Introduction

Dearomatization is a powerful method to generate molecular complexity, because this transformation can convert two-dimensional chemical feedstock arenes to highly valuable three-dimensional (alicyclic) architectures. Because of its potential, the development of dearomative methods is a topic of intense study in organic synthesis. Birch reduction and metal-catalyzed hydrogenations are the most established transformations, as well as oxidative dearomatizations. However, as a drawback, the vast majority of dearomative functionalizations rely on the electronic nature of the parent arenes. The dearomative reactions of non-activated arenes such as benzenes and naphthalenes have often seen a lack of reaction efficiency, requiring stoichiometric amounts of metal reagents and excess substrates. Although a few dearomative reactions of inactive arenes as a limiting agent (including catalytic fashion) have recently emerged, the development of dearomative methods of a new class of arenes is still highly valuable.

Dearomative difunctionalization of benzenoids is a useful and step-economical methodology to build three-dimensional carbon frameworks. As representative examples using benzenoids as a limiting reagent, photo-induced intramolecular cycloadditions, reactions of metal-arene complexes, and nucleophilic dearomatizations have been developed. Despite these advances, they still require the tedious preparation of metal-arene complexes and the presence of specific substituents such as oxazolines and iodanes. In this context, catalytic dearomative two-component C–C bond formations of nitroarenes with ylides were reported by Piettre and Trost, independently (Fig. 1A). These reactions enabled the dearomatization of one equivalent of nitroarenes. 1,2-Difunctionalized products were commonly obtained, and only one example of 1,4-difunctionalization was shown. Alternatively, we recently developed a Pd-catalyzed three-component dearomatization of bromoarenes using malonate nucleophiles, giving 1,4-difunctionalized products (Fig. 1B). The key of this reaction was the generation of a benzyl–palladium intermediate, which reacts with malonates to form a Pd–O-enolate species. Strikingly, the present method enabled rapid access to multi-substituted alicyclics through subsequent elaboration of dearomatized products.

Catalytic three-component C–C bond forming dearomatization of bromoarenes with malonates and diazo compounds†

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A Pd-catalyzed dearomative three-component C–C bond formation of bromoarenes with diazo compounds and malonates was developed. Various bromoarenes ranging from benzenoids to azines and heteroarenes were transformed to the corresponding substituted alicyclic molecules. The key to this reaction is the generation of a benzyl–palladium intermediate, which reacts with malonates to form a Pd–O-enolate species. Strikingly, the present method enabled rapid access to multi-substituted alicyclics through subsequent elaboration of dearomatized products.
Results and discussion

First, we explored optimized conditions for the dearomatative alkylation using 1-bromonaphthalene (1A), TMS-diazomethane (2), and diethylmalonate 3a as model substrates (Table 1). Through extensive investigations, we identified the best conditions with Pd(OAc)$_2$ (5.0 mol%) and L1 (20 mol%) as the catalyst, along with NaH, and 3 Å molecular sieves (MS) in toluene at 60 °C, obtaining desired dearomatized product 4AA in 88% yield (entry 1, see the ESI† for details). Of all the triarylphosphines tested in this screening, decreasing the electron-donating ability of the phosphine led to a lower yield of 4Aa (entries 2–4). Regarding to diphosphines, DPEphos had a comparable effect to L1, producing 4AA in a high yield (entry 5). The reaction in the absence of ligand generated no product (entry 6). The choice of base was critical: when less basic LiO$_2$Bu and Cs$_2$CO$_3$ were used instead of NaH, the yield of 4AA significantly dropped (entries 7 and 8). The reaction in the absence of 3 Å MS decreased the yield of 4AA (entry 9). It was found that preformed sodium enolate 3a' was also an applicable alkylating agent under the reaction conditions without NaH (entry 10). Additionally, this reaction favored non-polar solvents, as cyclohexane also afforded 4AA in 54% yield (entry 11). Through these studies, no benzylic substitution was observed.

With the optimized conditions in hand, we next investigated the substrate generality of this reaction (Scheme 1A). As π-extended aromatics, anthracene also showed good reactivity to deliver dihydroanthracene 4Ba in high yield. The reaction of dibromoanthracene 1C smoothly proceeded to give dearomatized product 4Ca in good yield by using one equivalent of malonate 3a. For the same substrate 1C, increasing the amounts of 2, 3a, and NaH to two equivalents each furnished tetrahydroanthracene 4Caa in 67% NMR yield. Bromoarene with steric hindrance around the C–Br bond was also applicable to this reaction, generating C2-methyl-substituted product 4Da in good yield albeit as a diastereoisomeric mixture (57 : 43). 5-Bromoisoquinoline (1E) was successfully dearomatized under the present conditions, giving 4Ea in moderate yield. It is noteworthy that less reactive and simple phenyl rings were successfully converted to the corresponding cyclohexadiene skeletons 4Fa and 4Ga (see the ESI† for details). Although rearomatization occurred during the reactions probably due to the low stability of the products, 4Fa and 4Ga can be isolated in 44% and 41% yields, respectively. Regarding the scope of malonates, it was found that the nature of the ester groups did not affect the reaction efficiency, yielding 4Ab in almost the same yield as 4AA. Moreover, we subjected diethylmalonates bearing phthalimidylalkyl (3c) as well as benzyl (3d) to this protocol, generating the corresponding products 4Ac and 4Ad in

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Table 1  Conditions optimization$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard conditions</th>
<th>4AA$//%$</th>
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<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>P(2-anisyl)$_2$ instead of L1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_3$ instead of L1</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>P(C$_6$F$_5$)$_2$ instead of L1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DPEphos (10 mol%) instead of L1</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Without L1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>LiO$_2$Bu instead of NaH</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Cs$_2$CO$_3$ instead of NaH</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Without 3 Å MS</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>3a' was used instead of 3a$^c$</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>Cyclohexane instead of toluene</td>
<td>54</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 1A (0.20 mmol), 2 (0.20 mmol), 3a (0.20 mmol), Pd(OAc)$_2$ (5.0 mol%), L1 (20 mol%), NaH (1.0 equiv.), 3 Å MS (50 mg), toluene (1.0 mL), 60 °C, 12 h. $^b$ NMR yield. $^c$ Without NaH and 3 Å MS at 70 °C.
moderate yields. Probably due to the steric hinderance around the active methine moiety, higher temperatures were required for the reaction of 3d. Under the present conditions, only malonates can be used and other active methylene compounds were ineffective (see the ESI† for details). On the other hand, in the case of "para-substituted" bromoarenes, the reaction occurred in a 1,2-difunctionalization fashion. 4-Methylbromonaphthalene (1H) as well as 2-bromonaphthalenes (1I and 1J) gave 1,2-difunctionalized compounds. Pleasingly, the dearomative three-component C–C bond formation of 4-bromoquinoline (1K) was successful, furnishing a 3,4-dihydroquinoline core in a good yield.

Scheme 1. Substrate scope. (A) Using six-membered bromoarenes. (B) Using bromoheteroles. (C) Using N-tosylhydrazones. aConditions. 1 or 5 (0.20 mmol), 2 (0.20 mmol), 3 (0.20 mmol), Pd(OAc)₂ (5.0 mol%), L1 (20 mol%), NaH (1.0 equiv.), 3 Å MS (50 mg), toluene (1.0 mL), 60 °C, 12 h. NMR yields were shown and numbers in parenthesis are isolated yield. bDPEphos was used instead of L1. cConditions. 1 or 5 (0.20 mmol), 2, 3 (0.20 mmol), Pd(OAc)₂ (5.0 mol%), L1 (20 mol%), NaH (1.0 equiv.), 3 Å MS (50 mg), toluene (1.0 mL), 60 °C, 12 h. NMR yields were shown and numbers in parenthesis are isolated yield. dDPEphos was used instead of L1. eConditions. 1A or 5A (0.20 mmol), 7 (0.30 mmol), Pd(OAc)₂ (5.0 mol%), L1 (20 mol%), NaH (3.0 equiv.), 3 Å MS (50 mg), 1,4-dioxane (1.0 mL), 50 °C, 36 h.
Bromoheteroles were also reactive under the present reaction system (Scheme 1B). 2-Bromothiophene (5A) dearomatively assembled with 2 and malonates 3 to afford the corresponding dihydrothiophenes 6Aa and 6Ab in good yields with moderate E-selectivity. C3-Substituted 2-bromothiophenes also smoothly underwent the dearomative reaction, giving 2,3-difunctionalized hetercycles (6Ba–6Da) with remarkable Z-selectivity due to the steric repulsion. 4-Phenyl-2-bromothiophene (6Ea) was converted to 6Fa in good yield. In contrast, bromoheteroles bearing substituents at the C5-position led to 2,3-difunctionalization, yielding the corresponding dearomatized products 6Fa–6La in moderate yield with exclusive Z-selectivity. 3-Bromothiophene was dearomatized in a 2,3-difunctionalization manner (6Ja).

Furthermore, although diazo esters were not applicable under these conditions (see the ESI† for details), we found that aryl N-tosylhydrazones can be used in this reaction instead of TMS–diazomethane (Scheme 1C). For instance, aryl N-tosylhydrazones successfully reacted with 1-bromonaphthalene (1A) as well as 2-bromothiophene (5A) to give the corresponding products in moderate yields. Dearomatized products with tetra-substituted olefins were also synthesized by using diphenyl N-tosylhydrazine 7b in acceptable yields.

The most significant value of the method is that the dearomatized product can be elaborated to various multiply-functionalized alicyclic systems (Scheme 2). Partial reduction of 4Aa under diimide conditions produced dihydronaphthalene 10 in high yield with remarkable diastereoselectivity. The remaining olefin of 10 can be further functionalized. For instance, the treatment of 10 with NBS furnished bromolactone 11 in good yield with high diastereoselectivity. mCPBA oxidation of 10 produced epoxide 12 as a single diastereoisomer; epoxide 12 was further converted by using BF₃·OEt₂ to construct trans C–O bonds on the cyclic skeleton (13). A similar structural diversification was operative for 1,2-difunctionalized product 4le. Diastereo- and site-selective reduction of 4le, followed by epoxidation, bromohydrin formation, or hydrogenation furnished the corresponding multiply-functionalized alicyclic systems (15–17). Heterocycle 6Aa was successfully converted to sulfone 18 in good yield. These results strongly support that the present dearomative method can lead to a diverse range of highly functionalized alicyclic systems.

Our proposed mechanism is outlined in Scheme 3. The first oxidative addition of a bromosarene, followed by a Pd-carbene formation with a diazo compound generates an Ar–Pd–carbene complex. The Pd–carbene species leads to migratory insertion of the aryl moiety, giving a Pd–benzyl complex. Subsequently, the Pd-benzyl complex reacts with a sodium malonate to produce a benzyl–Pd–malonate species. The final C–C bond formation from the Pd–O-enolate species releases a dearomatized product. In this reaction mechanism, the key for the final C–C bond formation would be the generation and reactivity of the benzyl–Pd–O-enolate intermediate. The highly coordinating ability of malonates probably favors formation of the benzyl–Pd–O-enolate species, which then allows the inner-sphere C–C bond formation to give 1,4-difunctionalized products. Although a detailed mechanism and the site-selectivity is unclear at this stage, in the case of C4-substituted arenes, the C–C bond formation at the C2 position takes place from a σ-benzyl–Pd–O-enolate. This likely occurs a 3,3'-sigmatropic reductive elimination mechanism, probably due to steric repulsion between the malonate moiety and the C4-substituent.
Conclusions

In summary, we have developed the dearomatizing three-component C-C bond formation of bromoarenes with diazo compounds and malonates by a palladium catalyst. The reaction was applicable to a variety of aryl bromides including azines and heteroles, which suggests that this reaction system is not restricted to the electronic nature of the arenes. The structural elaboration of the dearamatized products showcase the synthetic utility of the present method. Further studies to develop asymmetric dearylation using a chiral catalyst and to elucidate the reaction mechanism are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references


17 During the preparation of this manuscript, C–H alkylation involving a similar mechanism was reported, where a Pd-O-enolate benzyl complex was proposed as a key intermediate to construct a C–C bond at the C4 position. See: F. de Azambuja, M.-H. Yang, T. Feoktistova, M. Selvaraju, A. C. Brueckner, M. A. Grove, S. Koley, P. H.-Y. Cheong and R. A. Altman, *Nat. Chem.*, 2020, 12, 489–496.


20 Preliminary results toward an asymmetric reaction are provided in the ESL†