Iron-catalysed enantioselective carbometalation of azabicycloalkenes†

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The first enantioselective carbometalation reaction of azabicyclic alkenes has been achieved by iron catalysis to in situ form optically active organozinc intermediates, which are amenable to further synthetic elaborations. The observed chiral induction, along with the DFT and XAS analyses, reveals the direct coordination of the chiral phosphine ligand to the iron centre during the carbon–carbon and carbon–metal bond forming step. This new class of iron-catalysed asymmetric reaction will contribute to the synthesis and production of bioactive molecules.

Carbometalation reactions, the 1,2-addition of organometallic species to alkenes or alkynes, are a powerful synthetic tool for carbon–carbon (C–C) bond formation.1 In particular, the transition-metal-catalysed asymmetric carbometalation of oxo- and azabicyclic alkenes is an effective strategy for the enantioselective synthesis of chiral building blocks for various natural products.2 Lautens and co-workers have extensively studied the asymmetric transformations of bicyclic alkenes catalysed by rhodium3 and palladium,2b,4 where the enantioselective carbometalation brings about desymmetrisation of the meso-substrates.5 Subsequent ring-opening reactions of the carbometalation intermediates give optically active products bearing multiple stereocentres. Copper6 and iridium7 catalysts can also affect the asymmetric transformations of oxo- and azabicyclic alkenes (Scheme 1a).

The enantioselective carbometalation of azabicyclic alkenes without ring-opening is also of significant synthetic interest, as it can provide direct access to the azabicyclo[2.2.1]heptane skeleton of alkaloid derivatives, such as epibatidine and epiboxidine (Scheme 1b).8 Nevertheless, the catalytic asymmetric addition of organometallic species (i.e., carbon nucleophiles) to azabicyclic alkenes without the ring-opening remains virtually unexplored.9

Asymmetric iron catalyses have emerged rapidly in organic synthesis,10 while their use in enantioselective carbometalation remains limited to the highly strained cyclopropene substrates.5b This can be attributed to the unstable coordination of chiral ligands with the iron centre, of which the oxidation states often fluctuate during the catalytic cycle. Indeed, Bedford and coworkers discovered that phosphine ligands do not coordinate to the iron centre of the iron-catalysed Negishi coupling.11 On the other hand, we have observed evident asymmetric induction in iron-bisphosphine-catalysed enantioselective cross-coupling reactions,12 and an...
The electronic factors of alkene substrates seemed not to affect this carbometalation reaction: substrates having electron-withdrawing fluoro groups or electron-donating methoxy groups provided the corresponding products 3i and 3m in excellent yields (85% and 91%, respectively) and good enantioselectivities (78% and 75% ee, respectively). On the other hand, the reaction with an aliphatic azabicyclic alkene in became sluggish and did not proceed at \(0^\circ\text{C}\): the expected product 3n was obtained in 67% yield with 75% ee at an increased reaction temperature. As this reaction’s enantioselectivity is comparable to that of other substrates, the fused benzene ring has no significant effect on the enantioselectivity.

Trapping of the carbometalation intermediate with various electrophiles showed the stereospecific nature of the carbometalation/trapping sequence.\(^5,8\) The reaction of 1a with \(\sigma\)-tolylzinc reagent gave optically active organozinc intermediate 4, which underwent electrophilic trapping with \(\text{CD}_3\text{CO}_2\text{D}\) to give deuterated product 5a in 96% yield with 99% ee and >99% \(\text{cis}\)-selectivity (entry 1, Table 2). Similarly, when trapped with iodine as the electrophile, product 5b was obtained in 84% yield with 99% ee and a diastereomeric excess of 94% (entry 2, Table 2).\(^14\)

Preliminary mechanistic studies on the mixture of the iron salt, \((S,S)\)-chiraphos, and aryl zinc reagent by the combination of X-ray absorption spectroscopy (XAS) and DFT-calculations show that the diaryl iron(ii) species is the most likely intermediate responsible for this enantioselective carbometalation reaction. The direct coordination between the chiral phosphine ligand and iron centre inferred by the fact of chiral induction is also supported by the XAS analysis and the DFT calculations.

**Table 1** Scope of iron-catalysed enantioselective carbometalation reactions.\(^a\)

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Yield of 5a [%]</th>
<th>ee [%]</th>
<th>de [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CD$_3$OD/CD$_3$CO$_2$D = 80/20</td>
<td>96 (5a)</td>
<td>99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2 $\text{I}_2$</td>
<td>84 (5b)</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Reaction performed at 0\(^\circ\) C. 

\(^b\) Diastereomeric excess determined by $^3$H NMR analysis.

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2. Trapping of the carbometalation intermediate with various electrophiles showed the stereospecific nature of the carbometalation/trapping sequence.\(^5,8\) The reaction of 1a with \(\sigma\)-tolylzinc reagent gave optically active organozinc intermediate 4, which underwent electrophilic trapping with \(\text{CD}_3\text{CO}_2\text{D}\) to give deuterated product 5a in 96% yield with 99% ee and >99% \(\text{cis}\)-selectivity (entry 1, Table 2). Similarly, when trapped with iodine as the electrophile, product 5b was obtained in 84% yield with 99% ee and a diastereomeric excess of 94% (entry 2, Table 2).\(^14\)

3. Preliminary mechanistic studies on the mixture of the iron salt, \((S,S)\)-chiraphos, and aryl zinc reagent by the combination of X-ray absorption spectroscopy (XAS) and DFT-calculations show that the diaryl iron(ii) species is the most likely intermediate responsible for this enantioselective carbometalation reaction. The direct coordination between the chiral phosphine ligand and iron centre inferred by the fact of chiral induction is also supported by the XAS analysis and the DFT calculations.
The experimental and computational details are described in the ESI.\(^\text{15}\) Fig. 1 shows a plausible mechanism for the present carbometalation reaction. The catalytic cycle starts with diaryl iron(n)-(S,S)-chiraphos complex A, which is generated by the reduction of FeCl\(_3\) with an excess organozinc reagent (>3.0 equivalents) in the presence of (S,S)-chiraphos. The XAS and DFT analyses reveal that the geometry of A is tetrahedral. An azabicyclic alkene coordinates to the intermediate likely in an exo-fashion to give intermediate B. Enantioselective olefin insertion proceeds to form carboferration intermediate C. Subsequent transmetalation with the organozinc reagent leads to optically active organozinc intermediate D and regenerates iron(n) species A. Upon the sequential addition of electrophiles to the reaction mixture, intermediate D undergoes trapping to provide final product E. The sharp contrast between Bedfor’d and our observations can be attributed to the difference of the redox behaviours of the iron centre in cross-coupling and carbometalation; the latter reaction maintains iron(n) oxidation states during the catalytic cycle and the biphosphine ligand predominantly coordinated to the iron centre, rather than to the zinc centre.\(^\text{16,17}\)

In summary, we have developed the first enantioselective carbometalation reactions between various azabicycloalkenes and arylzinc reagents, which proceed under mild conditions by using a readily available FeCl\(_3\) and (S,S)-chiraphos catalytic system. Trapping experiments reveal the formation of a densely-functionalised optically active organozinc intermediate. XAS and DFT studies provided evidence for the direct coordination of the functionalised optically active organozinc intermediate. XAS and DFT analyses were supported by the JURC at ICR, Kyoto University. The synchrotron radiation experiments were performed at the BL14B2 (2015A0121, 2015B0121, 2016A0121, and 2016B0121) and BL02B1 (2016A0114) of SPring-8 with the approval of the Japan Synchrotron Radiation Research Institute (JASRI). The computations were performed at the Research Center for Computational Science, Okazaki, Japan.

**Conflicts of interest**

The authors declare no conflict of interest.

**Notes and references**


The absolute configuration of 3,4-dichlorophenyl-substituted product 3e was determined by X-ray single crystal analysis (Fig. S2, ESI†). Similar configurations are expected for the other products owing to the similarity of the \( ^1 \)H NMR coupling constants and the chiral HPLC retention times.


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The absolute configuration of iodo-substituted product 5b was determined by X-ray single crystal analysis (Fig. S3, ESI†).

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