group could be transformed into a synthetically useful triflate group in excellent yield, enabling subsequent Suzuki, Sonogashira, and C–N couplings (**17–19**).^[16] Alternatively, reduction followed by hydrolysis of the acrylate core was used to synthesize 1-indenone **21** and spirocycle **22**.^[24]

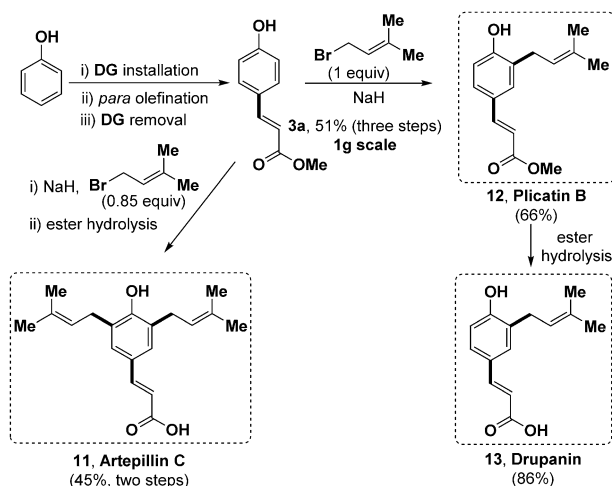
In conclusion, we have described a highly selective method for the *para* C–H functionalization of phenol derivatives that is based on the use of a silyl-biphenyl template. The applicability of this approach was demonstrated by the synthesis of various natural products. In future, the mechanistic details of this process as well as the usefulness of this strategy in drug development and polymer and material science will be studied.

Acknowledgements

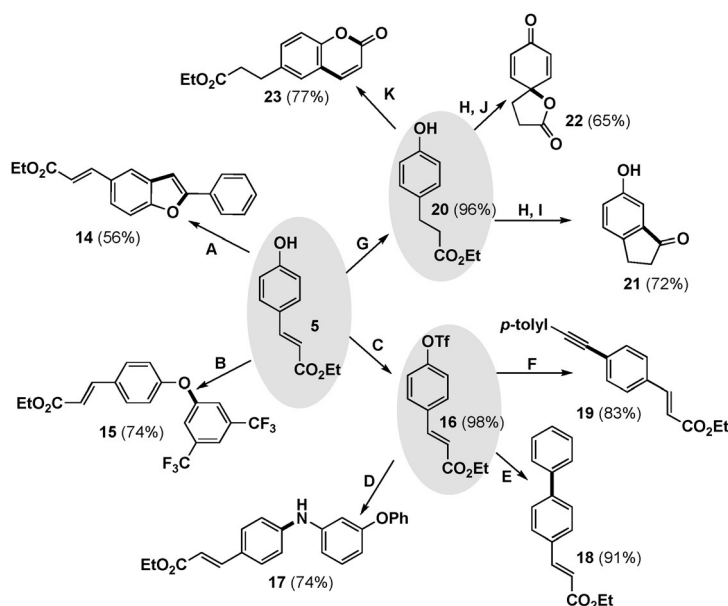
This work was supported by the SERB (EMR/2015/000164). Fellowships from UGC India (T.P. and S.B.), DST Fast Track (R.K.), and CSIR India (S.A. and A.M.) are gratefully acknowledged.



Scheme 3. Synthesis of phenol-based natural products.^[16]



Scheme 4. Synthesis of artemillin C, plicatin B, and drupanin.^[16]



Scheme 5. Postsynthetic modifications.^[16] A) Pd(OAc)₂, 1,10-phenanthroline, styrene; B) CuI, picolinic acid, aryl iodide; C) Tf₂O, K₃PO₄; D) Pd₂(dba)₃, dppe, 3-phenoxylaniline; E) Pd(PPh₃)₄/PhB(OH)₂; F) Pd(OAc)₂, PPh₃, *para*-tolylacetylene; G) Pd on C, H₂; H) LiOH; I) AlCl₃, NaCl; J) PIFA; K) Pd catalyst, methyl acrylate. dba = dibenzylideneacetone, dppe = 1,1'-bis(diphenylphosphino)ferrocene, PIFA = (bis(trifluoroacetoxy)iodo)benzene, Tf = trifluoromethanesulfonyl.

Keywords: C–H activation · olefination · palladium · silicon · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 7751–7755
Angew. Chem. **2016**, *128*, 7882–7886

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Received: February 26, 2016

Revised: March 26, 2016

Published online: May 9, 2016