Arene Functionalization

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Regioselective Threefold Aromatic Substitution of Benzoic Acid Derivatives by Dearomatization, Regioselective Functionalization, and Rearomatization**

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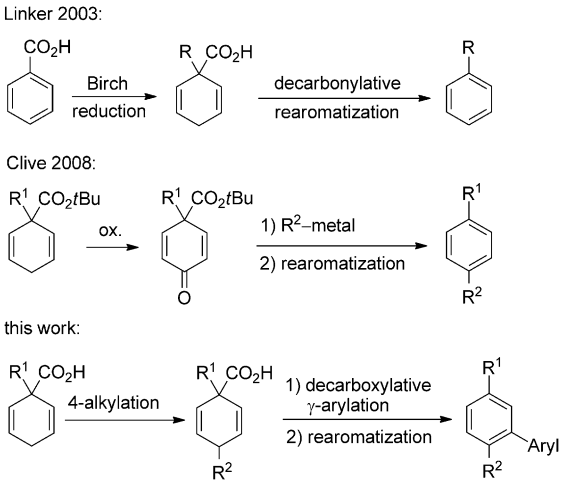
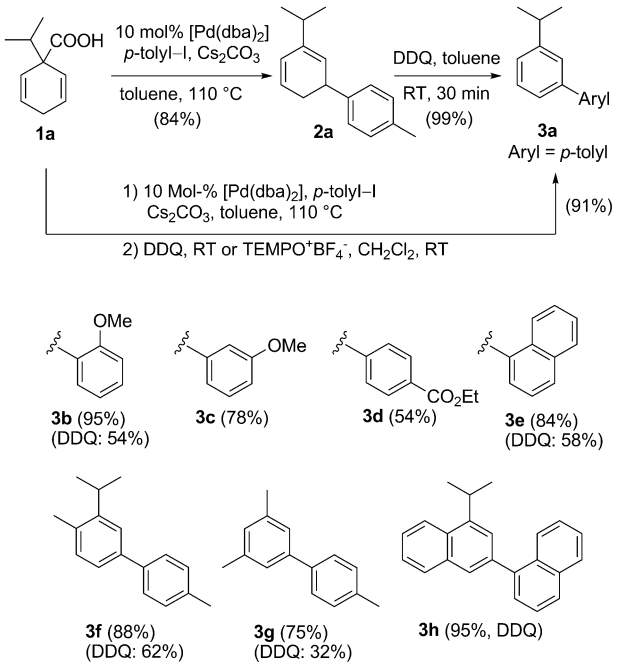
Substituted arenes are ubiquitous and important in various fields of modern science. They occur in natural products, in drugs, in agrochemicals, as ligands in catalysis, in biology, and in materials science. Despite the high efficiency of the classical functionalization methods, such as electrophilic, nucleophilic, and homolytic aromatic substitution, development of novel processes for regioselective functionalization of arenes is still of importance.[1] Transition-metal-mediated couplings have become highly valuable and recent research in this area has focused on the direct C–H functionalization of arenes and heteroarenes.[1,2] In many of these transformations a heteroatom or a functional group is necessary to direct the reaction towards a regioselective *ortho* functionalization.[2] More recently, reports have appeared on arene functionalization in *meta* position of a directing group[3] and even a few reports on the *para* arylation have been disclosed.[4] An alternative elegant approach for arene functionalization was introduced by Linker and co-workers (Scheme 1).[5] Benzoic acid derivatives were regioselectively *ipso*-alkylated by alkylative Birch reduction and subsequent decarbonylative rearomatization to eventually afford the corresponding *ipso*-substituted arene.

More recently, Clive and Sunasee extended that concept and developed a reaction sequence which allows for *ipso*, *para*-disubstitution of benzoic acids.[6] Herein we show that the dearomatization/rearomatization approach can be applied to the highly regioselective threefold aromatic substitution of the *ipso*, *meta*, and *para* position in various benzoic acid derivatives. By this route, highly substituted arenes are readily available.

We first tested our approach for *ipso*/*meta* disubstitution of benzoic acid derivatives. To this end, we prepared cyclohexadiene carboxylic acid **1a** by the established alkylative Birch reaction using NH_3, Li, and *i*PrI.[7] Functionalization of the 3-position was achieved by a palladium-catalyzed decarboxylative γ-arylation recently introduced by us.[8,9] Under slightly modified conditions, cyclohexadiene **2a** was isolated in 84% yield (Scheme 2). Quantitative oxidative rearomatization to **3a** was achieved with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 1.1–1.5 equiv) in toluene at room temperature.[10] We found that the 3-arylation and oxidation are most conveniently conducted as a one-pot process by



Scheme 1. Functionalization of benzoic acid derivatives by the Birch reaction, chemical modification, and rearomatization.



Scheme 2. Preparation of various 1,3-disubstituted arenes.

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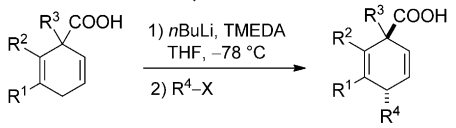
directly adding DDQ to the reaction mixture and **3a** was isolated in 91% overall yield. Various 1,3-disubstituted arenes **3b–e** were successfully prepared in good to excellent yields from **1a** by this method. However, in some cases the DDQ-mediated oxidation was not a clean reaction and rearomatization was better conducted with the $TEMPO^+BF_4^-$ salt[11] in CH_2Cl_2. Starting the sequence with substituted benzoic acid derivatives or with 1-naphthalene carbocylic acid, arenes **3f–h** were obtained (75–95% overall yield for the arylation and rearomatization steps).

We then studied the diastereoselective 4-alkylation of 1-substituted cyclohexa-2,5-diene-1-carboxylic acids of type **1**. The reaction was optimized on diene **1f** ($R^1 = H$, $R^2 = CH_3$, $R^3 = i$Pr, Table 1).[12] The challenge was to find a method

Table 1: Diastereoselective 4-alkylation of acids **1b,c,f–h**.



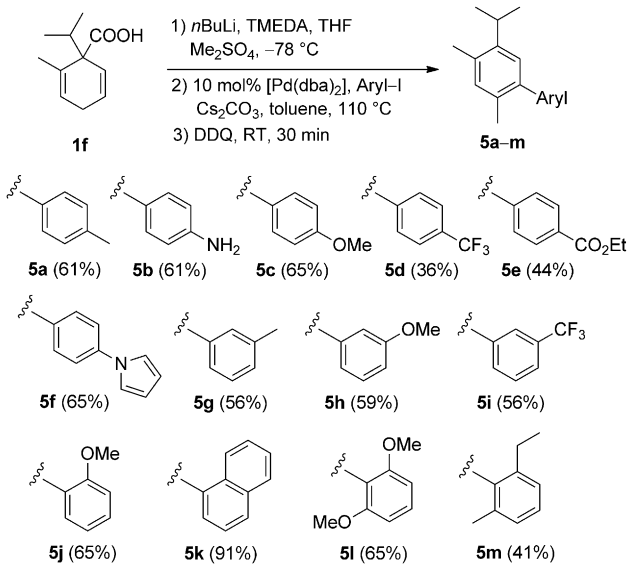
1b,c,f–h **4a–i**

Entry	R^1	R^2	R^3	R^4	Product	Yield [%]
1	H	CH_3	*i*Pr	CH_3	**4a**	95
2	H	CH_3	*i*Pr	CH_2CH_3	**4b**	74
3	CH_3	H	*i*Pr	CH_3	**4c**	76
4	H	CH_3	*i*Pr	*i*Pr	**4d**	55
5	H	CH_3	*i*Pr	Bn	**4e**	84
6	CH_3	H	*i*Pr	Bn	**4f**	70
7	CH_3	H	CH_3	CH_3	**4g**	90
8	CH_3	CH_3	*i*Pr	CH_3	**4h**	95
9		$-C_4H_4-$	*i*Pr	CH_3	**4i**	95

which allows for highly regioselective alkylation at the 4-position of the 2,5-diene. Moreover, alkylation had to be highly *trans*-diastereoselective because palladium-catalyzed decarboxylative γ-arylation does not work well on *cis*-4-alkyl-cyclohexa-2,5-diene-1-carboxylic acids.[13] Deprotonation was best conducted with *n*BuLi (2.2 equiv) in THF at −78 °C in the presence of tetramethylethylenediamine (TMEDA; 2.2 equiv). Alkylation with soft electrophiles, such as MeI provided **4a** in a low yield, because of competing single-electron transfer from the lithiated cyclohexadiene to MeI. However, methylation with Me_2SO_4 gave **4a** as a single diastereoisomer[14] in 95% yield (Table 1, entry 1). Other hard electrophiles, such as Et_2SO_4, *i*PrBr, and BnCl also provided good yields in the alkylation of **1f** (**4b**, **4d**, **4e**; entries 2, 4, and 5). Using the robust Birch chemistry other substrates of type **1** were prepared and subjected to the 4-alkylation to give **4c**, **4f–i** (entries 3, 6–9). In all cases, reaction occurred with complete stereocontrol.

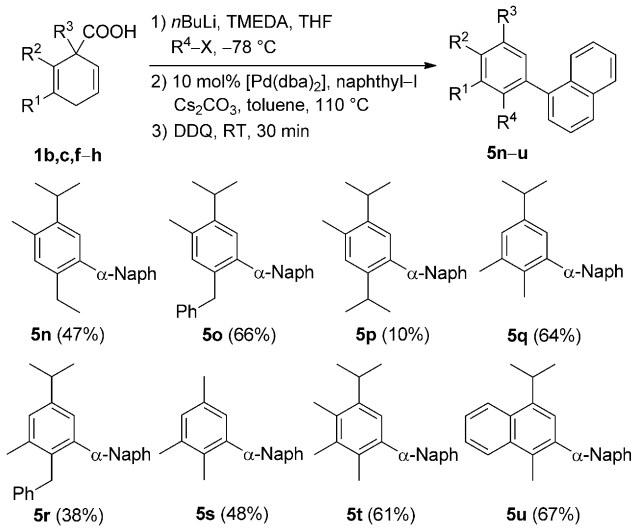
We tested the threefold arene substitution in a reaction sequence consisting of alkylative Birch reaction, 4-alkylation, decarboxylative γ-arylation, and DDQ-mediated rearomatization on various aromatic carboxylic acids. The Birch products were purified, but intermediates of type **4** obtained after the 4-alkylation were not purified and the γ-arylation/dearomatization was performed as a one-pot process according to Scheme 2. Hence, the sequence starting with readily storable Birch products represents a very robust convenient route for arene-library synthesis for which the intermediates of type **2** and **4** do not have to be purified. Yields given in Scheme 3 and 4 correspond to yields of isolated products over three steps starting with Birch products of type **1**.

To document the scope with respect to the aryl substituent we investigated the sequence using cyclohexadiene acid **1f**, Me_2SO_4 for the 4-alkylation, and various aryl iodides to give the tetrasubstituted arenes **5a–m** (Scheme 3). These multistep



Scheme 3. Transformation of **1f** to arenes **5a–m**.

transformations were generally conducted at the 0.3 mmol scale. A larger scale experiment (2 mmol) for the synthesis of **5c** showed a slightly lower but still good yield (65% versus 50%). Aryl iodides bearing electron-donating substituents at the *para* position provided higher yields than those containing electron-withdrawing groups. However, only small electronic effects were noted for the *meta*-substituted systems (**5g–i**). Pleasingly, the reaction sequence also worked well with more bulky aryl iodides bearing *ortho* substituents. Even, *ortho*,*ortho'*-disubstituted aryl iodides afforded the targeted products **5l** and **5m**. However, for the bulkiest congener **5m** a significantly lower yield was obtained. We also varied the R^1–R^4 substituents using α-naphthyliodide as the aryl component (Scheme 4). R^1 and R^2 substituents were readily varied by choosing the appropriately substituted benzoic acid derivatives for the initial Birch reaction. Variation of R^3 and R^4 was achieved by varying the electrophile in the two alkylation reactions. This sequence allowed differently substituted arenes **5n–u** to be prepared.[15] As shown for **5t**, fivefold substituted arenes are accessible. Steric demands of the R^4 substituent influenced reaction outcome and yields decreased in going from the methyl (see **5k** in Scheme 3) to benzyl (**5o**), ethyl (**5n**), isopropyl (**5p**). Derivatives with $R^1 \neq H$ were isolated in slightly lower yields (**5r**,**s**) and also substituted naphthalenes, such as **5u**, are available by this novel route with complete regiocontrol.



Scheme 4. Preparation of highly substituted arenes **5n–u**.

In conclusion, we reported a novel method for the preparation of highly substituted arenes[16] starting from readily available benzoic acid derivatives. The sequence consists of an alkylative Birch reduction, allylic cyclohexadiene alkylation, decarboxylative γ-arylation, and rearomatization. All the reactions used in this sequence are robust transformations which are experimentally easy to conduct.

Experimental Section

General procedure for the stereoselective alkylation of 2,5-cyclohexadiene-1-carboxylic acid derivatives, arylation by a palladium-catalyzed decarboxylative coupling reaction, and oxidation.

n-Butyllithium (1.6 M in *n*-hexane, 2.2 equiv) and TMEDA (2.2 equiv) were added slowly at −78 °C to a solution of the corresponding 2,5-cyclohexadiene-1-carboxylic acid in anhydrous THF (0.3 M) resulting in a yellow solution. After stirring for 30 min the alkylation reagent (1.1–2.0 equiv) was added dropwise. If the reaction mixture did not turn pale after 10 min, the mixture was allowed to warm slowly to room temperature until the point of discoloration. The discoloration temperature was maintained for 10 min before continuing warming to room temperature. The reaction was stopped by adding aq. HCl (2 M, 3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was dissolved in toluene (0.25 M) and the corresponding aryliodide (1.1 equiv), Cs_2CO_3 (1.1 equiv), and $[Pd(dba)_2]$ (10 mol%) were added. The resulting mixture was stirred under argon at 110 °C for 17–20 h. The reaction mixture was allowed to cool to room temperature and DDQ (1.5 equiv) was added in one portion. The reaction mixture was stirred for 1 h, the solids were removed by filtration, and the solvent was removed from the filtrate under reduced pressure. The crude mixture was purified by flash chromatography to afford the desired arene.

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[12] While our work was in progress, Elliot and co-workers published similar transformations, see: N. J. Bennett, M. C. Elliott, N. L. Hewitt, B. M. Kariuki, C. A. Morton, S. A. Raw, S. Tomasi, *Org. Biomol. Chem.* **2012**, *10*, 3859 – 3865.

[13] Decarboxylative arylation of *cis*-1-isopropyl-4-methylcyclohexa-2,5-diene-1-carboxylic acid with *p*-tolyl–I provided only 18% of the targeted *p*-toylated 2,4-cyclohexadiene (see Supporting Information).

[14] In the NMR spectrum of the crude product the other isomer was not identified.

[15] The remaining position *ortho* to the aryl group cannot be substituted by this chemistry since decarboxylative γ-arylation of 2,6-disubstituted 1-alkylcyclohexa-2,5-diene-1-carboxylic acids did not work.

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