Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 6488

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd January 2025
Accepted 11th March 2025

DOI: 10.1039/d5sc00014a

rsc.li/chemical-science

Observation of the solvent enantio-isotope effect in asymmetric ring-opening of cyclic diaryliodoniums with selenocyanate†

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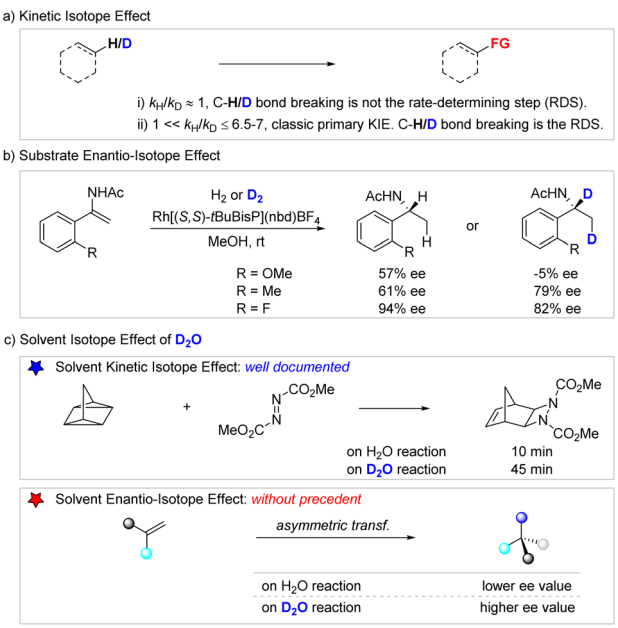
A Cu-catalyzed asymmetric coupling reaction between cyclic diaryliodoniums and the ambident nucleophile KSeCN was reported. Utilizing water as a co-solvent (CH_2Cl_2/H_2O) achieves high chemoselectivity by forming a nitrogen-hydrogen-bond, thereby blocking the N-site of ambident $NCSe^-$ species, thus realizing efficient C–Se coupling. In contrast to the well-known kinetic isotope effect used to evaluate whether the C–H/D bond cleavage is rate-determining, the influence of deuterium-containing solvents on enantioselectivity remained largely unexplored. In this reaction, we observed a notable enhancement in enantioselectivity upon replacing H_2O with D_2O.

Introduction

Kinetic isotope effect (KIE) experiments have been widely used in modern physical organic chemistry. KIEs, measured by H/D labeling and crossover experiments, are possibly the most widely used methods to establish C–H/D bond breaking as a rate-determining step (Scheme 1a).[1] Imamoto, Gridnev and co-workers observed that replacing H_2 with D_2 also significantly altered the enantioselectivity to various degrees in Rh-catalyzed hydrogenation of enamides (Scheme 1b).[2] In 2005, Sharpless *et al.* reported a significant solvent isotope effect in an aqueous emulsion [$2\sigma + 2\sigma + 2\pi$] based-cycloaddition, noting a marked decrease in the reaction rate when H_2O was replaced with D_2O (Scheme 1c).[3] McErlean *et al.* similarly observed that the conversion of an aromatic aza-Claisen rearrangement in D_2O was only 40%, compared to full conversion in H_2O over the same period.[4] While deuterium kinetic isotope effects have been investigated in some aqueous reactions by substituting H_2O with D_2O, the literature remains devoid of any reports of the solvent enantio-isotope effect, such as D_2O displaying an ability to improve enantioselectivity over H_2O.

Selenium is among the fourteen essential trace elements and plays a vital role in human health.[5] Chiral electrophilic selenium reagents have been used for the enantioselective functionalization of inactivated alkenes.[6] Significant progress has recently been achieved in synthesizing optically active chiral selenium compounds through asymmetric difunctionalization of alkenes.[7] Selenocyanate compounds showed broad utilities in preparing other types of organoselenium compounds.[8] However, coupling with ambident nucleophiles, such as KSeCN and KSCN, usually encounters chemo-selectivity challenges. A precedent from the Reiser group demonstrated that the C–S *versus* C–N selectivity in Cu-catalyzed coupling involving SCN anions can be manipulated through the electronic properties of free radicals: nucleophilic radicals preferentially attack the



Scheme 1 Deuterium isotope effects.

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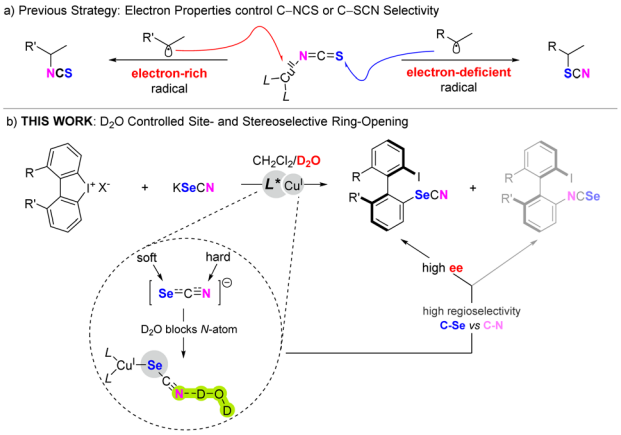
† Electronic supplementary information (ESI) available. CCDC 2373878 and 2373879. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5sc00014a



Scheme 2 Strategy for site-selective coupling of SeCN or SCN.

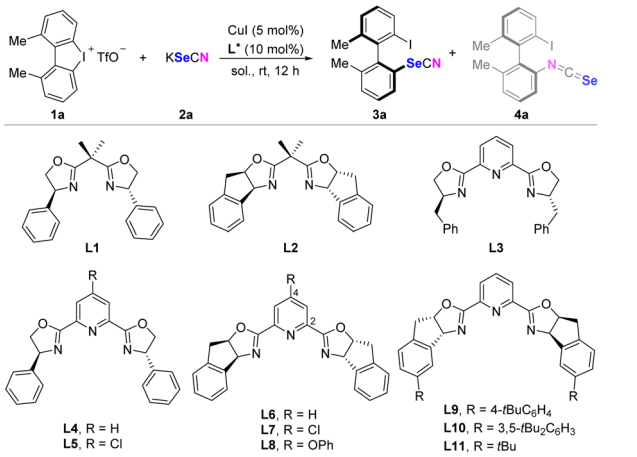
electrophilic Cu(II) center, generating a Cu(III) species that affords a C–N coupling product upon reductive elimination (Scheme 2a),[9] whereas radicals bearing an electron-withdrawing group favor direct attack at the sulfur site, forming a C–S bond directly *via* an outer-sphere mechanism. We reasoned that the softness and relatively larger size of the Se atom facilitate hydrogen bonding with the N atom (Scheme 2b). Considering the significance of selenocyanates and the broad utility of atropisomers,[10] we herein report a Cu-catalyzed asymmetric ring-opening/C–Se coupling reaction of cyclic diaryliodoniums with KSeCN, wherein co-solvent water blocks the N-site of the SeCN anion through hydrogen bonding. Intriguingly, we observed that D_2O (in contrast to H_2O) unexpectedly improved the enantioselectivity of this reaction.

Results and discussion

Optimization

Optimization studies were conducted using dimethyl substituted cyclic diaryliodonium **1a** and KSeCN as the model substrates in dichloromethane at room temperature, with CuI as the catalyst. Chiral bisoxazoline ligands **L1–L2** afforded high enantiomeric excesses of *N*-arylated product **4a**, while the stereoselectivity of Se-arylated product **3a** was below 40% ee. Moreover, the reaction exhibited poor chemoselectivity between Se-arylation and *N*-arylation, with **3a**/**4a** ratios ranging from 1 : 1.5 to 2 : 1 (Table 1, entries 1 and 2). Introduction of benzyl substituted pyridine-2,6-bis(oxazolines) (PyBox) **L3** enhanced the enantioselectivities, shifting the ratio of **3a**/**4a** to 5/1 (entry 3). However, the PyBox derived from phenylglycinol exhibited no improvement in stereo-inductivity (entries 4 and 5). Chiral indeno-PyBox ligands **L6–L8** led to excellent enantioselectivities for both **3a** and **4a**, while modifications of the pyridine ring's electronic properties with chloro or phenoxyl groups had minimal impact on the Se-arylation/*N*-arylation ratio (entries 6–8). Guided by our hypothesis that water might influence Se/N selectivity through differential hydrogen bonding affinities, we examined mixed solvent systems. Gratifyingly, employing CH_2Cl_2/H_2O (5 : 1) significantly improved chemoselectivity,

Table 1 Reaction condition optimization[a]

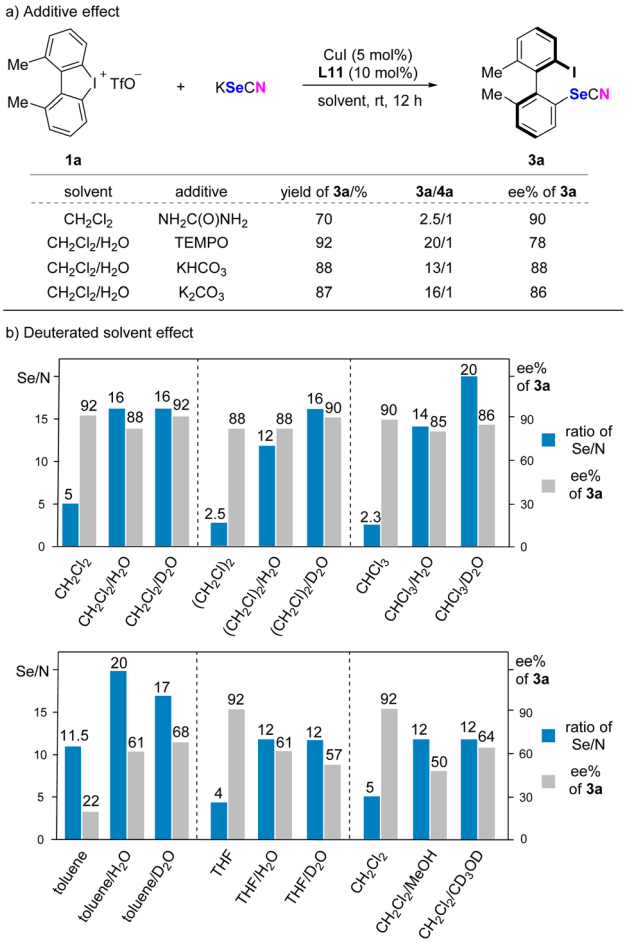


Entry	Ligand	Solvent	**3a**/**4a**[b]	Yield[c] (%)/ee (%) **3a**	**4a**
1	**L1**	CH_2Cl_2	2/1	54/38	30/94
2	**L2**	CH_2Cl_2	1/1.5	38/32	55/94
3	**L3**	CH_2Cl_2	5/1	74/84	20/90
4	**L4**	CH_2Cl_2	3/1	70/48	22/87
5	**L5**	CH_2Cl_2	3/1	68/56	18/88
6	**L6**	CH_2Cl_2	5/1	76/90	16/95
7	**L7**	CH_2Cl_2	4/1	73/90	20/96
8	**L8**	CH_2Cl_2	4/1	73/90	19/94
9	**L6**	CH_2Cl_2/H_2O	16/1	88/86	—/92
10	**L6**	CH_2Cl_2/D_2O	16/1	90/90	—/94
11[d]	**L9**	CH_2Cl_2/D_2O	12/1	83/92	—/92
12[d]	**L10**	CH_2Cl_2/D_2O	24/1	92/88	—/86
13[d]	**L11**	CH_2Cl_2/D_2O	20/1	90/94	—/90
14[d]	**L11**	CH_2Cl_2/H_2O	18/1	90/92	—/—

[a] Conditions: 0.10 mmol of cyclic diaryliodoniums (**1a**), 0.20 mmol KSeCN (**2a**), CuI (5 mol%), ligand (10 mol%) in CH_2Cl_2 (0.04 M) [or CH_2Cl_2/H_2O (5 : 1) or CH_2Cl_2/D_2O (5 : 1)] at room temperature. [b] NMR to determine the ratio. [c] Isolated yield. [d] *ent*-**3a** was obtained.

achieving a 16 : 1 ratio of **3a**/**4a**, although the enantioselectivity of **3a** decreased slightly to 86% (entry 9). An unexpected discovery was that deuterated water enhanced enantioselectivity, while maintaining a high Se/N ratio (entry 10). Further optimization efforts focused on modifying the indeno structure of PyBox, leading to the identification of the optimal ligand **L11**, which achieved the highest enantioselectivity (94% ee) for **3a** (entries 11–13). Under these optimized conditions with **L11**, using CH_2Cl_2/H_2O as the solvent system *in lieu* of CH_2Cl_2/D_2O resulted in slightly reduced enantiomeric excess (92% ee) (entry 14).

The addition of organic hydrogen bond donor urea did not obviously improve the Se/N selectivity (Scheme 3a). A radical pathway can be ruled out as TEMPO had a minimal effect on product formation. The most intriguing aspect of this reaction is the enhanced enantioselectivity observed with deuterated water (D_2O) compared to regular water (H_2O). While the isotope effect on enantioselectivity has been observed for reactions involving C–H/D bond formation or cleavage,[11] our observed



solvent	additive	yield of **3a**/%	**3a**/**4a**	ee% of **3a**
CH_2Cl_2	$NH_2C(O)NH_2$	70	2.5/1	90
CH_2Cl_2/H_2O	TEMPO	92	20/1	78
CH_2Cl_2/H_2O	$KHCO_3$	88	13/1	88
CH_2Cl_2/H_2O	K_2CO_3	87	16/1	86

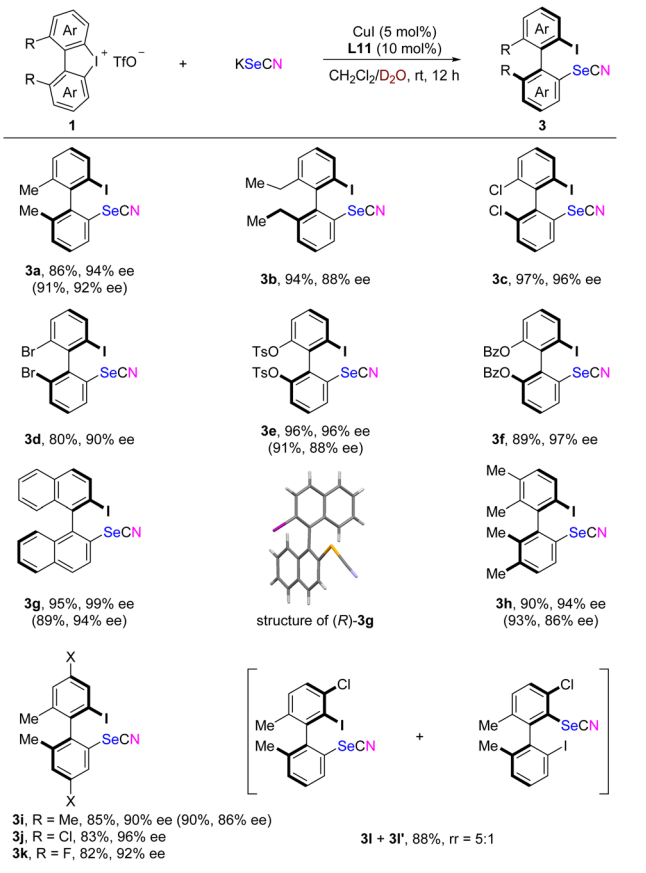
Scheme 3 Control experiments.

enhancement of enantioselectivity by D_2O is distinct as it occurs without breaking any chemical bonds of D_2O. Therefore, explaining such a deuterium isotope effect on stereoselectivity remains particularly challenging, as both chemical and physical properties, including viscosity, molecular polarizability, or the pK_a value, may contribute to the observed outcomes. Given the pH differences [pH(H_2O) = 6.9976 pD(D_2O) = 7.43 at 25 °C], $KHCO_3$ and K_2CO_3 were used to adjust the pH of the CH_2Cl_2/H_2O mixture; however, no noticeable improvement in enantioselectivity was observed. We further conducted a series of experiments combining either H_2O or D_2O with CH_2Cl_2, $(CH_2Cl)_2$, $CHCl_3$, toluene and THF as a mixed solvent (Scheme 3b). Notably, enantiomeric excess improvements can be observed in CH_2Cl_2, $(CH_2Cl)_2$, $CHCl_3$, or toluene when H_2O was replaced by D_2O. Conversely, an opposite trend was observed in THF/H_2O and THF/D_2O solvent systems. A similar enhancement was noted when the reaction was conducted in CH_2Cl_2/CD_3OD instead of CH_2Cl_2/CD_3OH, yielding compound **3a** with an ee value improved from 50% to 64%.

While a definitive explanation remains elusive, from the current literature[12] we reasoned three possible factors that possibly affect the enantioselectivity: (a) the previous *ab initio* calculations on hydrogen-bonded oligomers suggest that the bond strength in D_2O is 0.2–0.3 kcal mol^{-1} stronger than that in H_2O, suggesting a potential stronger hydrogen bond in the CH_2Cl_2/D_2O system. (b) Studies using X-ray measurements with molecular simulations indicate that the covalent O–D bond in D_2O is 3% shorter than the O–H bond in regular water. (c) The hydrogen-bond network in D_2O is more tetrahedral compared to that in H_2O. These distinctions may create a different three-dimensional environment compared to H_2O, potentially impacting enantioselectivity.

Substrate scope

Under optimized conditions, the substrate scope of various diaryliodonium salts was explored (Scheme 4). Pleasingly, high Se/N arylation ratios (typically exceeding 15 : 1) were consistently observed across all tested substrates. With 2,2′-diethyl-1,1′-biphenyl-derived cyclic diaryliodonium as the substrate, the reaction proceeded smoothly, albeit with slightly reduced stereocontrol (**3b**). Both dichlorinated and dibrominated cyclic diaryliodoniums exhibited good reactivity, resulting in excellent enantioselectivities (**3c** and **3d**). High enantiomeric excess (ee) values were also achieved for the *ortho*,*ortho*′-dioxygenated atropisomeric biaryls (**3e** and **3f**). The binaphthyl cyclic

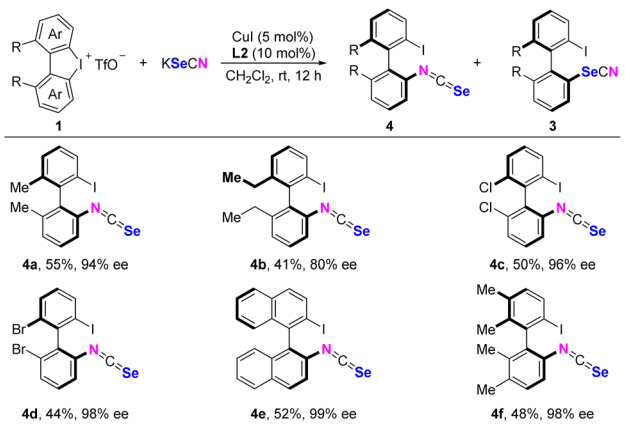


Scheme 4 Substrate scope of C–Se coupling. Reaction conditions: cyclic diaryliodonium **1** (0.2 mmol, 1.0 equiv.), KSeCN (0.40 mmol, 2.0 equiv.), CuI (1.9 mg, 0.01 mmol, 5 mol%), **L11** (10.1 mg, 0.02 mmol, 10 mol%) in CH_2Cl_2/D_2O (5 mL/1 mL) at 25 °C for 12 h. The values in parentheses refer to the results by using CH_2Cl_2/H_2O as the solvent.

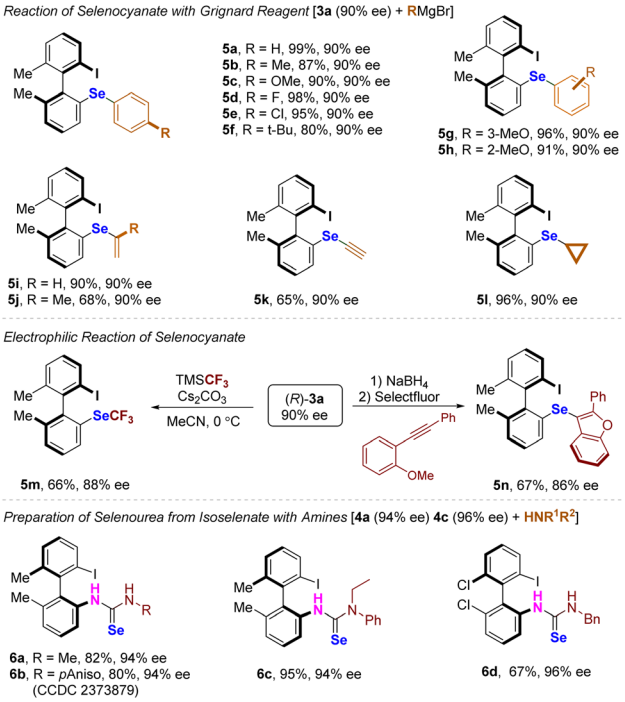
diaryliodonium underwent a smooth asymmetric ring-opening reaction, yielding excellent yield and near-perfect stereoselectivity (**3g**). This compound also facilitated the determination of the absolute configuration through single crystal X-ray diffraction analysis (CCDC 2373878). Cyclic diaryliodonium bearing additional methyl or chloro groups at the *para*- or *meta*-positions exhibited comparable reactivity and selectivity (**3h–k**). However, unsymmetric cyclic diaryliodonium with a substituent adjacent to the C–I bond displayed poor regioselectivity, consistent with our previous findings in the trifluoromethylthiolation reaction.[13] For instance, products **3l** and **3l′** were isolated in 18% and 70% yields, respectively, though both the products exhibited excellent ee values.

Isoselenocyanates represent valuable building blocks that were widely used in synthesizing selenium-containing compounds.[14] The classic synthesis involves a two-step modification of corresponding amines *via* Barton's protocol.[15] Although complete control of chemo-selective *N*-arylation remained elusive, we evaluated several substrates in anhydrous CH_2Cl_2 using CuI/**L2** as the catalyst, with N/Se ratios ranging from 1 : 1 to 1.5 : 1 (see the ESI† for details) (Scheme 5). All substrates tested provided the products in decent isolated yields. Similar to the Se-arylation reaction, the *N*-arylation reaction of 2,2′-diethyl-1,1′-biphenyl-derived cyclic diaryliodonium resulted in a diminished enantioselectivity (**4b**). Notably, cyclic diaryliodoniums bearing dimethyl, dichloro, or dibromo substituents, as well as the binaphthyl substrate, afforded products with excellent stereoselectivities (**4a** and **4c–f**).

The selenium atom in selenocyanate exhibits electrophilic character and readily reacts with Grignard reagents. This reactivity enabled the formation of selenanes **5a–h** in yields ranging from 80–99% without erosion of enantiopurity (Scheme 6). The reaction demonstrated compatibility with vinyl and alkynyl magnesium reagents, although 2-methylalkenyl selane **5j** and alkynyl selane **5k** were obtained in lower yields. Additionally, cyclopropyl magnesium bromide also proved compatible, smoothly yielding **5l** in 96% yield. Selenocyanate **3a** served as



Scheme 5 Substrate scope of C–N coupling[a]. [a]Reaction conditions: cyclic diaryliodonium **1** (0.2 mmol, 1.0 equiv.), KSeCN (0.40 mmol, 2.0 equiv.), CuI (1.9 mg, 0.01 mmol, 5 mol%), **L2** (7.0 mg, 0.02 mmol, 10 mol%) in CH_2Cl_2 (5 mL) at 25 °C for 12 h. The ratios of 4 : 3 range from 1 : 1 to 1.5 : 1, see the ESI† for details.



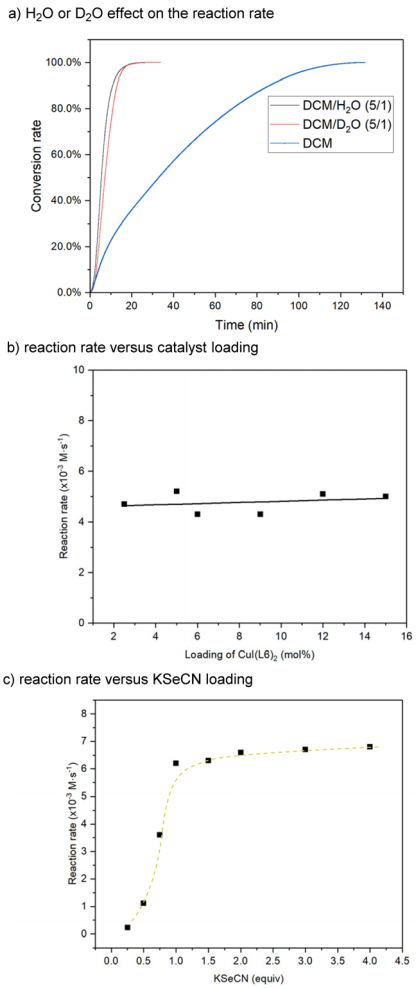
Scheme 6 Synthetic applications.

a versatile synthetic platform for accessing diverse functionalities. Treatment of (*R*)-**3a** with $TMSCF_3/Cs_2CO_3$ in MeCN yielded the atropisomeric trifluoromethyl selane **5m** in 66% yield. Reduction of **3a** with $NaBH_4$ produced a diselenide compound upon workup. Subsequent reactions with SelectFluor, followed by an electrophilic cyclization with 1-methoxy-2-(phenylethynyl) benzene, yielded the bicyclic selane **5n** in a moderate yield, albeit with a slight decrease in enantiopurity.

To further demonstrate synthetic utility, we sought to convert isoselenocyanate (*S*)-**4a** into substituted selenoureas. The transformation was accomplished by simply stirring a mixture of isoselenate (*S*)-**4a** with amines in CH_2Cl_2 at room temperature. Primary amines, *i.e.* methylamine and 4-methoxyaniline readily underwent an addition reaction to produce selenoureas **6a**, **6b** (CCDC 2373879) and **6d** in good yields without compromising stereochemical integrity. Secondary amine, *N*-ethylaniline, also efficiently coupled with isoselenate to provide **6c** in excellent yield.

Kinetic studies

The kinetic studies were conducted *via* calorimetry analysis, which enabled us to continuously collect *in situ* data throughout the reaction process.[16] Notably, both water and deuterated water were almost equally effective in accelerating the reaction, showing no obvious isotope effect on the reaction rate. Careful reaction calorimetry measurements showed that the reaction in CH_2Cl_2/D_2O was very slightly slower than that in CH_2Cl_2/H_2O (Scheme 7a). Furthermore, kinetic studies at 30 °C yielded two interesting observations: (i) the reaction exhibited zeroth-order kinetics with respect to the CuI/**L6** catalyst (Scheme 7b). (ii) After ensuring complete dissolution of KSeCN in H_2O, kinetics

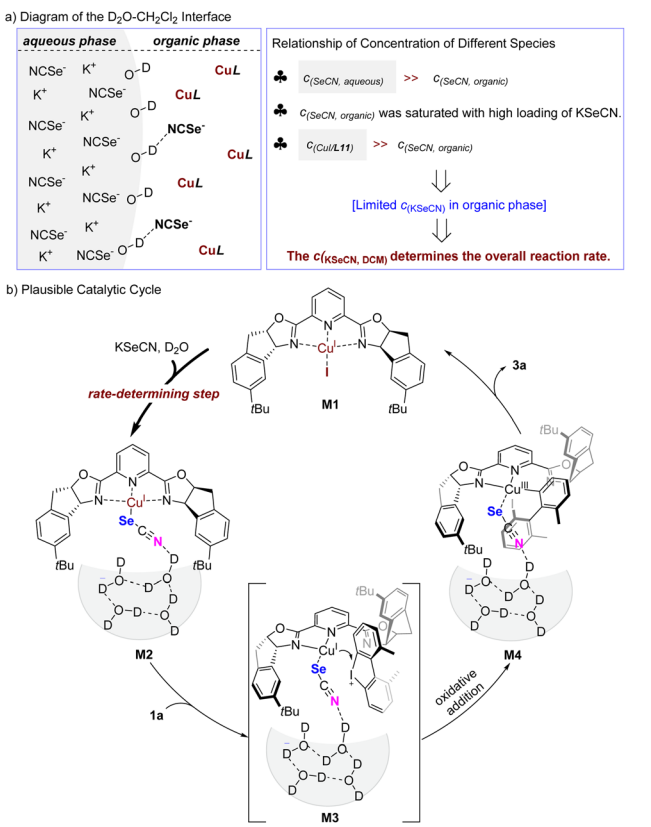


Scheme 7 Kinetic studies.

for varying the loadings of KSeCN were measured (Scheme 7c). The reaction exhibited pseudo-first-order kinetic dependence on KSeCN when the loading ranged from 0.50 to 1.0 equivalent [0.50 to 1.0 mol L^{-1} in H_2O]. However, at loadings of KSeCN exceeding 1.5 equivalents, the reaction exhibited pseudo-zeroth-order kinetics dependence on the KSeCN concentration.

In an [Ir(COD)py(PCy_3)]PF_6-catalyzed hydrogenation reaction, Rempel and co-workers observed zeroth-order kinetics with respect to catalyst concentration at high catalyst loadings.[17] In our system, the kinetic behavior can be rationalized through phase-transfer considerations. The transfer of KSeCN from the aqueous phase to the organic phase is concentration-dependent only up to 1.0 equivalent of KSeCN (1.0 mol L^{-1} in H_2O). Beyond this point, the concentration of SeCN anions in the organic phase reaches saturation, remaining relatively unchanged despite a further increase in KSeCN loading. Consequently, the high loading of KSeCN caused zeroth-order dependence on the KSeCN concentration. In contrast, the concentration of the CuI/**L6** catalyst remains in excess compared to KSeCN in the organic phase, causing the reaction to exhibit zeroth-order kinetics with respect to the copper catalyst.

The role of water in accelerating aqueous reactions can be explained using the Marcus–Jung model of hydrogen bonding between the dangling –OH and the lipophilic substrates or Kobayashi's three layers model, which involves partial polarization.[18] We reasoned that the catalytic cycle involves crucial deuterium bond (D–N) formation between D_2O and the SeCN anion (Scheme 8).[19] This biphasic reaction system presents specific concentration dynamics: (i) KSeCN distribution: the concentration of KSeCN in the aqueous phase significantly exceeds its concentration in the organic phase. (ii) SeCN species saturation: at high KSeCN loadings, the concentration of SeCN in the organic phase reaches saturation, resulting in rate independence from further KSeCN addition. (iii) Catalyst excess: the concentration of the copper catalyst remains in excess relative to the organic phase SeCN species, even at high KSeCN loadings. Mechanistically, the catalytic cycle commences with the association of copper/PyBox complex **M1** with selenium cyanate, a step identified as the rate-determining step through the kinetic analysis. Upon loading 2.0 equivalents of KSeCN, the concentration of KSeCN in the organic phase is controlled by its solubility in CH_2Cl_2, other than its mass transfer rate across the phase boundary.[20] The N-site blocking effect of the deuterium bond facilitates the formation of Cu–SeCN intermediate **M2**. This intermediate is capable of undergoing oxidative addition with cyclic diaryliodonium **1a** to yield atropisomeric biaryl Cu(III) complex **M4**. Finally, reductive elimination of **M4** produced the target axially chiral product **3a** and a monovalent copper species **M1**.



Scheme 8 Plausible catalytic cycle.

Conclusions

In summary, we have developed a Cu-catalyzed highly chemo- and atroposelective C–Se coupling reaction between cyclic diaryliodoniums and KSeCN in a CH_2Cl_2/D_2O mixed solvent system. The distinctive role of D_2O manifests in two critical ways: (a) as a deuterium bond donor that selectively blocks the N-site of $NCSe^-$ species, thereby promoting C–Se coupling over C–N coupling; (b) as an enhancer of enantioselectivity compared to regular water, D_2O exhibits noticeable improvement in enantioselectivity. This enhanced stereoselectivity likely stems from either the slightly shorter covalent O–D bond of D_2O than the O–H bond of regular water, or the enhanced tetrahedral ordering of the D_2O hydrogen-bond network. Our findings underscore the importance of the deuterium isotope effect in enantioselectivity control, establishing it as an additional factor worthy of consideration in asymmetric catalysis.

Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding authors.

Author contributions

Y. Li: methodology, investigation, data curation, writing – original draft. C. Tao: methodology, investigation. L. Duan: supervision, funding acquisition. Z. Gu: conceptualization, funding acquisition, writing – original draft, writing – review & editing. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Supercomputing Center of the University of Science and Technology of China for providing the computational resources. The authors are grateful for financial support from the National Key Research and Development Program of China (no. 2021YFA1500100), the National Natural Science Foundation of China (22301291 and 22471254), and the Open Research Fund of State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University.

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