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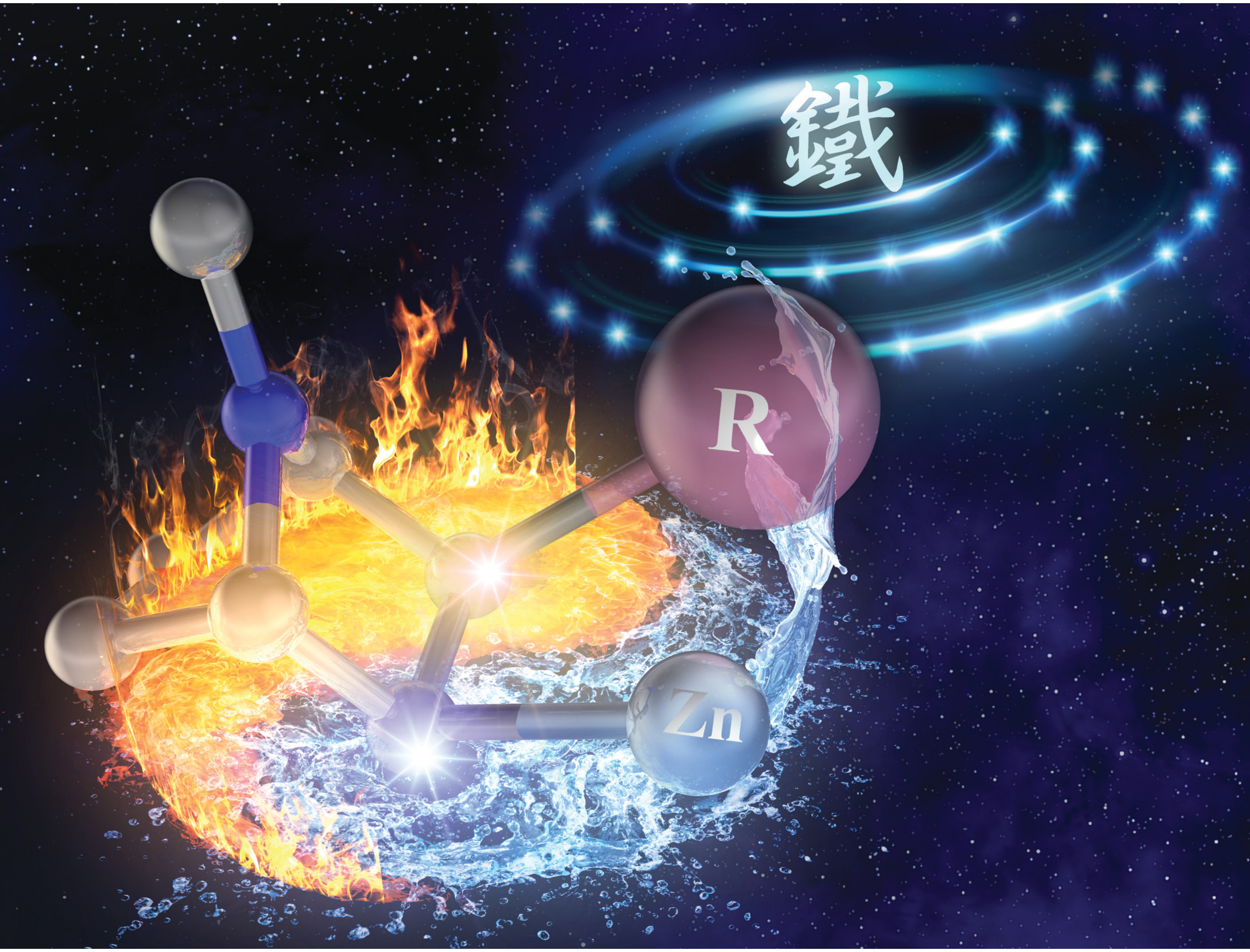

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Iron-catalysed enantioselective carbometalation of azabicycloalkenes†

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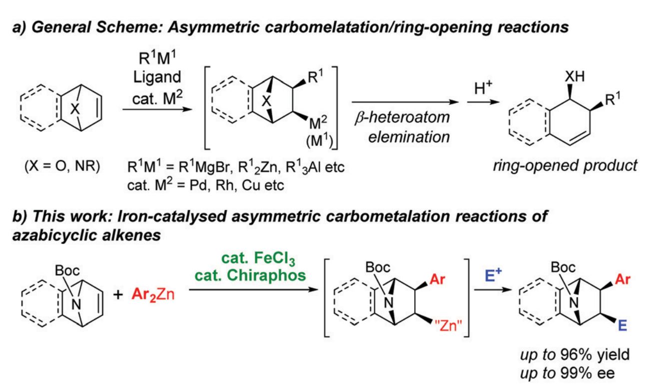
The first enantioselective carbometalation reaction of azabicycloalkenes has been achieved by iron catalysis to *in situ* form optically active organozinc intermediates, which are amenable to further synthetic elaborations. The observed chiral induction, along with the DFT and XAS analyses, reveals the 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 oxa- 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 rhodium[3] 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. Copper[6] and iridium[7] catalysts can also affect the asymmetric transformations of oxa- 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 in the iron-catalysed Negishi coupling.[11] On the other hand, we have observed evident asymmetric induction in iron-bisphospine-catalysed enantioselective cross-coupling reactions,[12] and an



Scheme 1 Transition-metal-catalysed asymmetric carbometalation reactions (E = electrophile).

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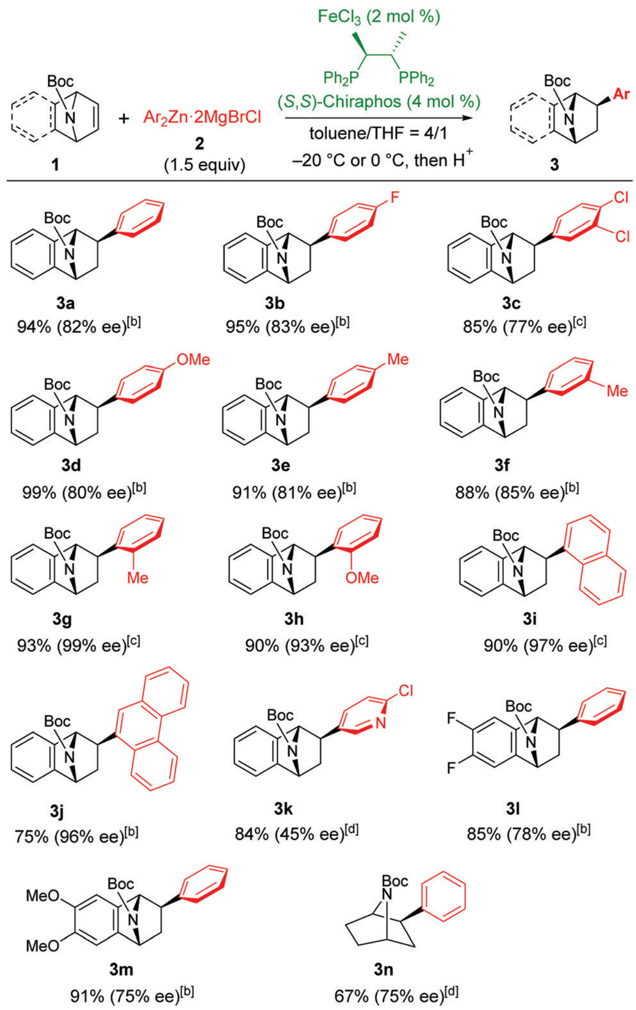
Table 1 Scope of iron-catalysed enantioselective carbometalation reactions.[a]



[a] Reactions were performed using 0.5–1.0 mmol of **1** and quenched with degassed MeOH/AcOH (80/20, 1.0 mL) unless otherwise noted. [b] Reaction performed at −20 °C. [c] Reaction performed at 0 °C. [d] Reaction performed at 30 °C. See the ESI for detailed reaction conditions.

acceleration effect of a chelate phosphine in the diastereoselective carbometalation of oxa- and azabicyclic alkenes with arylzinc reagents.[9b] These conflicting observations have led us to attempt an enantioselective carbometalation under iron catalysis.

The study began with chiral phosphine ligand screening based on our success in iron-catalysed enantioselective cross-coupling reactions.[12] We eventually found (*S*,*S*)-chiraphos as an optimal ligand for the carbometalation of azabicycloalkene with a phenylzinc reagent by using catalytic amounts of $FeCl_3$ (details are shown in the ESI†).

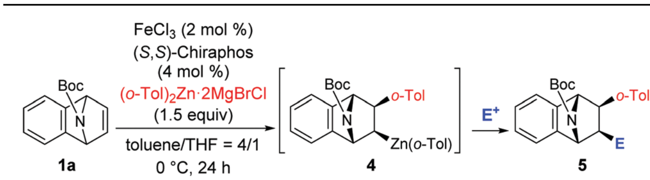
Table 1 displays the scope of the reaction under the optimised conditions: the reaction of **1a** with *para*- and *meta*-substituted arylzinc reagents gave the corresponding products **3a–3f** in 85–99% yield with good enantioselectivities (77–85% ee).[13] When an *o*-tolylzinc reagent was employed, the enantioselectivity increased dramatically to give **3g** in 93% yield with 99% ee. Other sterically hindered arylzinc reagents such as *o*-methoxyphenyl-, 1-naphthyl-, and 9-phenanthrylzinc reagents also provided the corresponding products (**3h–3j**) with high enantioselectivities (93–97% ee). The heteroaromatic 4-chloro-3-pyridylzinc reagent can also participate in the carbometalation to give **3k** in 84% yield with relatively low enantioselectivity (45% ee). The steric factor of aryl nucleophiles had a substantial impact on the enantioselectivity, suggesting that the spatial interaction of the aryl group and the alkene substrate leads to mutual orientation of the two reactants in the stereochemistry-determining carbometalation step.

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 **3l** 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 **1n** became sluggish and did not proceed at 0 °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.[5,9b] The reaction of **1a** with *o*-tolylzinc reagent gave optically active organozinc intermediate **4**, which underwent electrophilic trapping with CD_3CO_2D to give deuterated product **5a** in 96% yield with 99% ee and >99% *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 2 Electrophilic trapping of a carbozincation intermediate



Entry	Electrophile	*E*	Yield of 5[a] [%]	ee [%]	de[b] [%]
1	CD_3OD/CD_3CO_2D = 80/20	D	96 (**5a**)	99	>99
2	I_2	I	84 (**5b**)	99	94

[a] Isolated yield. [b] Diastereomeric excess determined by ^1H NMR analysis.

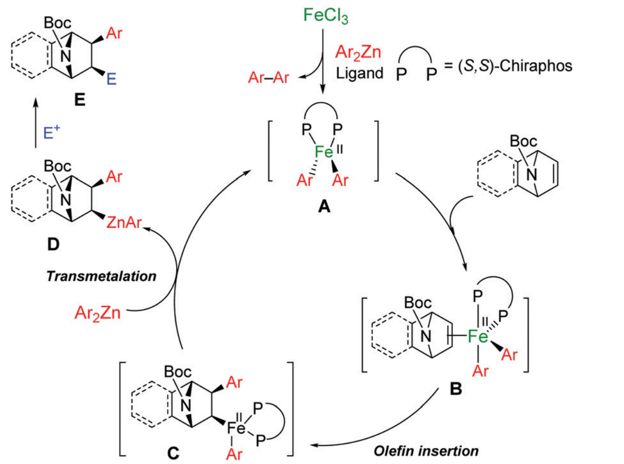


Fig. 1 Catalytic cycle based on the XAS and DFT analyses of the stoichiometric reactions.

(the experimental and computational details are described in the ESI†).[15] Fig. 1 shows a plausible mechanism for the present carbometalation reaction. The catalytic cycle starts with diaryl iron(II)–(*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(II) 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 Bedford's 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(II) oxidation states during the catalytic cycle and the bisphosphine ligand predominantly coordinated to the iron centre, rather than to the zinc centre.[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 chiral phosphine ligand to the iron(II) centre, even in the presence of an excess zinc species that can undergo competitive coordination of the phosphine ligands. The present findings demonstrate the potential of iron-catalysed stereoselective C–C bond formations for synthesising complex chiral molecules of biological relevance. Further mechanistic studies on the detailed multi-spin reaction pathway and the origin of the asymmetric induction are currently underway.

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Conflicts of interest

The authors declare no conflict of interest.

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