Article

Enantioselective transition-metal catalysis via an anion-binding approach

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Asymmetric transition-metal catalysis represents a powerful strategy for accessing enantiomerically enriched molecules[1–3]. The classical strategy for inducing enantioselectivity with transition-metal catalysts relies on direct complexation of chiral ligands to produce a sterically constrained reactive metal site that allows formation of the major product enantiomer while effectively inhibiting the pathway to the minor enantiomer through steric repulsion[4]. The chiral-ligand strategy has proven applicable to a wide variety of highly enantioselective transition-metal-catalysed reactions, but important scenarios exist that impose limits to its successful adaptation. Here, we report a new approach for inducing enantioselectivity in transition-metal-catalysed reactions that relies on neutral hydrogen-bond donors (HBDs)[5,6] that bind anions of cationic transition-metal complexes to achieve enantiocontrol and rate enhancement through ion pairing together with other non-covalent interactions[7–9]. A cooperative anion-binding effect of a chiral bis-thiourea HBD is demonstrated to lead to high enantioselectivity (up to 99% enantiomeric excess) in intramolecular ruthenium-catalysed propargylic substitution reactions[10]. Experimental and computational mechanistic studies show the attractive interactions between electron-deficient arene components of the HBD and the metal complex that underlie enantioinduction and the acceleration effect.

There exist several general scenarios in which the traditional chiral-ligand approach to metal-based asymmetric catalysis encounters real or potential obstacles. For example, the coordination geometry dictated by the metal centre may orient chiral ligand components in a remote relationship to the forming stereocentre, resulting in poor stereochemical communication[11]; the association of Lewis-basic chiral ligands may suppress the reactivity of the metal catalyst[12] or the ligands required for the desired reactivity of the metal complex are not easily amenable to chiral designs[13]. To circumvent such limitations, an alternate strategy has emerged that uses chiral anions associated with cationic metal complexes (Fig. 1a)[14,15]. Toste and List independently reported applications of chiral binaphthol-derived phosphate anions in highly enantioselective gold(I)-catalysed additions to allenes and palladium-catalysed α-allylations of aldehydes, respectively[16,17]. Matsunaga subsequently demonstrated the application of chiral disulfonate anions in enantioselective pyridyl-directed arene C–H functionalizations catalysed by pentamethylcyclopentadienyl (Cp*) rhodium(III) complexes[18]. Despite the highly promising nature of the chiral counteranion approach in transition-metal chemistry, its successful application in asymmetric catalysis has thus far proven limited, a fact that may be attributable to the strong coordinating abilities and/or basicities of the chiral anions[19–21]. Furthermore, although ion pairing has been often invoked to account for the enantioselectivity induced by chiral anions, the described properties of the anions give rise to mechanistic alternatives such as the chiral anion acting as a ligand, hydrogen-bond acceptor or Brønsted base[22–24]. We proposed that the use of chiral cocatalysts that can bind achiral anions with varying coordinating abilities to generate or activate cationic metal complexes could provide a versatile strategy for asymmetric transition-metal catalysis. Such an approach would allow for optimization of the chiral component independent of the inner coordination sphere of the metal complex while also affording broad control over the properties of the counterion.

Anion-binding catalysis has been demonstrated to be an effective strategy for achieving asymmetric induction in organic reactions involving charged intermediates[7,8]. In particular, chiral dual hydrogen-bond donors (HBDs) such as ureas, thioureas or squaramides bind a wide variety of anions associated with cationic organic intermediates to produce chiral ion pairs susceptible to highly enantioselective reactions[5,6]. Small-molecule HBD catalysts have been shown to achieve stereocontrol by engaging selectively in non-covalent interactions with substrates in enantioselectivity-determining events, loosely mimicking the principles that underlie enzymatic catalysis[9]. Furthermore, chiral HBDs have been demonstrated to interact cooperatively through anion binding with achiral catalysts such as Brønsted or main-group Lewis acids to modulate their reactivity and promote enantioselective reactions of interest[25–28].

Beneficial effects of HBDs in transition-metal catalysis have also been documented. Achiral HBDs have been applied as additives to enhance the reactivity of organometallic complexes, potentially by lowering the coordination strength of anionic ligands[29–31]. Dual HBD motifs have been incorporated into ligand structures of gold(I) chloride or phosphate complexes to sequester the anions responsible for inhibition

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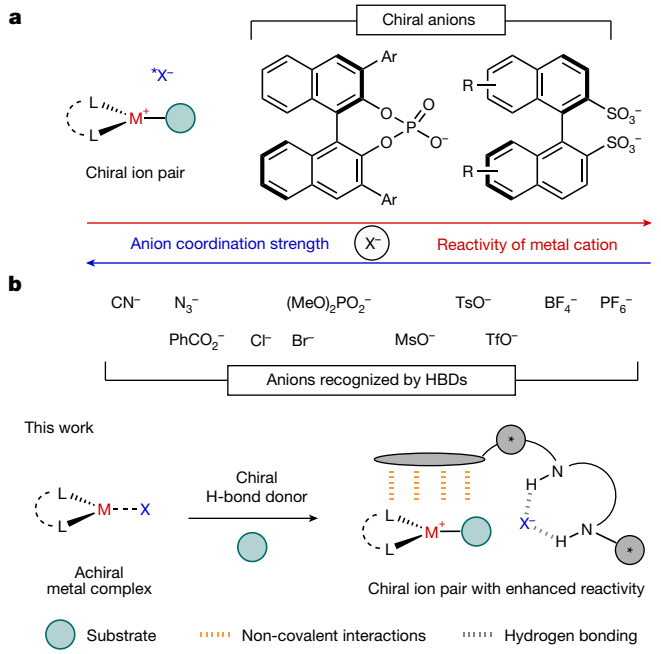


Fig. 1 | Strategies in asymmetric transition-metal catalysis. a, Chiral anions with demonstrated ability to impart high enantioselectivity in transition-metal-catalysed reactions are often highly coordinating to the corresponding metal cations. M, metal centre; L, neutral ligand; X, ionic ligand; green ball, substrate; *, chiral. **b**, The cocatalytic approach explored in this study. HBDs can bind a wide variety of achiral counterions commonly associated with transition-metal catalysts.

of the metal catalyst[32,33]. In addition, chiral organic compounds bearing HBD components have been used as cocatalysts in asymmetric transition-metal-catalysed transformations[34–39]. The proposed mechanisms of stereoinduction in the reported examples primarily involve the organocatalyst acting as a ligand on the metal or associating with other organic components in the reaction. However, in one intriguing report, Mattson and coworkers postulated an anion-binding interaction between a chiral binaphthyl-derived silanediol organocatalyst and a copper(II) triflate Lewis acid in moderately enantioselective conjugate additions of indoles to alkylidene malonates[39]. Inspired by the well-documented effectiveness of dual HBDs in promoting asymmetric reactions through ion-pairing mechanisms, we envisioned that anion binding with chiral HBDs could serve as a broadly applicable principle for achieving highly enantioselective cocatalysis with achiral organometallic complexes (Fig. 1b).

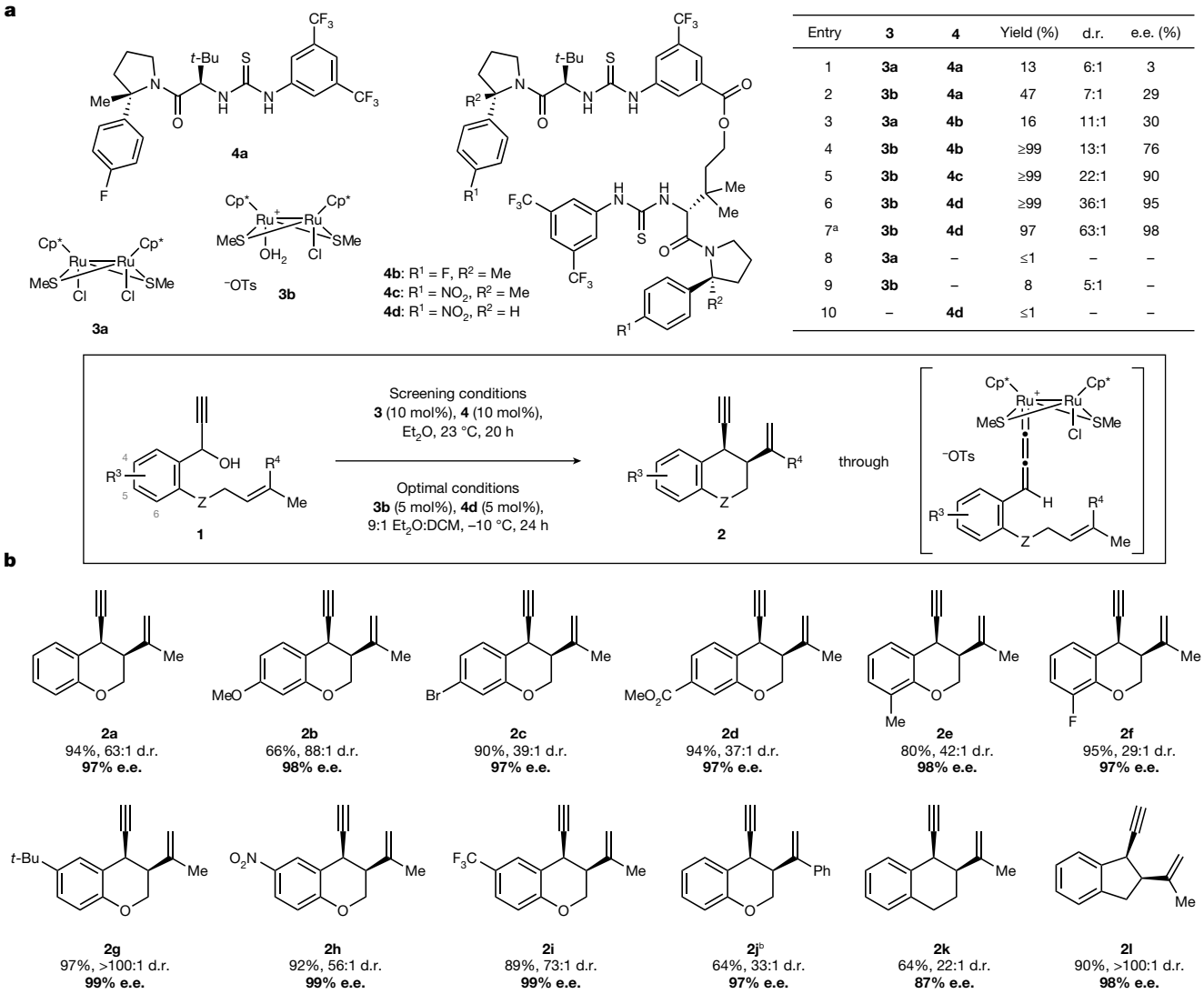
We explored the concept of cooperative catalysis between chiral HBDs and transition-metal complexes in the context of an intramolecular ruthenium-catalysed substitution of racemic propargylic alcohols (**1**) to access chiral chromane derivatives (**2**) (Fig. 2). In pioneering work, Nishibayashi and coworkers demonstrated that thiolate-bridged diruthenium complexes (**3**) activate propargylic alcohols to form ionic ruthenium–allenylidene intermediates that can react with a variety of nucleophiles[10,40–43]. Although an asymmetric variant of the intramolecular propargylic substitution was developed using chiral thiolates[44], incorporation of sterically hindered ligands was observed to impart diminished reactivity of the diruthenium catalyst[10]. We proposed that chiral HBDs (**4**) could bind the anion of the diruthenium complex to increase the reactivity of the metal centre and induce enantioselectivity through attractive non-covalent interactions within the ion pair.

We found that the combination of HBD **4a**[45,46] and the commercially available diruthenium dichloride complex **3a** catalysed the substitution of propargylic alcohol **1a** to form chromane **2a** in low yield and enantioselectivity (Fig. 2a, entry 1). The ionic diruthenium tosylate complex **3b** together with **4a** promoted the cyclization more effectively, albeit still with low enantioselectivity (entry 2). Marked improvements in both yield and enantioselectivity were obtained using bis-thiourea HBD **4b** as a cocatalyst (entries 3 and 4). This observation reveals a new application of this class of specifically linked HBDs, which were originally designed to facilitate cooperative anion abstraction from chloroacetals[47] and subsequently demonstrated as effective catalysts in glycosylation reactions with phosphate electrophiles[48–51]. The aryl-pyrrolidine components of the HBD catalysts have been previously shown to exert profound effects on the outcomes of various reactions involving organic electrophiles by engaging in specific attractive π interactions[52,53]. Variation of the aryl substituents in the present system also proved fruitful, leading to the identification of catalyst **4c**, which promoted the model reaction in 90% enantiomeric excess (e.e.) and 22:1 diastereomeric ratio (d.r.) (entry 5). A further notable improvement in the reaction outcome was achieved using the desmethyl analogue **4d** (entry 6). Lowering the reaction temperature and using a solvent blend to improve solubility of the catalysts enabled a decrease of the loading of **3b** and **4d**, and resulted in formation of **2a** in 98% e.e. and 63:1 d.r. (entry 7). Control experiments demonstrated that the cooperative effect between **3b** and **4d** is essential for the observed reactivity, as little or no product formation was observed in the absence of either the HBD (entries 8 and 9) or the diruthenium complex (entry 10).

The substrate scope of the developed cocatalytic cyclization reaction was examined (Fig. 2b, further examples in Supplementary Figs. 2 and 3). Aryl alkynyl carbinols bearing a variety of substituents at positions 4–6 underwent cyclization to the corresponding chromane products in generally high yields, greater than or equal to 20:1 d.r. and enantioselectivities in the range of 94–99% e.e. A substrate containing a phenyl-substituted (*Z*)-alkene moiety demonstrated a lower reactivity in the propargylic substitution reaction but provided **2j** with high selectivity. Other classes of linked alkenyl propargylic alcohols proved to be effective substrates, allowing the generation of tetralin **2k** and indane **2l** with high enantioselectivity.

We sought to unravel the mechanistic basis of the highly enantioselective cooperative effect between the bis-thiourea HBD and the diruthenium complex, with the goal of identifying principles that might guide the discovery of other transition-metal-catalysed reactions amenable to this cocatalytic approach. As noted above, the development of the stereoselective propargylic substitution was inspired by the possibility of applying the anion-binding effect of the chiral HBD to form a chiral ion-pair complex with the diruthenium catalyst. However, an alternative scenario wherein **4d** acts as a chiral ligand coordinated to the reactive diruthenium cation through any of its Lewis-basic functional groups could also potentially occur. Therefore, we directed the first line of our inquiry towards distinguishing between these two fundamentally different mechanistic possibilities.

Diruthenium complexes containing a variety of different anions promoted the reaction in combination with **4d** with moderate-to-high e.e., indicating the potential extension of this cocatalytic strategy to other transition-metal complexes containing various common anions. By contrast, racemic product was obtained in the reaction cocatalysed by the diruthenium complex possessing the tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr^F_4) anion (**3c**). In an effort to explain this notable anion effect on enantioselectivity, we performed a ^{1}H nuclear magnetic resonance (NMR) study of the interaction of **4d** with tosylate (**5a**) and BAr^F_4 (**5b**) salts of an analogue of the catalytically relevant ruthenium–allenylidene intermediate lacking the nucleophilic moiety. Addition of **4d** to a solution of **5a** in a 19:1 mixture of benzene-d_6:dichloromethane-d_2 (DCM-d_2) led to shifts in the resonances corresponding to both the ruthenium–allenylidene cation (labelled **[Ru]**$^+$) and the tosylate anion (labelled **OTs**$^-$) (part II in Fig. 3a). By contrast, addition of **4d** to a solution of **5b** resulted in no detectable shifting of signals, consistent with the absence of any interaction between the BAr^F_4 salt **5b** and **4d** (part I in Fig. 3a). Association of the



Entry	3	4	Yield (%)	d.r.	e.e. (%)
1	**3a**	**4a**	13	6:1	3
2	**3b**	**4a**	47	7:1	29
3	**3a**	**4b**	16	11:1	30
4	**3b**	**4b**	≥99	13:1	76
5	**3b**	**4c**	≥99	22:1	90
6	**3b**	**4d**	≥99	36:1	95
7[a]	**3b**	**4d**	97	63:1	98
8	**3a**	–	≤1	–	–
9	**3b**	–	8	5:1	–
10	–	**4d**	≤1	–	–

Fig. 2 | Reaction optimization and representative products of the stereoselective propargylic substitution reaction. a, Optimization studies. Experiments were run using substrate **1a** (R^3 = H, R^4 = Me, Z = O; 0.05 mmol) at 20 mM concentration. NMR yields are reported. [a]Reaction was run with 5 mol% of **3b** and 5 mol% of **4d** in a 9:1 mixture of Et_2O:DCM at –10 °C. **b**, Representative product scope. Reactions were conducted using 0.2 mmol of **1** at 20 mM concentration. Isolated yields are reported. The absolute configuration of **2h** was determined by X-ray crystallographic analysis, and the configuration of all other products was assigned by analogy. [b]Reaction was run for 48 h.

HBD to the diruthenium complexes thus depends directly on the identity of the anion, and this interaction is tied to effective stereocontrol in the propargylic substitution reaction.

The nature of the interactions between the sulfonate anion of the metal complex and the HBD was probed by NMR analysis of a representative 1:1 ruthenium–allenylidene–HBD complex (stoichiometry determined by Job plot analysis: Supplementary Fig. 34 and accompanying discussion). The mesylate salt **5c** and the conformationally constrained monomethylated bis-thiourea **4e** were selected as the closest analogues to the optimal system that afforded clearly interpretable rotating-frame Overhauser effect spectroscopy (ROESY) NMR data (Supplementary Information). The solution structure deduced from the spectral data shows that the mesylate anion of **5c** is positioned in similar proximity to both thiourea groups of **4e**, consistent with a cooperative hydrogen-bonding interaction between the HBD and the anion of **5c** (Fig. 3b).

In addition to the counterion effect on e.e., profound solvent effects were observed in the propargylic substitution reaction (Fig. 3a, right). The inverse correlation between enantioselectivity and the dielectric constant of the reaction medium indicates that tight ion pairing between the HBD-bound tosylate anion and the cationic diruthenium complex is necessary for efficient enantioinduction[16,54–56]. In support of this mechanistic interpretation, ^{1}H NMR titration experiments between **5a** and **4d** performed using DCM-d_2 as the solvent showed little effect on the chemical shifts of signals corresponding to **[Ru]**$^+$ after addition of **4d**, as would be expected in the case of a solvent-separated ion pair (part III in Fig. 3a). The chemical shifts of signals corresponding to **OTs**$^-$ were still affected by addition of the HBD, consistent with the preservation of the hydrogen-bonding interaction between **OTs**$^-$ and **4d** in the polar solvent. We conclude from these results that the association between diruthenium complexes and the bis-thiourea HBDs relies on anion binding and does not involve any dative bonding interactions.

In addition to promoting high enantioselectivity, bis-thiourea **4d** was found to induce a 20-fold rate enhancement in the enantioselective propargylic substitution reaction catalysed by the diruthenium complex **3b** (part I in Fig. 4a). By contrast, the presence of **4d** had no effect on the rate of the propargylic substitution catalysed by the diruthenium BAr^F_4 complex **3c** (part II in Fig. 4a), demonstrating that not only enantioselectivity but also rate enhancement induced by **4d** in

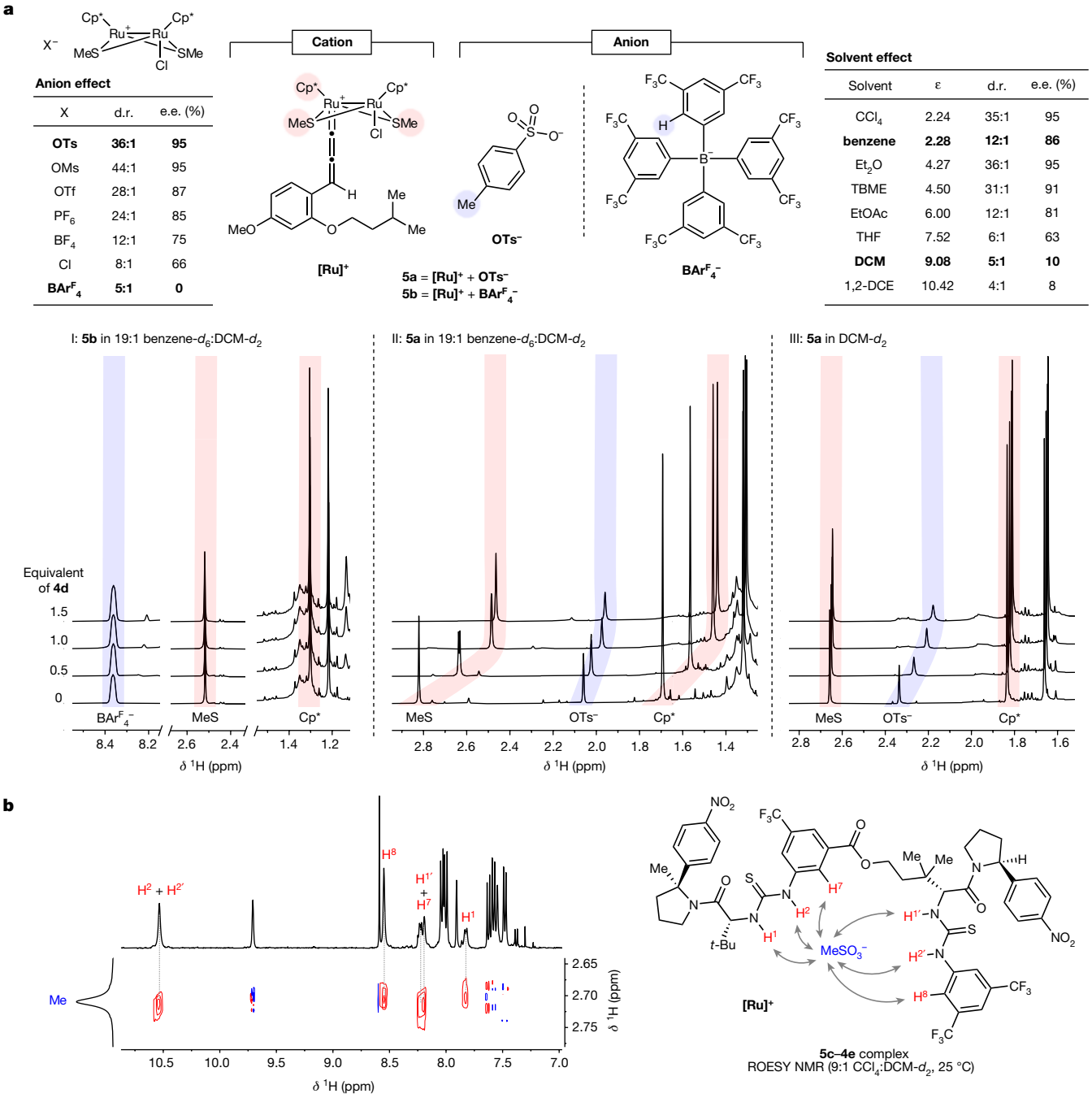


Fig. 3 | Study of the mode of interaction between HBDs and diruthenium complexes in the stereoselective propargylic substitution. a, Effects of the anion identity of the diruthenium complex and reaction solvent on enantioselectivity of the propargylic substitution. Experiments were run using **1a** (0.05 mmol) at 20 mM concentration in Et_2O at 23 °C with 10 mol% of **4d** and 10 mol% of **3b** unless noted otherwise. Dielectric constant values (ε) were taken from the literature[57]. ^{1}H NMR titration study (bottom). Part I shows the addition of 0–1.5 equivalents of **4d** to a solution of **5b** in a 19:1 mixture of benzene-d_6:DCM-d_2. Part II shows the addition of 0–1.5 equivalents of **4d** to a solution of **5a** in a 19:1 mixture of benzene-d_6:DCM-d_2. Part III shows the addition of 0–1.5 equivalents of **4d** to a solution of **5a** in DCM-d_2. **b**, ROESY NMR study of a 1:1 **5c**–**4e** complex.

combination with **3b** is correlated to anion binding. The rate of the reaction catalysed by **3b** in the presence of **4d** was higher than the rate of the reaction catalysed by **3c** containing the non-coordinating BAr^F_4 anion. This observation suggests that the acceleration effect of **4d** in the **3b**-catalysed reaction cannot be ascribed simply to attenuated coordinating ability of the tosylate anion when binding to the HBD, and points to the existence of stabilizing non-covalent interactions between **4d** and the diruthenium–substrate complex in the rate-determining event.

The nature of these putative non-covalent interactions and their role in enantioinduction was probed in a kinetic analysis of the propargylic substitution using structurally modified HBD cocatalysts. As noted above in the discussion of catalyst optimization studies, the aryl-pyrrolidine components of the bis-thioureas were found to have a significant effect on the enantioselectivity of the reaction. In particular, bis-thiourea catalysts with sterically unencumbered aryl-pyrrolidine groups containing electron-deficient arenes afforded the highest levels of enantioselectivity (Fig. 4b and Supplementary Figs. 4–7). Further analysis of the effect induced by the aryl groups of the HBD catalysts showed that enantioselectivity correlates positively with the rate of the propargylic substitution reactions cocatalysed by HBDs bearing aryl

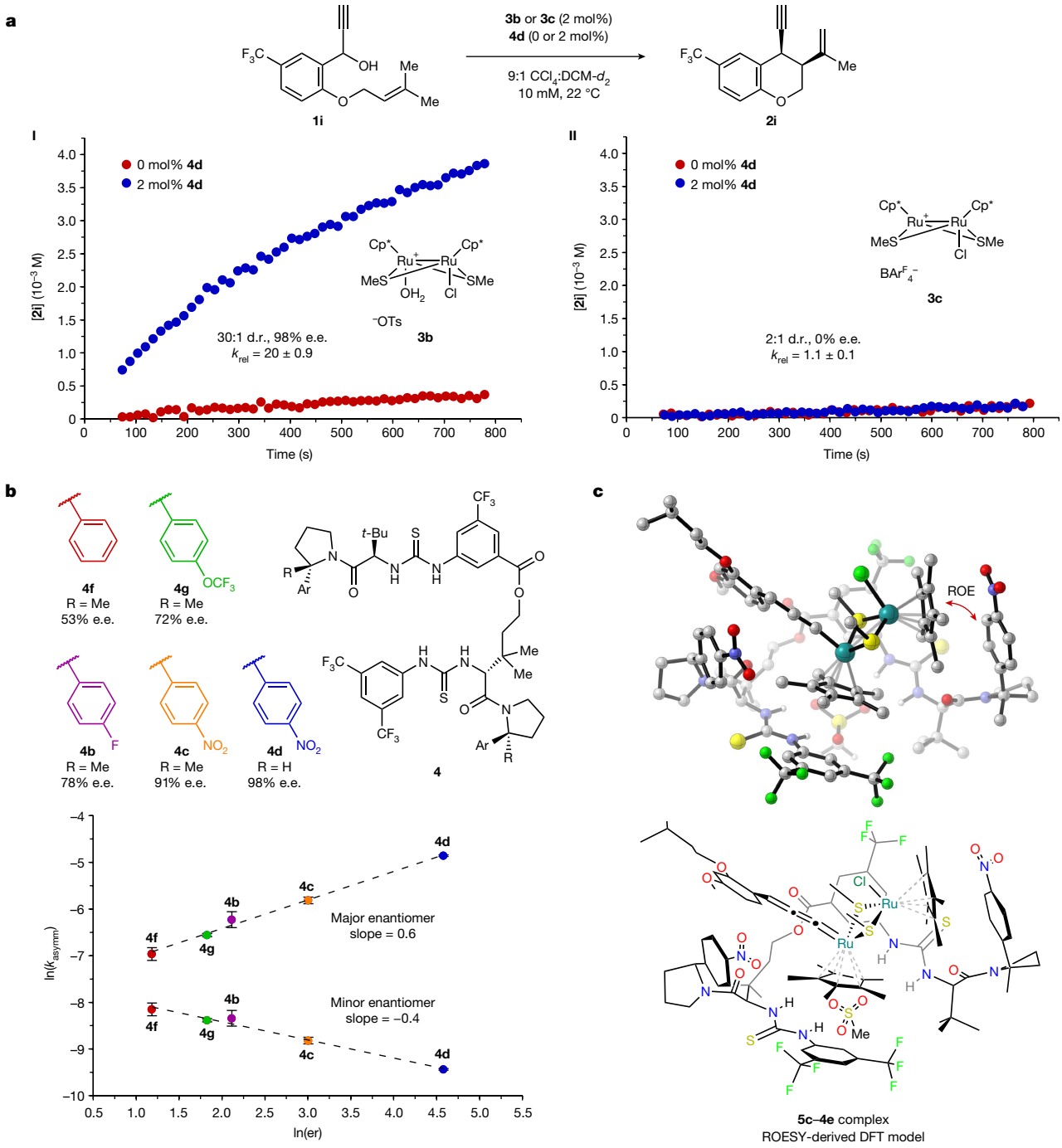


Fig. 4 | Study of non-covalent interactions responsible for enantioselectivity and rate acceleration. a, Study of the effect of HBD **4d** on the rate of the propargylic substitution cocatalysed by either diruthenium tosylate complex **3b** (I) or diruthenium BAr^F_4 complex **3c** (II). **b**, Correlation between enantioselectivity and rate of the propargylic substitution catalysed by HBDs **4b**–**4d**, **4f** and **4g** (see Supplementary Information for details). **c**, Lowest-energy structure of the ROESY-derived solution structure of the **5c**–**4e** complex. Calculations were carried out at the ωB97X-D/SDD(Ru),6-311++G(d,p),PCM(CCl_4)//B3LYP/LANL2DZ(Ru),6-31G(d) level of theory. DFT, density functional theory.

groups with different substituents. Decomposition of the observed rate into contributions from the two enantiomeric pathways revealed that the increased enantioselectivity stems from an acceleration of the pathway leading to the major enantiomer and a simultaneous but lower deceleration of the pathway to the minor enantiomer (Fig. 4b). These results indicate that the aryl groups of the bis-thiourea cocatalysts effect selective stabilization of the rate-determining transition state leading to the major product enantiomer in the ruthenium-catalysed propargylation reaction. Enantioselectivity and reaction rate catalysed by the desmethyl HBD **4d** follow the same correlation, suggesting that the less sterically encumbered aryl-pyrrolidines allow more effective transition-state stabilization by the aryl groups. Closer analysis of the ROESY NMR data corresponding to the 1:1 complex of **5c**–**4e** revealed that both *p*-nitrophenyl groups of **4e** reside in proximity to the electron-rich Cp* ligands of **5c**. A density functional theory analysis of the **5c**–**4e** complex informed by the ROESY NMR data led to the identification of several low-energy conformations that all included at least one face-to-face stacking interaction between the electron-deficient arenes of **4e** and the Cp* ligands of **5c** (Fig. 4c and Supplementary Information).

This study provides compelling evidence that chiral HBDs can associate with ruthenium complexes by binding their anions and induce enantioselectivity and rate enhancement through ion pairing in combination with other non-covalent interactions. Given the wide variety of anions recognized by HBDs and the number of synthetically valuable transformations catalysed by organometallic complexes containing ligands such as Cp* groups capable of engaging in non-covalent interactions, we anticipate that the cooperative anion-binding strategy explored in this study may find broad application in asymmetric transition-metal catalysis.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-023-05804-3.

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Data availability

The data that support the findings in this work are available within the paper and Supplementary Information.

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Additional information

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