Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: B. Wang, Y. Wang, Y. Jiang, M. Chu, S. Qi, W. Ju and D. Xu, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB01943F.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB01943F

Organic & Biomolecular Chemistry

PAPER

Asymmetric Fluorination of Indanone-2-carboxylates Using A Polystyrene-supported Diphenylamine-linked Bis(oxazoline) Complex

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

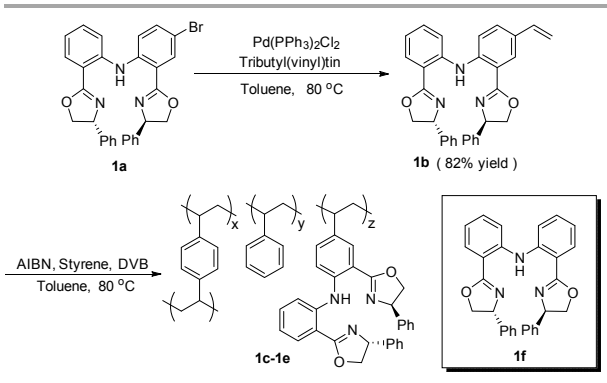
Biao Wang,[a] Yifeng Wang,[a,*] Yidong Jiang,[a] Mingming Chu,[a] Suosuo Qi,[a] Wanzhen Ju[a] and Danqian Xu[a,*]

A highly enantioselective fluorination of Indanone-2-carboxylates catalyzed by a polystyrene-supported diphenylamine-linked bis(oxazoline) (PS-box)-Cu(OTf)$_2$ complex has been developed in a continuous flow system. The supported complex exhibited extremely efficient catalytic performance in high activity, affording the corresponding products in excellent yields (up to 99% yield) with excellent enantioselectivities (up to 99% ee) and more than 4000 turnover number (TON).

Introduction

Chiral bis(oxazoline) ligands are widely used in enantioselective reactions ascribe to its high efficiency and ready availability.[1] However, the high catalyst loading hinders the application for large scale-up, and the possible contamination of metal leaching also increases the risk in pharmaceutical product, which prompts the development of their heterogeneous counterparts. In this regard, different kinds of chiral bis(oxazoline) ligands immobilized by grafting to insoluble organic materials[2] and inorganic materials,[3] or by polymerization,[2,4] have shown their utility in many asymmetric organic reactions like cyclopropanation, glyoxylate-ene, Diels-Alder, Friedel-Crafts alkylation, aldol, 1,4-addition reactions, etc. Particularly, the diphenylamine-linked bis(oxazoline) ligands,[5] belonging to chiral tridentate ligands and expected to form a deeper chiral concave pocket around the metal center, have shown quite different reactivity in asymmetric reactions, which arouse attention to develop the immobilization of these tridentate ligands. Recently, the tridentate diphenylamine-linked bis(oxazoline) ligand immobilized by grafting onto Fréchet-type dendrimers and a C_3-symmetric core structure was reported, which achieved similar enantioselectivities and substrate compatibilities to the homogeneous ligand system for the asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes.[6] Notably, in terms of enantioselective catalytic performance of polymer-supported catalyst, polymerization has provided, in some cases, better results than grafting,[7] which prompt us to develop the strategy of polymerization for immobilized diphenylamine-linked bis(oxazoline) ligand, which may further improve the efficiency of the catalyst.

Catalytic asymmetric fluorination of β-keto esters has attracted more and more attentions due to their wide synthetic potential.[8] Since the pioneering work reported by Togni and co-workers,[9] both chiral metal complexes[10] and organocatalysts[11] have been developed for these transformations, including using the bis(oxazoline) metal complexes.[12] Specifically, diphenylamine-linked bis(thiazoline)-Cu(OTf)$_2$ complexes have shown high activity and good enantioselectivity in fluorination of β-keto esters.[5k] However, to the best of our knowledge, few immobilized catalyst has been developed for asymmetric fluorination of β-keto esters.[10b] On the other hand, flow operation is arguably the best alternative for realizing the full potential of immobilized catalysts.[13] In this regard, we believe that the asymmetric fluorination reaction in continuous flow catalyzed by the immobilized diphenylamine-linked bis(oxazoline)-Cu(OTf)$_2$ complex is a promising way to realize the efficiency of this reaction. The methodology can combine the both advantages of immobilized catalyst and continuous flow, making the immobilized catalyst suffer less physical damage and have a longer lifetime.[13]



[a] State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Key Laboratory of Green Pesticides and Cleaner Production Technology of Zhejiang Province, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: wangyifeng@zjut.edu.cn, chrc@zjut.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental details and characterization of compounds. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8OB01943F

Scheme 1. The synthesis of the polystyrene-supported bis(oxazoline) ligand **1c**-**1e** and The parent ligand **1f**.

Results and discussion

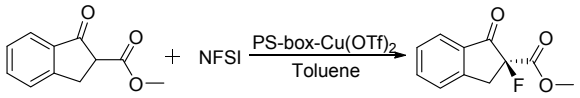
The synthesis of the key intermediate **1b** for immobilization of the diphenylamine-linked bis(oxazoline) is depicted in Scheme 1. The vinyl group was introduced by Stille coupling between tributyl(vinyl)tin and 4-bromodiphenylamine-linked bis(oxazoline) **1a** which can be synthesized from dimethyl 2,2'-azanediyldibenzoate in four steps following the reported procedures.[6] Using styrene as the diluting monomer, divinylbenzene (DVB) as the cross-linker, toluene as the porogen solvent and AIBN as the initiator, by changing the degree of cross-linking, different co-polymerization of **1b** was then carried out in toluene (Table 1).[14] The IR spectrum of the PS-box showed the typical box C=N stretching at about 1634-1635 cm^{-1}, corresponding to that of the monomer **1b** (1636 cm^{-1}).

Table 1 PS-box of different cross-linking degree in this work[a]

PS-box	Polymerization mixture (%)			Box[b] (mmol/g)
	DVB(x)	Styrene(y)	Box(z)	
1c	45.8	45.8	8.4	0.555
1d	30.5	61.1	8.4	0.569
1e	15.2	76.4	8.4	0.626

[a] Polymerization conditions: toluene/monomer mixture= 2.5 (w/w), 80 °C, 24 h. The PS-box was washed with THF, dried by suction and crushed in a ball mill, and then washed in a Soxhlet apparatus with THF for 24 h and dried under vacuum at 50 °C overnight. [b] The loading of bis(oxazoline) was determined by elemental analysis calculated from nitrogen analysis.

Table 2 Optimization of different cross-linking degree of PS-box for the fluorination of 1-indanone-2-carboxylate **2a** in batch condition[a]



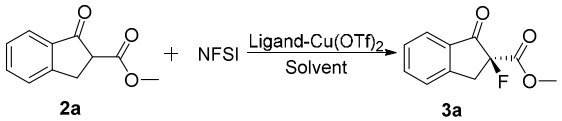
2a **3a**

PS-box	Run	Yield[%][b]	ee[%][c]
1c	1	96	86
	2	93	76
	3	90	48
1d	1	96	95
	2	97	96
	3	94	88
	4	88	49
1e	1	95	90
	2	97	92
	3	88	80
	4	84	48

[a] Typical reaction conditions: To a tube a mixture of PS-box (0.005 mmol, 0.2 mol%) and $Cu(OTf)_2$ (0.004 mmol) with 25 mL toluene were added, **2a** (2.5 mmol, 1 equiv.) and NFSI (3.0 mmol, 1.2 equiv.) were added successively. The reaction mixture was shaken for 120 min. The PS-box-$Cu(OTf)_2$ complex was centrifuged, washed with toluene (5 mL × 3) and recycled for next run. [b] Isolated yields. [c] Determined by chiral HPLC.

The reaction of 1-indanone-2-carboxylate **2a** and NFSI catalyzed by PS-box-$Cu(OTf)_2$ complex was selected as a model reaction in batch condition for the optimization of continuous flow counterpart at room temperature. Based on pioneering researches,[2,4] variations in the degree of cross-linking of the PS-box could have an important effect on their activity and stability. Therefore, recycling of different cross-linking degree of PS-box was tested, and the results were gathered in Table 2. As can be seen, the best catalyst (**1d**-$Cu(OTf)_2$) was recycled for three times, with similar efficiencies observed in the first two recycles but a marked decrease in enantioselectivity in the third recycle. The lower enantioselectivity in the first run may be ascribed to the presence of residual non-box-complexed copper centers, which were completely removed in the first recycle, and the similar result was found when **1e** was used. Meanwhile, the optimum proportions of $Cu(OTf)_2$/**1d** (0.8) was also screened (see ESI†, Table S1).

Table 3 Optimization of the fluorination of 1-indanone-2-carboxylate 2a catalyzed by the PS-supported **1d**-$Cu(OTf)_2$/parent ligand system **1f**-$Cu(OTf)_2$ in batch condition[a]



2a **3a**

Entry	Ligand	Solvent	Yield[%][b]	*ee*[%][c]
1	**1d** (1 mol%)	MeOH	95	90
2	**1d** (1 mol%)	DMF	52	17
3	**1d** (1 mol%)	Acetonitrile	43	80
4	**1d** (1 mol%)	1,4-dioxane	92	90
5	**1d** (1 mol %)	EtOAc	98	92
6	**1d** (1 mol%)	THF	97	95
7	**1d** (1 mol %)	CH_2Cl_2	97	95
8	**1d** (1 mol %)	Toluene	97	97
9	**1d** (0.2 mol %)[d]	THF	98	94
10	**1d** (0.2 mol %)[d]	CH_2Cl_2	93	92
11	**1d** (0.2 mol %)[d]	Toluene	96	95
12	**1f** (10 mol %)	Toluene	98	96
13	**1f** (1 mol %)	Toluene	94	90
14	**1f** (0.2 mol %)	Toluene	94	76

[a] Typical reaction conditions: to a tube a mixture of **1d**-$Cu(OTf)_2$ ($Cu(OTf)_2$/**1d** = 0.8) or **1f**-$Cu(OTf)_2$ complex with 5.0 mL solvent were added, and then **2a** (0.5 mmol, 1 equiv.) and NFSI (0.6 mmol 1.2 equiv.) were added successively. The reaction mixture was shaken for 120 min. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 2.5 mmol **2a** in 25 mL solvent was used.

Since the solvent acts the role in the preferential stabilization of a given transition state, which is the key point of good activity and enantioselectivity of the PS-box ligand,[15] the immobilized ligand **1d**

View Article Online
DOI: 10.1039/C8OB01943F

was screened in different solvents, which exhibited excellent yields and high enantioselectivities with 1 mol% catalyst loading when THF, CH_2Cl_2 and toluene were chosen as solvent (Table 3, entries 6-8). Notably, the reaction proceeded well in toluene and THF even at 0.2 mol% catalyst loading with only slightly decreased result (entries 9, 11), while the enantioselectivity getting worse obviously with the reduction of the amount of homogeneous **1f**-Cu(OTf)$_2$ complex (entries 12-14), depicting that the (PS-box)-Cu(OTf)$_2$ showed significantly enhanced catalytic activities and stable enantioselectivities.

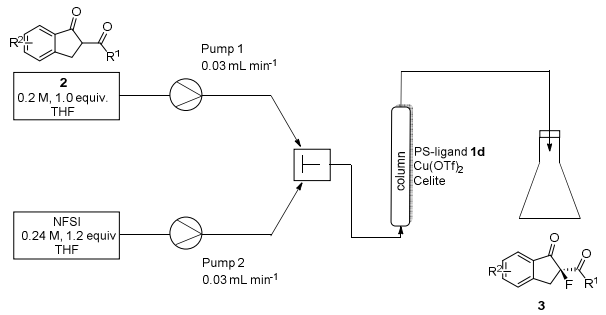
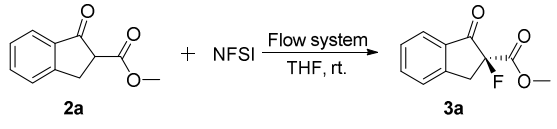


Figure 1. Experimental setup for fluorination of indanone-2-carboxylates **2** in continuous flow.

Encouraged by above results, the asymmetric fluorination was investigated in a continuous flow system for testing the activity and stability of the **1d**-Cu(OTf)$_2$ complex (Table 4). The implementation of a continuous system was represented in Figure 1. A 150 mm × 4.6 mm id stainless steel column packed with PS-box, celite and Cu(OTf)$_2$ was connected to the pump, 1-indanone-2-carboxylate **2a** (0.2 M, 1 equiv.) and NFSI (0.24 M, 1.2 equiv.) were introduced from the bottom of the column from respective solution and mixed in a T-shape connector, then channeled through the inlet of the column and to the flask for collection. The flow rate optimization of the continuous flow was performed using 1-indanone-2-carboxylate **2a** as a substrate (see ESI†, Table S2). After stabilizing the continuous

Table 4 Selected result of long period experiment in continuous flow in THF[a]

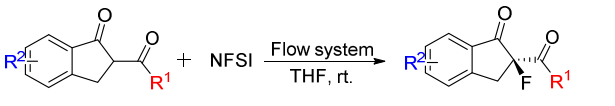


2a **3a**

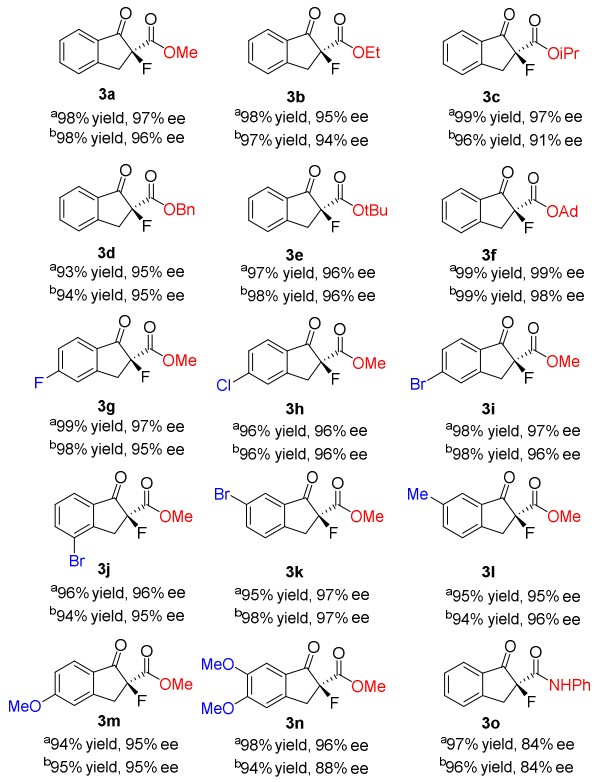
Time [h]	Yield[b] [%]	ee[c] [%]	Time [h]	Yield[b] [%]	ee[c] [%]
48-48.5	99	96	432-432.5	99	93
96-96.5	99	95	480-480.5	99	95
144-144.5	99	96	528-528.5	97	95
192-192.5	99	95	576-576.5	98	93
240-240.5	97	94	624-624.5	96	94
288-288.5	99	94	672-672.5	95	93
336-336.5	98	95	720-720.5	96	92
384-384.5	99	95	768-768.5[d]	95	92

[a] The reactions were performed with PS-box **1d** (0.12 g, 0.068 mmol) and celite (0.8 g) in a column which was charged with Cu(OTf)$_2$ at room temperature, and then **2a** (0.2 M, 1.0 equiv.) and NFSI (0.24 M, 1.2 equiv.) were pumped into the column at 30 μL min^{-1} from respective THF solutions (60 μL min^{-1} total flow rate, 0.1 M concentration of **2a** in the column). [b] Isolated yields. [c] Determined by chiral HPLC. [d] Recharge Cu(OTf)$_2$ into the column.

Table 5 Scope of fluorination in continuous flow with immobilized catalyst **1d**[a] and in batch condition with its parent ligand **1f**[b]



2 **3**



[a] Typical continuous flow conditions: the reactions were performed with PS-box **1d** (0.12 g, 0.068 mmol) and celite (0.8 g) in a column which is charged with Cu(OTf)$_2$ at room temperature, and then **2** (0.2 M, 1.0 equiv.) and NFSI (0.24 M, 1.2 equiv.) were pumped into the column at 30 μL min^{-1} from respective THF solutions (60 μL min^{-1} total flow rate, 0.1 M concentration of **2** in the column). Each substrate carried out for 12 h. The same PS-box was used for all the substrates. Residence time under these conditions was 28 min. [b] Typical batch conditions: to a tube a complex of **1f**-Cu(OTf)$_2$ (0.05 mmol) with 5.0 mL toluene were added, and then **2** (0.5 mmol, 1.0 equiv.) and NFSI (0.6 mmol, 1.2 equiv.) were added into the tube. The reaction mixture was shaken for 120 min. [c] Isolated yield. [d] Determined by chiral HPLC.

flow system for 12 h, each fraction was collected for 30 min every 12 h. Excellent yields and enantioselectivities were achieved in the

View Article Online
DOI: 10.1039/C8OB01943F

first 4 days when toluene was used as solvent in continuous flow condition with about 500 TON (see ESI†, Table S3), but unfortunately, the column was always blocked in the later reaction time, possibly for the significant swelling of PS in toluene.[16] To our delight, the yields and enantioselectivities of the batch condition were exactly replicated in continuous flow process when THF was used as solvent, 99% yields and high enantioselectivities (95-96% ee) were achieved in the first 4 days (Table 4). In such a satisfactory condition, the reaction time was further extended, obtaining a total amount of 276.5 mmol of the product with only a slight decrease in yield and enantioselectivity after 32 days. The TON in these experiments reached more than 4000 with an impressive 40-folds improvement with respect to its homogeneous counterparts and nearly 3-folds to its heterogeneous counterparts in batch condition. Meanwhile, the catalyst was still in a good condition when we stopped the continuous flow system. After 30 days running, we recharged the column with additional $Cu(OTf)_2$ in dry THF for 2 h, and then washing with THF for 2 h. After that, the two solutions were pumped into the column at the same flow rate from respective THF solutions, but no increased result was obtained for yields or enantioselectivities, demonstrating that the decreased results in the long time reaction is not caused by leaching of the copper ions, probably caused by the slightly degradation of PS-box.

With the optimized condition in hand, we further tested the possibility of using the continuous flow system catalyzed by **1d**-$Cu(OTf)_2$ complex for various indanone-2-carboxylates (**2a**-**2o**), and the parallel reactions catalyzed by the homogeneous counterpart **1f**-$Cu(OTf)_2$ were carried out in batch condition (Table 5). Since high TON had been achieved, the same **1d**-$Cu(OTf)_2$ complex in the column was used to catalyze all the substrates. After 12 h running for each substrate (4.32 mmol, TON was about 63.3), the column was washed with THF for 2 h before the next indanone-2-carboxylates passed through. As shown in Table 4, all the reactions in the continuous flow obtained high yields and excellent enantioselectivities. The alkoxy group in the β-keto ester caused little influence on enantioselectivity of the product in continuous flow condition (**3a**-**3f**). Notably, when the ester alkoxy substituent was isopropoxy group, the enantioselectivity of the reaction in continuous flow was obviously better than that in batch condition (**3c**, 97% vs 91%). Most of the continuous flow process and the batch process led to practically identical results in terms of yields and enantioselectivities regardless of electron-rich and electron-withdrawing groups on the aromatic rings of indanone-2-carboxylate derivatives (**2g**-**2m**). Especially, the enantioselectivity in continuous flow was improved significantly for 5,6-dimethoxy group substituent (**3n**, 96% vs 88%). In case of indanone carboxamide **2o**, excellent yield but a moderate decrease in enantioselectivity was obtained in both conditions. We also tried other simple aliphatic β-keto esters, however, the supported catalyst could not initiate the reaction efficiently (see ESI†, Table S4). With all these results to the substrates it was found that the (PS-box)- $Cu(OTf)_2$ complex in continuous flow condition had the same or better activity and enantioselectivity to its homogeneous counterpart for the asymmetric fluorination reaction, further demonstrating the high efficiency and stability of the supported complex.

Conclusions

In summary, we described the design of a new, insoluble polystyrene-supported diphenylamine-linked bis(oxazoline) ligand (PS-box) by polymerization. The newly developed (PS-box)-$Cu(OTf)_2$ complex exhibited very high yields and excellent enantioselectivities in a continuous flow system for a variety of indanone-2-carboxylate substrates, which is even more enantioselective than its homogeneous counterparts. It appears to be the first example using a heterogeneous catalyst for asymmetric fluorination reaction. And the continuous flow system has the admirable activity and stability with more than 4000 TON, providing a high potential for practical application in continuous asymmetric catalytic fluorination reactions.

Experimental

General methods

Flash chromatography (FC) was carried out using silica gel (200–300 mesh). Monitoring of reactions was performed by TLC on silica gel precoated on glass plates, and spots were visualized with UV light at 254 nm. ^1H and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker AVANCE III (500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR). TMS served as an internal standard (δ = 0 ppm) for ^1H NMR and $CDCl_3$ was used as an internal standard (δ = 77.0 ppm) for ^{13}C NMR; ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on an Agilent 6545 Q-TOF LCMS spectrometer equipped with an ESI source and controlled by using MassHunter software. Electrospray ionization (ESI) mass experiments were performed on a Thermo LCQ fleet. HPLC experiments were carried out using a JASCO LC-2000 Plus system with MD-2010 HPLC diode array detector. IR were recorded on an EQUINOX 55. The HPLC pump (HITACHI-L 7000) was used for continuous flow system. The milling instrument consists of a main disk which can rotate at a speed of 100-800 rpm and accommodates two grinding bowls (45 mL). Both bowls and balls (2 mm diameter) are made of stainless steel. All the reactions were carried out under atmosphere without any special protection. Unless otherwise stated, chemicals were used without purification as commercially available. The parent ligand **1f** and the intermediate ligand **1a**, and compounds **2a**-**2n**, **2o** were synthesized according to the reported procedures.[6, 10a, 11d, 15, 17-19]

General procedure for the synthesis of the key intermediate 1b

The obtained 4-Br-bis(oxazoline) (3.10 mmol) and $Pd(PPh_3)_2Cl_2$ (0.1 eq, 0.31 mmol) were combined in a 100 mL flask. Then toluene (94 mL) and tributyl(vinyl)tin (3.0 eq, 9.20mmol) were added. The reaction mixture was heated at 80 °C. After 1 h, the reaction mixture was cooled to room temperature, filtrated and evaporated in vacuo. The residue was diluted with actonitrile (50 mL) and was washed with hexane (4 × 50 mL) and evaporated. The residue was purified by column chromatography (Hex: EtOAc = 3:1) to obtain the product.

4-vinyl-2-[(4*S*,5*S*)-4,5-diphenyloxazolin-2-yl]-*N*-{2-[(4*S*,5*S*)-4,5-diphenyloxazolin-2-yl]phenyl} aniline (1a)

Yellow solid; 89% yield; ^1H NMR (500 MHz, $CDCl_3$) δ = 11.19 (s, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 7.93 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.45–7.36 (m, 3H), 7.29–7.25 (m, 6H), 7.20–7.15 (m, 4H), 7.04–6.98 (m, 1H), 5.20 (ddd, *J* = 10.0, 8.2, 4.0 Hz, 2H), 4.51 (ddd, *J* = 10.2, 8.3, 2.9 Hz, 2H), 4.03 (dd, *J* = 17.0, 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.88, 162.91, 142.48, 142.43, 142.31, 142.20, 134.21, 132.88, 131.51, 130.63, 128.50, 128.46, 127.34, 127.28, 126.56, 126.55, 120.59, 119.07, 118.62, 116.66, 116.46, 111.01, 73.73, 73.71, 70.02, 69.95. IR (KBr) *v* 3027, 1637, 1577, 1509, 1453, 1310, 1265, 1056, 975, 750, 697. HRMS: *m/z* calculated for $C_{30}H_{24}BrN_3O_2$ $[M + H]^+$: 538.1125, found: 538.1115.

View Article Online
DOI: 10.1039/C8OB01943F

4-vinyl-2-[(4*S*,5*S*)-4,5-diphenyloxazolin-2-yl]-*N*-{2-[(4*S*,5*S*)-4,5-diphenyloxazolin-2-yl]phenyl} aniline (1b)

Pale yellow solid; 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.20 (s, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.55 (dd, *J* = 17.7, 8.5 Hz, 2H), 7.45 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.41–7.34 (m, 1H), 7.28–7.23 (m, 6H), 7.20–7.16 (m, 4H), 6.99–6.95 (m, 1H), 6.70 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.70 (d, *J* = 17.5 Hz, 1H), 5.26–5.12 (m, 3H), 4.50 (dd, *J* = 9.7, 8.6 Hz, 2H), 4.07–3.97 (td, *J* = 8.2, 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 164.09, 164.04, 142.79, 142.53, 142.49, 135.79, 131.50, 130.61, 129.37, 128.95, 128.75, 128.50, 128.49, 127.31, 127.29, 126.64, 120.13, 118.53, 117.90, 116.01, 115.24, 111.79, 73.75, 73.73, 69.98. IR (KBr) *v* 3061, 3027, 1636, 1581, 1515, 1454, 1315, 1271, 1056, 979, 749, 698. HRMS: *m/z* calculated for $C_{32}H_{27}N_3O_2$ $[M + H]^+$: 486.2176, found: 486.2176.

General procedure for the synthesis of Polymer-supported bis(oxazoline)(PS-box) 1c~1e

A solution of the monomers and AIBN in a mixture toluene (Table 1) was heated at 80 °C. After 24 h, the polymer was washed with THF and dried by suction filter. The polymer was then crushed in a ball milling device and washed in a Soxhlet apparatus with THF for 24 h and dried under vacuum at 50 °C overnight. The loading of bis(oxazoline) was determined by elemental analysis.

Polymer-supported bis(oxazoline) (1c)

Elemental analysis calcd. (%) for $(C_{10.92}H_{10.50}N_{0.25}O_{0.17})_n$: C 88.71, H 7.11, N 2.37, O 1.81; found C 88.87, H 7.02, N 2.33, O 1.78; Loading of bis(oxazoline): 0.555 mmol/g; IR (KBr) *v* 3057, 3024, 2918, 1634, 1584, 1513, 1451, 1315, 1272, 1056, 986, 756, 700.

Polymer-supported bis(oxazoline) (1d)

Elemental analysis calcd. (%) for $(C_{10.62}H_{10.20}N_{0.25}O_{0.17})_n$: C 88.61, H 7.09, N 2.44, O 1.86; found C 88.83, H 6.95, N 2.39, O 1.82; Loading of bis(oxazoline): 0.569 mmol/g; IR (KBr) *v* 3058, 3024, 2920,1635, 1600, 1514, 1451, 1316, 1271, 1056, 984, 757, 700.

Polymer-supported bis(oxazoline) (1e)

Elemental analysis calcd. (%) for $(C_{10.31}H_{9.89}N_{0.25}O_{0.17})_n$: C 88.50, H 7.08, N 2.51, O 1.91; found C 87.94, H 7.43, N 2.63, O 2.00; Loading of bis(oxazoline): 0.626 mmol/g; IR (KBr) *v* 3057, 3024, 2918, 1635, 1584, 1514, 1451, 1314, 1271, 1055, 979, 754, 698.

General procedure for using PS-box in batch condition

To a tube a mixture of PS-box (0.005 mmol, 0.2 mol%) and $Cu(OTf)_2$ (0.004 mmol) with 25 mL toluene were added, then **2a** (2.5 mmol, 1 equiv.) and NFSI (3.0 mmol, 1.2 equiv.) were added successively. The reaction mixture was shaken for 120 min. The (PS-box)-$Cu(OTf)_2$ complex was centrifuged and washed with toluene (5 mL × 3) and recycled for next run, the filtrate was evaporated in vacuo, the crude product was purified by column chromatography (hexane: ethyl acetate = 3:1) to afford the desired product. The enantioselectivity was determined by HPLC analysis of the product.

General procedure for TON testing in continuous flow condition

A 150 mm × 4.6 mm id stainless steel column packed with PS-box **1d** (0.12 g, 0.068 mmol) and celite (0.8 g) was connected to the pump and charged with the copper salt by slowly pumping through the ligand bed with an excess of $Cu(OTf)_2$ in dry THF, then washed with THF for 2 h to make sure that no free $Cu(OTf)_2$ was left in the column. **2a** (0.2 M, 1 equiv.) and NFSI (0.24 M, 1.2 equiv.) were pumped into the column at 30 μL min^{-1} from respective solutions (60 μL min^{-1} total flow rate, 0.1 M concentration of **2a** in the reactor). After stabilizing the continuous flow system for 12 h, each fraction was collected for 30 min every 12 h. The collections were evaporated to remove the solvents under reduced pressure, and the crude product was purified by column chromatography (hexane: ethyl acetate = 3:1) to afford the desired product. The enantioselectivity was determined by HPLC analysis of the product.

General procedure for the scope of indanone-2-carboxylates in continuous flow condition

The same PS-box was used in the column to catalyze all the substrates. A 150 mm × 4.6 mm id stainless steel column packed with PS-box **1d** (0.12 g, 0.068 mmol) and celite (0.8 g) was connected to the pump and charged with the copper salt by slowly pumping through the ligand bed an excess of $Cu(OTf)_2$ in dry THF, then washing with THF for 2 h to make sure that no free $Cu(OTf)_2$ was left in the column. Indanone-2-carboxylate **2** (0.2 M, 1 equiv.) and NFSI (0.24 M, 1.2 equiv.) were pumped into the column at 30 μL min^{-1} from respective THF solutions (60 μL min^{-1} total flow rate, 0.1 M concentration of **2** in the reactor). After stabilizing the continuous flow system for 12 h, each fraction was collected for 30 min. Then the column was washed with THF for 2 h before the next Indanone-2-carboxylate **2** has been passed through. Each collection was evaporated to remove the solvent under reduced pressure, and the crude product was purified by column chromatography (hexane: ethyl acetate = 3:1) to afford the desired product. The enantioselectivity was determined by HPLC analysis of the product.

Methyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3a)[11b]

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 7.7 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), δ 7.46 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.80 (dd, *J* = 17.7, 11.3 Hz, 1H), 3.44 (dd, *J* = 23.4, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.10 (d, *J* = 18.3 Hz), 167.70 (d, *J* = 28.0 Hz), 150.82 (d, *J* = 3.8 Hz), 136.77, 133.16, 128.65, 126.60, 125.62, 94.58 (d, *J* = 201.4 Hz), 53.20, 38.20 (d, *J* = 23.9 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm) t_R = 11.093 min (minor), t_R = 12.760 min (major). MS (ES^+): m/z =209.15 ($[M+H]^+$)

Ethyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3b)[5k]

Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.78 (dd, *J* = 17.7, 11.5 Hz, 1H), 3.41 (dd, *J* = 23.4, 17.7 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.24 (d, *J* = 18.2 Hz), 167.16 (d, *J* = 27.9 Hz), 150.84 (d, *J* = 3.6 Hz), 136.66, 133.03, 128.48, 126.52, 125.33, 94.36 (d, *J* = 201.0 Hz), 62.41, 38.08 (d, *J* = 24.0 Hz), 13.80. HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 9.307 min (minor), t_R = 10.400 min (major). MS (ES^+): m/z =223.10 ($[M+H]^+$)

Isopropyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3c)[5k]

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 7.7 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 5.13 (dt, *J* = 12.5, 6.3 Hz, 1H), 3.76 (dd, *J* = 17.6, 11.7 Hz, 1H), 3.41 (dd, *J* = 23.3, 17.6 Hz, 1H), 1.23 (dd, *J* = 12.5, 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.36 (d, *J* = 18.2 Hz), 166.84 (d, *J* = 27.6 Hz), 150.94 (d, *J* = 3.5 Hz), 136.61 (s), 133.31 (s), 128.54 (s), 126.55 (s), 125.52 (s), 94.40 (d, *J* = 201.3 Hz), 70.66 (s), 38.22 (d, *J* = 24.0 Hz), 21.52 (s), 21.41 (s). HPLC (Daicel Chiralpak AD-H, Hexane: *i*-PrOH = 99: 1, flow rate 0.5 mL/min, 254 nm): t_R = 32.358 min (major), t_R = 36.824 min (minor). MS (ES^+): m/z =236.81 ($[M+H]^+$)

Benzyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3d)[5k]

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 7.4 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.50–7.46 (m, 2H), 7.34-7.30 (m, 3H), 5.25 (dd, *J* = 31.6, 12.3 Hz, 2H), 3.77 (dd, *J* = 17.6, 11.4 Hz, 1H), 3.43 (dd, *J* = 23.2, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.04 (d, *J* = 20.3 Hz), 167.14 (d, *J* = 28.9 Hz), 150.79, 136.73, 135.85, 134.65, 133.27, 129.83, 129.47, 128.62, 128.54, 127.99, 126.58, 125.67, 94.61 (d, *J* = 201.7 Hz), 67.83, 38.22

View Article Online
DOI: 10.1039/C8OB01943F

(d, *J* = 24.0 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 95: 5, flow rate 0.7 mL/min, 254 nm): t_R = 14.639 min (minor), t_R = 16.532 min (major). MS (ES^+): m/z =285.01 ($[M+H]^+$)

Tert-butyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3e)[11b]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 7.7 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.72 (dd, *J* = 17.5, 10.7 Hz, 1H), 3.39 (dd, *J* = 22.9, 17.5 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.78 (d, J= 18.4 Hz), 166.23 (d, J= 27.7 Hz), 150.95 (d, *J* = 3.8 Hz), 136.45, 133.52, 128.44, 126.46, 125.38, 94.35 (d, J_{CF} = 201.6 Hz), 84.10, 38.30 (d, J_{CF} = 24.1 Hz), 27.77. HPLC (Daicel Chiralpak AD-H, Hexane: *i*-PrOH = 99: 1, flow rate 0.5 mL/min, 254 nm): t_R = 26.118 min (major), t_R = 34.318 min (minor). MS (ES^+): m/z =251.01 ($[M+H]^+$)

(3*R*,5*R*,7*R*)-adamantan-1-yl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3f)[12a]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.72 (dd, *J* = 17.5, 10.4 Hz, 1H), 3.38 (dd, *J* = 22.8, 17.5 Hz, 1H), 2.13 (s, 3H), 2.03 (d, *J* = 3.1 Hz, 6H), 1.60 (t, *J* = 3.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.81 (d, *J* = 18.5 Hz), 165.75 (d, *J* = 27.8 Hz), 150.94 (d, *J* = 3.8 Hz), 136.37, 133.57, 128.38, 126.42, 125.32, 94.26 (d, *J* = 201.5 Hz), 84.07, 40.98, 38.38 (d, *J* = 24.1 Hz), 35.83, 30.81. HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 7.640 min (minor), t_R = 10.707 min (major). MS (ES^+): m/z =351.19 ($[M+H]^+$)

Methyl (*S*)-2,5-difluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3g)[12c]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.92-7.78 (m, 1H), 7.20 (s, 1H), 7.19 (t, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.81 (dd, *J* = 17.8, 10.9 Hz, 1H), 3.44 (dd, *J* = 22.9, 17.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.14 (d, *J* = 18.4 Hz), 169.22, 167.53, 167.23 (d, *J* = 20.0 Hz), 153.81 (dd, *J* = 10.7, 3.8 Hz), 128.23 (d, *J* = 10.6 Hz), 117.21 (d, *J* = 23.9 Hz), 113.56 (d, *J* = 23.1 Hz), 94.60 (d, *J* = 202.6 Hz), 53.34, 38.10 (dd, *J* = 24.3, 2.0 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 12.439 min, t_R = 14.372 min (major). MS (ES^+): m/z =226.97 ($[M+H]^+$)

Methyl (*S*)-5-chloro-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3h)[11d]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.2 Hz, 1H), 7.50 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 3.78 (s, 3H), 3.75 (dd, *J* = 17.9, 11.1 Hz, 1H), 3.41 (dd, *J* = 22.9, 17.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.65 (d, *J* = 18.4 Hz), 167.31 (d, *J* = 27.9 Hz), 152.14 (d, *J* = 3.8 Hz), 143.49, 131.61, 129.56, 126.87, 126.69, 94.47 (d, *J* = 202.6 Hz), 53.34, 37.90 (d, *J* = 24.2 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 99: 1, flow rate 1.0 mL/min, 254 nm): t_R = 32.278 min (minor), t_R = 38.651 min (major). MS (ES^+): m/z =243.01 ($[M+H]^+$)

Methyl (*S*)-5-bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3i)[11d]

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 3.77 (dd, *J* = 10.5, 17.5 Hz, 1H), 3.41 (dd, *J* = 23.0, 17.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.90 (d, *J* = 18.4 Hz), 167.30 (d, *J* = 27.8 Hz), 152.17 (d, *J* = 3.7 Hz), 132.45, 132.04, 132.03, 129.98, 126.73, 94.41 (d, *J* = 202.9 Hz), 53.37, 37.85 (d, *J* = 24.2 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 13.519 min (minor), t_R = 16.425 min (major). MS (ES^+): m/z =287.27 ($[M+H]^+$)

Methyl (*S*)-4-bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3j)[12c]

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.76 (dd, *J* = 18.1, 11.6 Hz, 1H), 3.39 (dd, *J* = 23.2, 18.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 194.52 (d, *J* = 18.3 Hz), 167.32 (d, *J* = 27.8 Hz), 150.69 (d, *J* = 3.9 Hz), 139.42, 135.19, 130.39, 124.43, 121.90, 94.09 (d, *J* = 202.7 Hz), 53.41, 39.35 (d, *J* = 24.8 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 11.333 min (minor), t_R = 13.160 min (major). MS (ES^+): m/z =287.09 ($[M+H]^+$)

Methyl (*S*)-6-bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3k)[12c]

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 3.81 (s, 3H), 3.72 (dd, *J* = 18.2, 11.5 Hz, 1H), 3.35 (dd, *J* = 23.3, 18.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 194.42 (d, *J* = 18.3 Hz), 167.17 (d, *J* = 28.0 Hz), 150.56 (d, *J* = 3.7 Hz), 139.34, 135.03, 130.34, 124.29, 121.76, 93.98 (d, *J* = 202.4 Hz), 53.31, 39.21 (d, *J* = 24.8 Hz). HPLC (Daicel Chiralpak AD-H, Hexane: *i*-PrOH = 99: 1, flow rate 1.0 mL/min, 254 nm): t_R = 29.984 min (minor), t_R = 34.051 min (major). MS (ES^+): m/z =287.15 ($[M+H]^+$)

Methyl (*S*)-2-fluoro-6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3l)[11d]

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.65 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.76 (dd, *J* = 17.5, 11.0 Hz, 1H), 3.40 (dd, *J* = 23.2, 17.5 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 195.16 (d, *J* = 18.2 Hz), 167.85 (d, *J* = 28.0 Hz), 148.26 (d, *J* = 3.7 Hz), 138.88, 138.06, 133.40, 126.26 (d, *J* = 0.9 Hz), 125.53, 95.01 (d, *J* = 201.6 Hz), 53.21, 37.96 (d, *J* = 23.8 Hz), 21.09. HPLC (Daicel Chiralpak AD-H, Hexane: *i*-PrOH = 95: 5, flow rate 1.0 mL/min, 254 nm): t_R = 10.506 min (minor), t_R = 11.346 min (major). MS (ES^+): m/z =223.17 ($[M+H]^+$)

Methyl (*S*)-2-fluoro-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3m)[12c]

Yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.6 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.90 (s, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.72 (dd, *J* = 17.7, 11.0 Hz, 1H), 3.34 (dd, *J* = 23.1, 17.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 192.86 (d, *J* = 18.3 Hz), 167.85 (d, *J* = 28.1 Hz), 166.85, 153.99 (d, *J* = 3.9 Hz), 127.30, 126.10, 116.75, 109.68, 94.97 (d, *J* = 200.8 Hz), 55.84, 53.04, 38.10 (d, *J* = 24.1 Hz). HPLC (Daicel Chiralpak AD-H, Hexane: *i*-PrOH = 95: 5, flow rate 0.7 mL/min, 254 nm): t_R = 32.144 min (major), t_R = 36.157 min (minor). MS (ES^+): m/z =239.25 ($[M+H]^+$)

Methyl (*S*)-2-fluoro-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3n)[12c]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.16 (s, 1H), 6.88 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.67 (dd, *J* = 17.4, 10.4 Hz, 1H), 3.30 (dd, *J* = 22.5, 17.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 193.27 (d, *J* = 18.6 Hz), 167.89 (d, *J* = 28.2 Hz), 157.14, 150.22, 146.85 (d, *J* = 4.1 Hz), 125.77 (d, *J* = 0.9 Hz), 107.27, 105.26, 94.97 (d, *J* = 200.8 Hz), 56.38, 56.05, 53.03, 37.81 (d, *J* = 24.1 Hz). HPLC (Daicel Chiralpak OD-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 30.051 min (minor), t_R = 32.998 min (major). MS (ES^+): m/z =269.80 ($[M+H]^+$)

(*S*)-2-fluoro-1-oxo-N-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (3o)[5k]

White solid; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 4.08 (dd, *J* = 17.4, 11.3 Hz, 1H), 3.43 (dd, *J* = 24.0, 17.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 196.36 (d, *J* = 18.4 Hz), 164.74 (d, *J* = 21.6 Hz), 151.84 (d, *J* = 4.1 Hz), 136.89, 136.56, 133.19, 129.12, 128.56, 126.56, 125.60, 125.23, 120.06, 97.02 (d, *J* = 205.0 Hz), 37.40 (d, *J* = 22.6 Hz). HPLC (Daicel Chiralpak IC-H, Hexane: *i*-PrOH = 90: 10, flow rate 1.0 mL/min, 254 nm): t_R = 13.732 min (minor), t_R = 18.185 min (major). MS (ES^+): m/z =270.05 ($[M+H]^+$)

View Article Online
DOI: 10.1039/C8OB01943F

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The research was supported by National Key R&D Program of C hina (2017YFB0307200) and National Natural Science Foundati on of China (21402176).

Notes and references

1 For selected reviews, see: (a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1-45; (b) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.*, 2003, **103**, 3119-3154; (c) H. A. McManus, P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151-4202; (d) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.*, 2006, **106**, 3561-3651; (e) G. C. Hargaden, P. J. Guiry, *Chem. Rev.*, 2009, **109**, 2505-2550; (f) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.*, 2011, **111**, PR284-437.

2 For selected reviews, see: (a) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.*, 2002, **102**, 3275-3300; (b) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.*, 2002, **102**, 3385-3466; (c) D. Rechavi, M. Lemaire, *Chem. Rev., 2002*, **102**, 3467-3494; (d) R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.*, 2002, **102**, 3717-3756; (e) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.*, 2006, **45**, 4732-4762; (f) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.*, 2009, **109**, 418-514; (g) J. Lu, P. H. Toy, *Chem. Rev.*, 2009, **109**, 815-838.

3 For selected reviews, see: (a) C. E. Song, S.-G. Li, *Chem. Rev.*, 2002, **102**, 3495-3524; (b) C. Li, *Catal. Rev.*, 2004, **46**, 419-492; (c) M. Tada, Y. Iwasawa, *Chem. Commun.*, 2006, 2833-2844; (d) J. M. Fraile, J. I. Garcia, J. A. Mayoral, *Chem. Rev.*, 2009, **109**, 360-417.

4 For selected reviews, see: M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401-3430.

5 (a) H. A. McManus, P. J. Guiry, *J. Org. Chem.*, 2002, **67**, 8566-8573; (b) J.-A. Ma, D. Cahard, *Tetrahedron: Asymmetry*, 2004, **15**, 1007-1011; (c) S.-F. Lu, D.-M. Du, S.-W. Zhang, J. Xu, *Tetrahedron: Asymmetry*, 2004, **15**, 3433-3441; (d) D.-M. Du, S.-F. Lu, T. Fang, J. Xu, *J. Org. Chem.*, 2005, **70**, 3712-3715; (e) S.-F. Lu, D.-M. Du, J. Xu, S.-W. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 7418-7419; (f) S.-F. Lu, D.-M. Du, J. Xu, *Org. Lett.*, 2006, **8**, 2115-2118; (g) H. A. McManus, P. G. Cozzi, P. J. Guiry, *Adv. Synth. Catal.*, 2006, **348**, 551-558; (h) H. Liu, J. Xu, D.-M. Du, *Org. Lett.*, 2007, **9**, 4725-4728; (i) S. C. McKeon, H. Müller-Bunz, P. J. Guiry, *Eur. J. Org. Chem.*, 2009, 4833-4841; (j) V. Coeffard, M. Aylward, P. J. Guiry, *Angew. Chem. Int. Ed.*, 2009, **48**, 9152-9155; (k) J. Peng, D.-M. Du, *RSC Adv.*, 2014, **4**, 2061-2067; (l) H.-J. Wang, Y.-F. Wang, C. Zhang, Y.-D. Jiang, M.-M. Chu, Z.-B. Li, D.-Q. Xu, *Org. Biomol. Chem.*, 2017, **15**, 4191–4198; (m) Y.-F. Wang, J.-J. Shao, B. Wang, M.-M. Chu, X.-H. Du, D.-Q. Xu, *Adv. Synth. Catal.*, 2018, **360**, 2285–2290.

6 H. Liu, D.-M. Du, *Eur. J. Org. Chem.*, 2010, 2121-2131.

7 (a) S. Itsuno, Y. Sakurai, K. Ito, T. Maruyama, S. Nakahama, J. M. J. Fréchet, *J. Org. Chem.*, 1990, **55**, 304-310; (b) K. Kamahori, S. Tada, K. Ito, S. Itsuno, *Tetrahedron: Asymmetry*, 1995, **6**, 2547-2555; (c) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis, R. V. Salvador, M. J. Vicent, *Tetrahedron: Asymmetry*, 1999, **55**, 12897-12906; (d) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, S. V. Luis, J. A. Mayoral, *Org. Lett.*, 2000, **2**, 3905-3908; (e) M. I. Burguete, J. M. Fraile, J. I. García, E. García-Verdugo, C. I. Herrerías, S. V. Luis, J. A. Mayoral, *J. Org. Chem.*, 2001, **66**, 8893-8901; (f) A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, S. V. Luis, V. Martínez-Merino, J. A. Mayoral, *J. Org. Chem.*, 2005, **70**, 5536-5544; (g) J. Lloret, M. Stern, F. Estevan, M. Sanaú, M. A. Úbeda, *Organometallics*, 2008, **27**, 850-856; (h) M. Rueping, E. Sugiono, A. Steck, T. Theissmann, *Adv. Synth. Catal.*, 2010, **352**, 281-287; (i) D. S. Kundu, J. Schmidt, C. Bleschke, A. Thomas, S. Blechert, *Angew. Chem. Int. Ed.*, 2012, **51**, 5456-5460; (j) L. Li, H. Zhao, R. Wang, *ACS Catal.*, 2015, **5**, 948-955; (k) I. Sagamanova, C. Rodríguez-Escrich, G. I. Molnár, S. Sayalero, R. Gilmour, M. A. Pericàs, *ACS Catal.*, 2015, **5**, 6241-6248; (l) L. Clot-Almenara, C. Rodríguez-Escrich, L. Osorio-Planes, M. A. Pericàs, *ACS Catal.*, 2016, **6**, 7647-7651; (m) P. Llanes, S. Sayalero, C. Rodríguez-Escricha, M. A. Pericàs, *Green Chem.*, 2016, **18**, 3507-3512.

8 For selected reviews, see: (a) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887-3964; (b) H. Ibrahim, A. Togni, *Chem. Commun.*, 2004, 1147-1155; (c) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.*, 2010, **352**, 2708-2732; (d) A. M. R. Smith, K. K. Hii, *Chem. Rev.*, 2011, **111**, 1637-1656.

9 L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.*, 2000, **39**, 4359-4362.

10 (a) Y. Hamashima, K. Yagi, H. Takano, L. Tamás, M. Sodeoka, *J. Am. Chem. Soc.*, 2002, **124**, 14530-14531; (b) Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.*, 2003, **5**, 3225-3228; (c) J.-A. Ma, D. Cahard, *J. Fluorine Chem.*, 2004, **125**, 1357-1361; (d) A. Assalit, T. Billard, S. Chambert, B. R. Langlois, Y. Queneau, D. Coe, *Tetrahedron: Asymmetry*, 2009, **20**, 593-601; (e) A. Bertogg, L. Hintermann, D. P. Huber, M. Perseghini, M. Sanna, A. Togni, Helv. *Chim. Acta*, 2012, **95**, 353-403; (f) K. Mori, A. Miyake, T. Akiyama, *Chem. Lett.*, 2014, **43**, 137-139.

11 (a) D. Y. Kim, E. J. Park, *Org. Lett.*, 2002, **4**, 545-547; (b) X. Wang, Q. Lan, S. Shirakawa, K. Maruoka, *Chem. Commun.*, 2010, **46**, 321-323; (c) E. M. Tanzer, W. B. Schweizer, M. O. Ebert, R. Gilmour, *Chem.-Eur. J.*, 2012, **18**, 2006-2013; (d) J. Xu, Y. Hu, D. Huang, K.-H. Wang, C. Xu, T. Niu, *Adv. Synth. Catal.*, 2012, **354**, 515-526; (e) Y. Wang, H. Yuan, H. Lu and W.-H. Zheng, *Org. Lett.*, 2018, **20**, 2555-2558.

12 (a) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.*, 2005, **44**, 4204-4207; (b) Q.-H. Deng, H. Wadepohl, L. H. Gade, *Chem.-Eur. J.*, 2011, **17**, 14922-14928; (c) Y.-F. Wang, H.-J. Wang, Y.-D. Jiang, C. Zhang, J.-J. Shao, D.-Q. Xu, *Green Chem.*, 2017, **19**, 1674–1677.

13 For selected reviews, see: (a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. Tyler McQuade, *Chem. Rev.*, 2007, **107**, 2300-2318; (b) X. Y. Mak, P. Laurino, P. H. Seeberger, Beilstein, *J. Org. Chem.*, 2009, **5**, 1-11; (c) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.*, 2011, **47**, 4583-4592; (d) T. Noël, S. L. Buchwald, Chem. Soc. Rev., 2011, **40**, 5010-5029; (e) A. Puglisi, M. Benaglia, V. Chiroli, *Green Chem.*, 2013, **15**, 1790-1813; (f) T. Tsubogo, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.*, 2013, **52**, 6590-6604; (g) D. Zhao, K. Ding, *ACS Catal.*, 2013, **3**, 928-944; (h) V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem*, 2013, **6**, 746-789; (i) C. Rodríguez-Escrich, M. A. Pericàs, *Eur. J. Org. Chem.*, 2015, 1173-1188; (j) F. G. Finelli, L. S. M. Miranda, R. O. M. A. de Souza, *Chem. Commun.*, 2015, **51**, 3708-3722; (K) I. Atodiresei, C. Vila, M. Rueping, *ACS Catal.*, 2015, **3**, 1972-1985.

14 T. Tsubogo, Y. Yamashita, S. Kobayashi, *Chem.-Eur. J.*, 2012, **18**, 13624-13628.

15 (a) E. Alza, C. Rodríguez-Escrich, S. Sayalero, A. Bastero, M. A. Pericàs, *Chem.-Eur. J.*, 2009, **15**, 10167-10172; (b) X. Fan, S. Sayalero, M. A. Pericàs, *Adv. Synth. Catal.*, 2012, **354**, 2971-2976; (c) R. Martín-Rapún, S. Sayalero, M. A. Pericàs, *Green Chem.*, 2013, **15**, 3295-3301.

View Article Online
DOI: 10.1039/C8OB01943F

16 (a) N. T. S. Phan, D. H. Brown, P. Styring, *Green Chem.*, 2004, **6**, 526–532. (b) P. Styring, A. I. R. Parracho, Beilstein, *J. Org. Chem.*, 2009, **5**, 1-10.
17 S.-F. Lu, D.-M. Du, S.-W. Zhang and J. Xu, *Tetrahedron: Asymmetry*, 2004, **15**, 3433-3441.
18 (a) S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita and N. Shibata, *Chem. Sci.*, 2014, **5**, 2754-2760. (b) J. Peng and D.-M. Du, *RSC Adv.*, 2014, **4**, 2061-2067.
19 C. De Fusco, S. Meninno, C. Tedesco and A. Lattanzi, *Org. Biomol. Chem.*, 2013, **11**, 896-899.