Carbene-catalyzed enantioselective oxidative coupling of enals and di(hetero)arylmethanes †

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Di(hetero)arylmethane is a unique structural motif for natural and synthetic functional molecules. To date, it remains challenging to functionalize the diaryl methyl sp3 carbon–hydrogen bond directly in an enantioselective manner. This is likely due to the relatively inert nature of the carbon–hydrogen bond and the difficult enantiofacial discrimination of two sterically similar aryl substituents. Here we disclose an N-heterocyclic carbene-catalyzed direct oxidative coupling of enals and di(hetero)arylmethanes. Our method allows for highly enantioselective transformation of diaryl methanes and quick access to benzimidazole fused lactams.

Introduction

Diarylmethyl units are widely present in functional molecules and natural products. Examples of such molecules include the antidepressant drug Sertraline,1 Bz–IB conjugates with anti-inflammatory activities2 and the natural product voacamine3 with cannabinoid CB1 receptor antagonistic activity (Fig. 1a). Notably, the diaryl methyl sp3 carbon in these bioactive molecules is often present as a chiral center.4 To date, the most well-studied approach for the incorporation of diaryl methane unit relies on reactions between diarylmethyl carbocations and nucleophilic substrates5 (Fig. 1b). Diarylmethyl carbocation intermediates are typically generated in situ from their precursors such as diarylmethanols.6 In contrast, as a potentially more straightforward approach, direct modification of diarylmethanes is much less studied (Fig. 1c). This is in part due to the weak acidity of the methyl C–H and the difficult enantiofacial discrimination of two sterically similar aryl substituents. Deprotonation of such a benzylic C–H bond typically requires the use of a strong base such as "BuLi or Na.7 As an alternative choice, oxidative transformations of diarylmethanes via benzylic organometallic species8 or benzylic radicals9 can be realized under milder conditions. However, in all these approaches, direct enantioselective modification of diarylmethane remains challenging. Limited examples in this direction include oxidative or photoredox transformations via o-quinone methides (o-QM)10 or o-quinodimethanes (o-QDM)11 as the key intermediates, and recent Rh-mediated asymmetric C–H arylation of diarylmethane.12

Fig. 1 Diarylmethyl compounds and their enantioselective synthesis.
Herein we disclose an N-heterocyclic carbene (abbreviated as NHC or carbene) organic catalyst-mediated formal oxidative coupling of enal β-carbon and diarylmethanes (Fig. 1d). Our initial designing consideration is to generate a diarylmethyl radical from a diarylmethane substrate as a key intermediate under oxidative conditions (Fig. 1c). It is known that the tendency for deprotonation and radical formation of benzylic carbons can be well-tuned by altering the electronic properties of the aryl substituents 13 (Fig. 1c). We therefore eventually introduce heterocyclic benzimidazole as one of the aryl units of the diarylmethane substrate in order to achieve suitable reactivity. The selection of benzimidazole units also provides two additional benefits: benzimidazole is a structural analogue of purine and a potential pharmacophore; 14 the NH group in benzimidazole can facilitate the turnover of the NHC catalyst via the formation of a lactam product at the end of the catalytic cycle. 15 Mechanistic studies suggest that some of our carbene-catalyzed reactions likely go through single-electron-transfer (SET) processes and radical intermediates in the key steps, although an electron pair pathway cannot be completely ruled out.

### Results and discussion

Key results in searching for suitable conditions by using cinnamaldehyde (1a) and diarylmethane 2a as model substrates are summarized in Table 1. We firstly used achiral triazolium salt A 16 as the NHC pre-catalyst, DABCO as the base, and 3,3’,5,5’-tetra-tert-butyl-4,4’-diphenoquinone (DQ) as the oxidant. 17 With 2-benzyl benzimidazole 2a as the substrate, the proposed lactam product was not observed in an appreciable amount under various conditions. We then introduced an electron-withdrawing nitro group into the phenyl ring of dialkylmethane (using 2b as the substrate), and obtained the corresponding lactam product in 22% yield (entry 2). The use of amino indanone-derived triazolium carbene pre-catalyst B 18 led to the lactam product in 36% yield with excellent ee (95% ee, entry 3). Several chiral NHC catalysts evaluated here did not provide better results in terms of both yields and ee values (entries 4–6). We then decided to use pre-catalyst B for further condition optimization (entries 7–12). The switch of the base from DABCO to DMAP significantly improved the yield from 36% (entry 3) to 60% (entry 7) with a slight increase of ee (from 95% to 98% ee) as well. Further optimization by using 1.5 equivalents of 1a and DQ and performing the reaction at 40 °C gave a better result of 84% yield and 98% ee (entry 8). Several oxidants (phenazine, 19 hexachloroethane 20 and 4-nitro pyridine N-oxide 21) previously used in oxidation and single-electron-transfer (SET) radical reactions could also mediate the reaction with low to moderate yields and excellent ee values (entries 9–11). Finally, the reaction outcome with B as the catalyst could be further improved by lowering the reaction concentration (entry 12).

With an acceptable condition in hand (Table 1, entry 12), we evaluated the scope of enals by using 2b as a model dialkylmethane substrate (Table 2). Placing halogens, carboxylic esters, nitro groups, methyl, and methoxyl units as substituents at the para-position of the enal β-carbon ring was well tolerated (3a–3h). The absolute configuration of 3c was unambiguously confirmed by single-crystal X-ray diffraction analysis (for details, see the ESI†). The use of enals with different substitution patterns on the phenyl ring all gave products with excellent yield, dr, and ee values (3i–3k). Heterocyclic, naphthalene, and alkene substituents were all tolerated in β-substitution of enals (3l–3o). Enal with a β-carboxylate substituent gave product 3p in moderate yield with excellent dr and good ee. The use of enals with a β-alkyl substituent led to products with low yields (around 10% yields as estimated via NMR).

We next studied the scope of diarylmethanes by using cinnamaldehyde 1a as the model enal substrate (Table 3). The nitro substituent in 2b can be replaced with other electron-withdrawing units such as CN, CO2CH3, SO2CH3, CF3, and Br (4b–4f). Placing nitro groups at the ortho- or meta-position of the benzyl group of substrate 2 led to some decrease in reaction yields without affecting enantioselectivities (4g–4h). We also investigated the effect of substituents on the benzimidazole framework, and found that various substituents and substitution patterns were well tolerated (4i–4o). When unsymmetrical benzimidazoles were used, the corresponding lactam products were obtained as a mixture of two regio-isomers (4k–4o, see the

### Table 1 Screening of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>NHC, base Oxidant Yield/%</th>
<th>ee/%</th>
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<tbody>
<tr>
<td>1</td>
<td>2a, A, DABCO DQ Trace</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>2b, A, DABCO DQ 22</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>2b, B, DABCO DQ 36</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>2b, C, DABCO DQ 27</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>2b, D, DABCO DQ 18</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>2b, E, DABCO DQ 25</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>2b, B, DMAP DQ 60</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>2b, B, DMAP DQ 84</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>2b, B, DMAP Phenazine 46</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>2b, B, DMAP CCl3 7</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>2b, B, DMAP 4-Nitropyridine N-oxide 40</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>2b, B, DMAP 92</td>
<td>98</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.06 mmol, 1.2 equiv.), 2 (0.05 mmol, 1.0 equiv.), NHC (20 mol%), base (0.5 equiv.) and oxidant (1.2 equiv.) in 0.5 mL THF at rt. * Determined by 1H NMR, with 1,3,5-trimethoxybenzene as an internal standard. * Determined by chiral-phase HPLC analysis. * 1.5 equiv. of 1a and oxidant were used; reaction temperature was 40 °C. * In 1 mL THF. DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-dimethylaminopyridine.
This regio-isomer issue can be circumvented via one additional step in a one-pot operation: the lactam ring opened in acid alcohol in quantitative yield with ee and dr retained (as exemplified in 2k to 5, Table 3, one-pot procedure).

Substrate bearing simple imidazolidine can also be used, giving product 4p in 69% yield, 10 : 1 dr, and 98% ee.

To understand the reaction pathways, we performed several control experiments. We performed H/D exchange experiments for diarylmethane substrates 2b and 2f (Scheme 1a). With 2b as the substrate, deuterated adduct D-2b was observed in 50% yield (NMR yield, see the ESI† for details). However, when 2f (an effective substrate in our oxidative coupling reaction, Table 3, product 4f) was used, no H/D exchange was observed. This result suggested that the formation of an enamine intermediate was not necessary in our catalytic coupling reaction. When 2b was mixed with the radical scavenger BHT (butylated hydroxytoluene) in the presence of a DQ oxidant, adduct 7 could be obtained in 47% yield (Scheme 2b), suggesting the existence of benzylic radical intermediates. It is also worth noting that ketones 6 derived from 2 via oxidation of the benzylic carbon were observed as the main side products in nearly all examples. 2q-dimer generated from homo-coupling of benzylic carbon was also observed when 2q was used as a substrate (Scheme 1c). This evidence suggested the presence of benzylic radical intermediates (see the ESI† for details of other mechanism study).

Two possible reaction pathways are illustrated in Scheme 2. In the 1st possible pathway (Scheme 2a), oxidation of 1a under Table 2: Examples of enal substrates

Table 3: Examples of di(hetero)arylmethane substrates

Unless otherwise noted, all reactions were run on a 0.2 mmol scale under the standard conditions (Table 1, entry 12). Yield refers to isolated yield. The reaction temperature was 80 °C.
NHC catalysis leads to \( \alpha,\beta \)-unsaturated azolium ester intermediate I.\(^{23} \) Isomerization of 2 to an enamine intermediate II. Nucleophilic addition of II to I via an electron-pair pathway\(^{23} \) (direct 1,4-addition\(^{24} \) or Claisen rearrangement\(^{25} \) route) leads to III. Cyclization of III leads to product 3a with regeneration of the NHC catalyst. In the 2nd possible pathway (Scheme 2b), NHC-bound radical cation intermediate V is formed via a SET oxidative process\(^{26,27} \) starting from enal 1a. Under oxidative conditions, diarylmethane 2 is converted to a benzylic radical intermediate VI.\(^{9} \) Coupling of radical intermediates V and VI via a SET process\(^{27} \) leads to intermediate III, which is subsequently converted to product 3a. Ketones 6 derived from 2 via oxidation of the benzylic carbon, as well as the homo-coupling generated 2-dimer (Scheme 1c), were observed as the main side products in nearly all examples, suggesting the presence of radical intermediate VI.\(^{9} \)

The oxidative coupling products from our catalytic reactions can undergo further transformations under simple conditions (Scheme 3). For example, adduct 3a was reduced by DIBAL-H to \( \text{N}_{2} \text{O} \)-acetal 8 in 84% yield. Nitro group reduction with simultaneously ring opening of lactam can also transform 3a to ester 9 in 86% yield. Reduction of adduct 4e with LiAlH\(_4\) efficiently gave alcohol 10 (89% yield), which was further cyclized under MsCl to afford benzimidazole fused piperidine 11 in 98% yield. In all cases, the ee and dr of the molecules were completely retained during the transformations.

**Conclusions**

In summary, we have developed an NHC-catalyzed highly enantioselective oxidative coupling of \( \text{di(hetero)arylmethanes} \) and enals to give benzimidazole fused lactams. Ongoing studies include the development of effective methods for enantioselective oxidative coupling of more challenging inactivated carbon–hydrogen bonds, application of this method for assembly or modification of pesticides and active components of Chinese medicines, and bioactivity evaluations of relevant molecules.

**Conflicts of interest**

There are no conflicts of interest to declare.

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**Notes and references**