Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400603

Enantioselective Fluorination of β-Ketoamides Catalyzed by Ar-BINMOL-derived Salan–Copper Complex

Long-Sheng Zheng,[a] Yun-Long Wei,[a] Ke-Zhi Jiang,[a] Yuan Deng,[a] Zhan-Jiang Zheng,[a] and Li-Wen Xu[a,b,*]

[a] Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University
Fax: (+86)-571-28868915; e-mail: liwenxu@hznu.edu.cn

[b] Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education (MOE), and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi′an 710062, P. R. China
E-mail: licpxulw@yahoo.com

Received: June 21, 2014; Revised: September 6, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400603.

Abstract: A facile and powerful enantioselective construction of C–F containing molecules was successfully developed through asymmetric fluorination of β-ketoamides catalyzed by Ar-BINMOL-derived salan–Cu^{II} system (Ar-BINMOL = 1,1′-Binaphthalene-2-α-arylmethanol-2′-ol, Cu = copper). The present catalytic system exhibited excellent enantioselectivity and a broad substrate scope for indanone-derived β-ketoamides under mild conditions (up to 99% *ee* and 99% yields). Notably, the biomimetic salan-copper complex was demonstrated for the first time to be a highly efficient catalyst in the fluorination of β-ketoamides. Experimental results and mechanistic studies indicated that both excess amount of copper salt and electrophilic attack of cationic fluorine to activated methylene assisted by amide group on the β-ketoamides were key factors for high yield and excellent enantioselectivity, respectively, in this enantioselective fluorination, which was controlled by the two-point binding between the salan–copper complex with cyclic β-ketoamides and hydrogen-bonding activation of the electrophilic fluorinating reagent.

Keywords: Asymmetric catalysis; Fluorination; Homogeneous catalysis; Ketoamides; Salan

The catalytic and enantioselective incorporation of fluorine into organic molecules is one of the most powerful and widely established strategies for the stereoselective construction of chiral C–F bonds in organic synthesis.[1] The resulting chiral organofluorine compounds are very fascinating in the field of organic and medicinal chemistry as well as modern material science.[2,3] Especially, the unique electronic properties, size, hydrophobic/lipophilicity, and promising hydrogen-bonding activity of a fluorine atom can dramatically influence chemical reactivity and make organic molecules with C–F bonds useful candidates for drug development.[3] On this basis, the catalytic asymmetric fluorination of carbonyl compounds have received much attention as one of the most efficient strategies for the synthesis of chiral fluorine-containing compounds, in which a lot of research has focused on the development of chiral catalysts, including cinchona alkaloid or secondary amine-based organocatalysts and metal complexes.[4–8] Notably, the first breakthrough related to the enantioselective construction of a fluorinated stereogenic center through electrophilic fluorination was made by Togni and Hintermann with chiral titanium complex in 2000.[5] Following this pioneering work, rapid advances in the catalytic fluorination of α-substituted β-ketoester substrates reported by several groups have led to significant improvement over the past decade.[6] These improved methodologies with transition metal-based catalysts,[7,8] including palladium, nickel, or copper, made great contributions to both organofluorine chemistry and asymmetric catalysis. However, the levels of the enantioselectivity were not high enough in most cases, especially for the copper complex derived from nitrogen-containing ligands, such as bis(oxazoline) or its analogues.[8,9] In this context, the copper-catalyzed fluorination of α-substituted β-ketoester substrates has been reported by Ma and Cahard early in 2004, however, the copper(II) triflate-bis(oxazoline)-catalyzed fluorination only resulted in moderate enantioselectivity.[8a] And interestingly, there is no report on the enantioselective fluorination

of α-substituted β-ketoesters catalyzed by salen–copper or salan–copper complex. Thus the development of new catalytic copper system for this fluorination reaction as well as the highly enantioselective construction of a quaternary carbon-stereocenter[10] linked with amides is required.

As part of a program focused upon the development of a copper catalyst for broadly useful reactions, we recently found that the Ar-BINMOL-derived salan ligand (Ar-BINMOL = 1,1′-Binaphthalene-2-α-arylmethanol-2′-ols) exhibited unusual molecular recognition for the copper salt, and the corresponding salan–copper(II) complex gave a high level of catalytic efficiency in the asymmetric Henry reaction of aldehydes in terms of enantioselectivities and conversions.[11] Based on the experimental results in the Henry reaction, we hypothesized that the Ar-BINMOL-derived salan ligands bearing a crowded aromatic π-wall would exhibit remarkable and privileged enantioselectivity in various catalytic asymmetric reactions. The modulation of multifunctional Ar-BINMOL-derived salen or salan ligands can take full advantage of electronic and steric properties of the aromatic substituents and chiral moieties (Figure 1), which could lead to the development of highly efficient ligands with excellent enantioselectivity for catalytic asymmetric transformation according to the need of improvement and modification of Ar-BINMOL-derived salan or salen ligands (Figure 1 shows four possible approaches for the modular modification of Ar-BINMOL-derived salan ligands for catalytic asymmetric catalysis). Herein, we further advance this type of Ar-BINMOL-derived salan ligands and report a highly efficient fluorination of β-ketoamides for the enantioselective construction of fluorinated carbon stereogenic centers by copper catalyst.

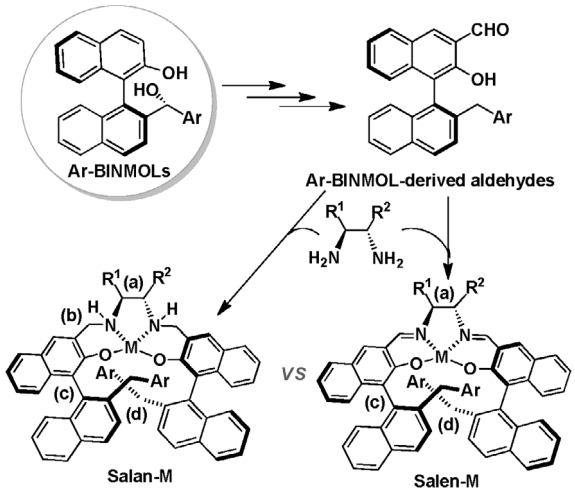
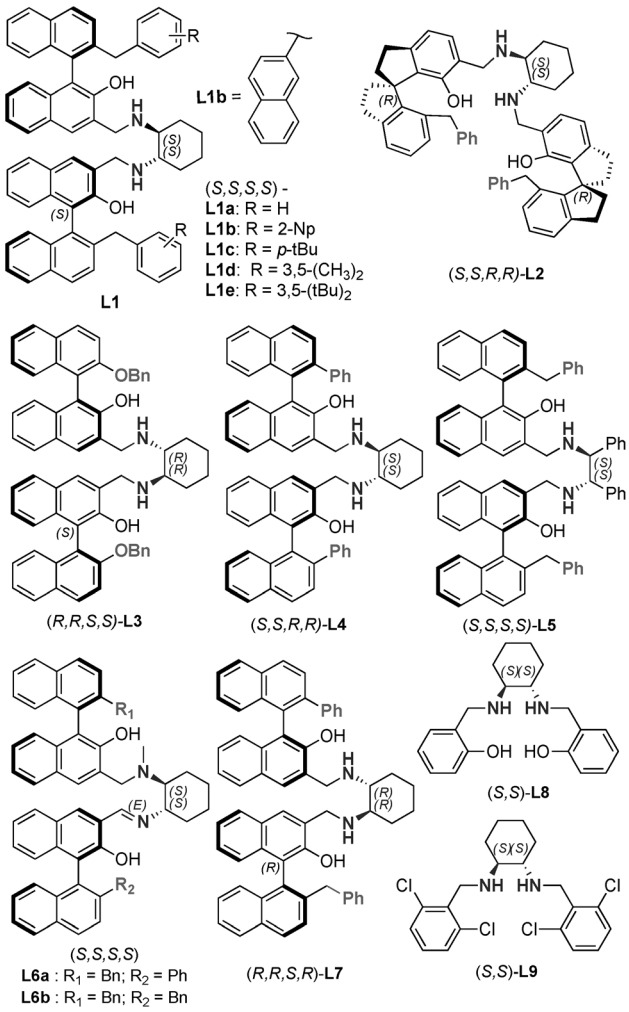
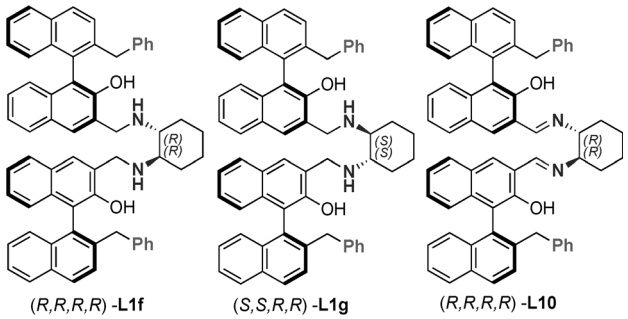


Figure 1. Ar-BINMOL-derived salens or salans as a family of chiral ligands for transition metal (M)-catalyzed organic transformation. Easy modification of Ar-BINMOL-derived salan ligands as following: (**a**) Chiral diamine; (**b**) Secondary amine moieties; (**c**) C_2-axial chirality and substituted group on binaphthyl moieties; (**d**) Aromatic or benzylic substituents (-CH_2-Ar).

To achieve excellent enantioselectivity in the catalytic fluorination, we designed and synthesized, as far as possible, substituted salan ligands from enantiomerically pure diamines (commercial available cyclohexane-1,2-diamine and 1,2-diphenylethane-1,2-diamine with different absolute configuration) with BINOL-derivatives, including 1,1′-binaphthalene-2-α-arylmethanol-2′-ols (Ar-BINMOLs),[12] 1,1′-spirobiindane-7-α-phenylmethanol-7′-ol (SPINMOL),[13] and 1,1′-Binaphthalene-2-phenyl-2′-ol,[14] where axial and sp^3 central chirality as well as Schiff base and secondary amine moieties on salan, salalen, or salen ligands were systematically modulated (**L1** to **L10**, Scheme 1 and Scheme 2). The syntheses of these ligands were accomplished by the coupling of an Ar-BINMOL-derived aldehyde and a chiral diamine in analogy to the reported procedures (see Supporting Information).[11]



Scheme 1. Various salan ligands (**L1**–**L9**) derived from chiral diamines and Ar-BINMOLs, SPINMOL, or BINOL for copper-catalyzed fluorination.



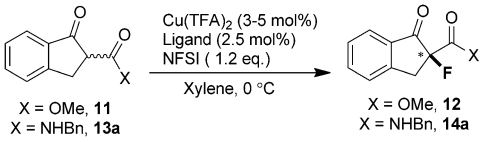
Scheme 2. Different salan/salen ligands prepared from Ph-BINMOL-derived aldehyde with different diamines.

In addition, to support the privileged structure of Ar-BINMOL-derived salan **L1**, we also evaluated the simple salan ligands **L8** and **L9** derived from (*S*,*S*)-cyclohexane-1,2-diamine with 2-hydroxybenzaldehyde or 2,6-dichlorobenzaldehyde respectively. Notably, the information of chirality mismatching or matching of chiral diamine and BINOL-derivatives was also provided in Scheme 2, where various salan ligands **L1 f** and **L1 g** with different configuration was modulated to determine the contributions from the chiral secondary amine and the BINOL-derived back bone with C_2-axial chirality.

At the outset, we chose methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **11** as the model nucleophilic partner for copper-catalyzed fluorination reaction. Thus on the basis of this synthetic work, we tested the copper-catalyzed fluorination of β-ketoester **11** with (*R,R,R,R*)- **L1 f** (Scheme 2) as salan ligand for the initial establishment of optimal reaction conditions (see the Supporting Information, Table S1-S3). Further experiments conducted with a series of salan ligands and it analogues showed in Scheme 1 and Scheme 2, in which the catalytic results were provided in Table 1. It was revealed that (*S,S,S,S*)- **L1 a** resulted in the desired product in same level of enantioselectivity and yield in comparison to that of (*R,R,R,R*)- **L1 f** in this reaction (Table 1, entry 1 and entry 15). After surveying an array of reaction parameters including various copper salts, solvent, temperature, and the ratio of copper to salan ligand (**L1 f**), we determined that $Cu(TFA)_2$/**L1 f** can catalyze the fluorination of β-ketoester **11** in good enantioselectivity and yield (82% *ee* in xylene, Entry 15 of Table 1). Notably, the ratio of copper to salan ligand would be crucial to the reaction rate in xylene, for example, the order of yield after 12 h is 5/2.5 (99%) > 3/2.5 (90%) > 2.5/2.5 (88%), and the enantioselectivity was also decreased in sequence as 81% > 78% > 77% *ee*. Under similar reaction conditions, the structures of salan ligands **L1 a-e** were proved to be important since the introduction of larger and sterically bulky groups, such as methyl or *tert*-butyl substituent on 3,5-position of phenyl ring of Ar-BINMOL-based back bone, led to poorer enantioselective activity (Entries 4 and 5, 44-48% *ee*). It should be noted that there are no obvious improvement in enantioselectivity when the aromatic group is 2-naphthyl or 4-*tert*-butylphenyl in this salan ligand (Entries 2 and 3 respectively).

Unexpectedly, chiral 1,1′-spirobiindane-7,7′-diol (SPINOL)-derived salan ligand **L2** exhibited quite low enantioselectivity (19% *ee*, entry 6), which indicates that the rotatable binaphthyl moiety is very important in the achievement of high level of enantioselectivity in this reaction. Also interestingly, when the benzyl group was replaced by benzylic ether on this salan ligand, the resulted ligand **L3** was not good enough to induce the enantioselective fluorination of β-ketoester **11** (Entry 7, only 56% *ee*). Although Katsuki's salen ligands have been applied widely in various organic transformations with high enantioselectiv-

Table 1. Catalytic evaluation of various salan ligands and their analogues in the copper-catalyzed fluorination of β-ketoester **11** or β-ketoamide **13 a**[a]



Entry	X	[Cu] /mol%	Ligand	yield/%[b]	*ee*/%[c]
1	OMe	5	(*S,S,S,S*)-**L1 a**	99	-81(*R*)
2	OMe	3	(*S,S,S,S*)-**L1 b**	99	-73(*R*)
3	OMe	3	(*S,S,S,S*)-**L1 c**	96	-81(*R*)
4	OMe	3	(*S,S,S,S*)-**L1 d**	99	-44(*R*)
5	OMe	3	(*S,S,R,R*)-**L1 e**	95	-48(*R*)
6	OMe	5	(*S,S,R,R*)-**L2**	99	-19(*R*)
7	OMe	3	(*R,R,S,S*)-**L3**	99	56(*R*)
8	OMe	3	(*S,S,R,R*)-**L4**	99	-29(*R*)
9	OMe	3	(*S,S,R,R*)-**L5**	97	-54(*R*)
10	OMe	3	(*S,S,S,S*)-**L6 a**	99	-12(*R*)
11	OMe	3	(*S,S,S,S*)-**L6 b**	99	-11(*R*)
12	OMe	3	(*R,R,S,R*)-**L7**	94	-45(*R*)
13	OMe	3	(*S,S*)-**L8**	75	-22(*R*)
14	OMe	3	(*S,S*)-**L9**	68	-24(*R*)
15	OMe	5	(*R,R,R,R*)-**L1 f**	99	82(*S*)
16	OMe	3	(*S,S,S,S*)-**L1 g**	99	47(*S*)
17	OMe	5	(*R,R,S,S*)-**L10**	42	-5(*R*)
18	NHBn	5	(*R,R,R,R*)-**L1 f**	99	**99** (*S*)
19	NHBn	5[d]	(*R,R,R,R*)-**L1 f**	99	97(*S*)
20	NHBn	5[e]	(*R,R,R,R*)-**L1 f**	99	55(*S*)
21	NHBn	5	(*S,S*)-**L8**	70	11(*S*)

[a] Reaction conditions: [Cu]: $Cu(OCOCF_3)_2 \cdot xH_2O$ (3-5 mol%), ligand (2.5 mol%), β-ketoester **11** or β-ketoamide **13** (0.25 mmol), NFSI (1.2 eq), in xylene (1.5 mL), all the reactions were carried out at 0 °C for 12 h;
[b] Isolated yields
[c] Determined by chiral HPLC analysis.
[d] The copper salt is $Cu(OAc)_2$, and the mixture solvent of DCM/xylene (1:1) did not enhanced enantioselectivity in this reaction.
[e] The copper salt is $Cu(OTf)_2$.

ity,[15] its salan derivative (**L4**) has not achieved excellent catalytic performance in any transformations. The poor result in enantioselectivity (29% *ee*) suggested that the phenyl substituent on the 2-position of BINOL-derived the salan ligand (**L4**) was unfavorable because of its low enantioselective induction in this catalytic asymmetric reaction (Entry 8).

To confirm the special role of chiral cyclohexane-1,2-diamine moiety on the Ar-BINMOL-derived salan, (*S,S*)-1,2-diphenylethane-1,2-diamine (DPEN)-derived salan **L5** was employed as ligand in this reaction. As expected, **L5** was not suitable ligand because of only moderate enantioseleectivity (Entry 9, 54% *ee*). We also evaluated the effect of altering the salan ligand by changing the secondary amine to imine or tertiary amine on the diamine moiety. Although these ligands, **L6** (Scheme 1) and **L10** (Scheme 2), look possibly effective in the achievement of highly enantioselective fluorination, the reaction proceeded at a quite low level of enantioselectivity (5-12% *ee*, entries 10, 11, and 17). Thus it was reasonable to conclude that the salan ligand bearing secondary amine would be responsible for the well-organized transition state promoted by hydrogen bonding. Additionally, further optimization of the salan ligand focused on the construction of unsymmetrical salan ligand (**L7**), and the study of chirality matching (**L1f** and **L1g** of Scheme 2). However, no improvement or even diminished enantioselectivity was obtained when these salan ligands were employed (Entries 12 and 16). As a supplement, we also evaluated the catalytic activity of simple salan ligand **L8** and diamine **L9** (Entries 13 and 14), and the reaction results supported the necessary modulation of Ar-BINMOL-derived salan ligand with crowded aromatics. In the development of concept of macromolecular catalysis, List and coworkers very recently have described that a macromolecular SPINOL-derived chiral phosphoric acid with potential π-π stacking interaction enables long-range control to induce enantioselectivity on the nanoscale.[16]

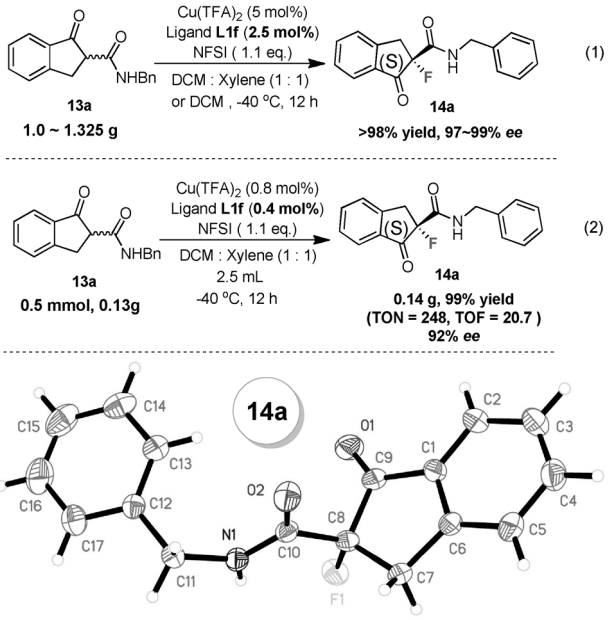
To summarize the above results, the key initial observations were: (1) The hydrogen bonding would be a positive factor in the enantioselective copper-catalyzed fluorination, as the secondary amine moiety of salan ligand played a crucial role in term of enantioselectivity; (2) The rotatable aromatic π-wall/substituent[11a] on the Ar-BINMOL-derived partner exhibited unexpected potential in this model reaction, which would be explained by the existence of aromatic interactions between catalyst and substrate; (3) These experiments also underscore the importance of chirality matching within the ligand and chiral cyclohexane-1,2-diamine moiety. Therefore, we reasoned that the noncovalent interaction including aromatic interaction and hydrogen bonding between salan-Cu catalyst and functional substrate could be exploited for the development of highly enantioselective fluorination.

On the basis of this hypothesis, we sought an effective directing group on carbonyl compounds that could provide the desired control of stereochemistry during fluorination of the α-position of functional molecules. Thus this new fluorination reaction is based on the use of β-ketoamide **13a** as a model substrate, an activated methylene compound with N-H moiety on amide featuring multi-point binding. Notably, although advances in enantioselective fluorination of β-ketoesters have been achieved, there is almost no successful study on enantioselective fluorination of β-ketoamides. The only example reported by Du and coworkers[9] suggested that the amide motif could not serve as an advantageous group in copper-catalyzed fluorination because of decreased enantioselectivity in comparison to β-ketoester analogues.

With the promising results achieved by salan(**1f**)-Cu catalyst in hand (Entry 15 of table 1), we continued to investigate the effects of solvent, temperature, and various metal salts on enantioselective fluorination of β-ketoamide **13a** (see Table S4 of Supporting Information). Fortunately, we were pleased to observe that under the optimal reaction conditions described above, the β-ketoamide **13a** containing benzylic amide was found to be an ideal structure in the enantioselective fluorination, which could be a model reaction to support the powerful potential of salan(**L1f**)-Cu complex with noncovalent interaction in this reaction. The desired fluorinated product was formed in almost perfect yield and enantioselectivity (99% yield and 99% *ee*, Entry 18 of Table 1). Notably, the absolute configuration of product **14a** was determined by X-ray diffraction analysis.[17]

The efficiency of this protocol is also illustrated in the fluorination of β-ketoamide **13a** with NFSI on a preparative scale using 2.5 mol% of salan ligand (Scheme 3, equation 1). The product **14a** of this reaction was obtained in excellent yield and enantioselectivity. Prompted by the excellent activity of salan-(**L1f**)-Cu catalyst system in this reaction, we then investigated the fluorination of **13a** with low catalyst loading. Surprisingly, when β-ketoamide **13a** was used a model substrate in the copper-catalyzed fluorination, even with 0.4 mol% of salan ligand **L1f**, the reaction could also proceed smoothly in the presence of 0.8 mol% of copper salt (calculated for salan-copper complex, S/C = 250). As shown in Scheme 3 (equation 2), the catalytic fluorination reaction were completed within 12 h to afford product **14a** in good isolated yields and excellent enantioselectivities (TON = 248 and TOF = 20.7, 99% isolated yields, 92% *ee*).

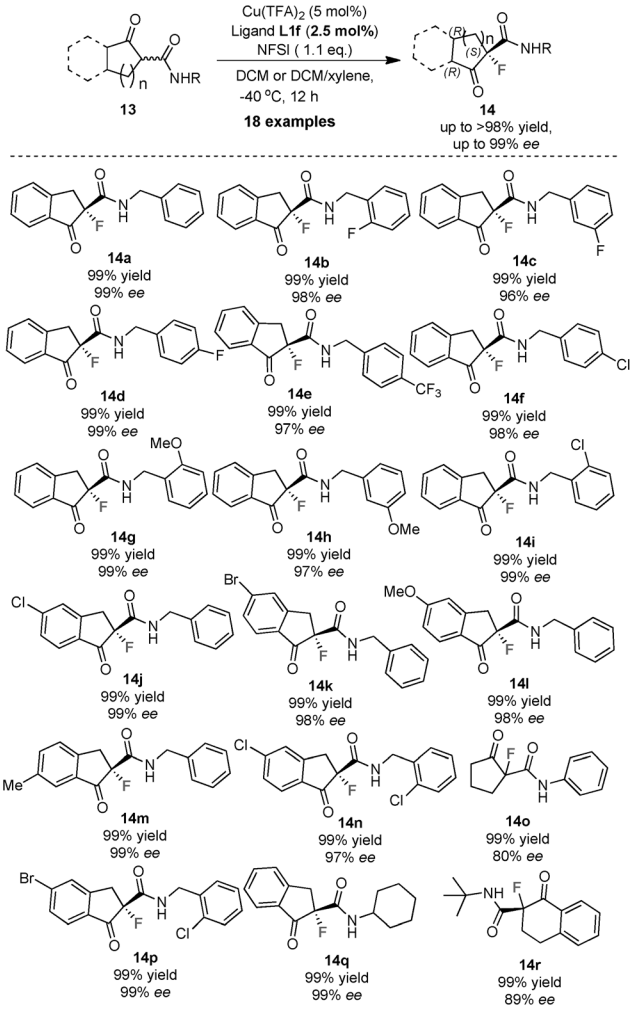
In light of the above experimental results and having optimized conditions to control the stereochemistry of fluorination, we next examined the generality of the asymmetric fluorination of various β-ketoamides. As highlighted in Scheme 4, the introduction of electron-donating and electron-withdrawing



Scheme 3. Copper-catalyzed fluorination of β-ketoamide **13a** to the preparative-scale synthesis of (*S*)-**14a** under the optimized reaction conditions; and the X-ray crystal structure of **14a** is provided (CCDC 1002368).

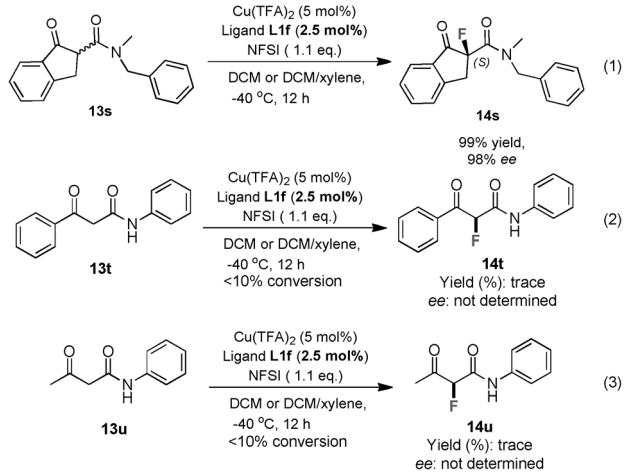
substituents on both indanone core and the amide group uniformly gave excellent enantioselectivity by using NFSI as the fluorination reagent (up to 99% *ee*). Thus the salan-Cu derived from (*R,R,R,R*)- **L1f** proved to be a highly active catalyst in this fluorination and gave full conversion to the desired products. Moreover, this protocol was highly efficient with indanone-derived β-ketoamides bearing N-H group and a wide range of groups on the aryl rings, giving excellent yields and enantioselectivities. In most case, the fluorinated products were obtained with *ee* values of $\geq$ 98% (13 examples, β-ketoamides **13a-n** and **13p**). The reaction is also well suited for alkyl amine-derived β-ketoamide **13q**, which led to the corresponding product **14q** in excellent yield and enantiomeric excess (99% yield, 99% *ee*).

Although there is no report on the asymmetric fluorination of **13r** and it is well-known that the fluorination of tetralone-derived β-ketoesters is a very challenging transformation for the achievement of highly enantioselective induction,[18] the fluorinated product **14r** can be readily obtained with excellent yield and good enantiomeric excess (89% *ee*). We then tested the fluorination reaction of the tertiary amine-substituted β-ketoamide (**13s**) under the above-described reaction conditions (Scheme 5). To our delight, the fluorination of **13s** also resulted in high yield and excellent enantioselectivity in the presence of Ar-BINMOL-derived salan **L1f** and copper catalyst system (99% yield, 98% *ee*). Therefore, the aliphatic tertiary amide-containing β-ketoamide is also a suitable substrate in this reaction. Unfortunately, the use of acyclic β-ketoamides **13t** and **13u** in this reaction led to poor conversion, and only trace products were detected by TLC. The enantiomeric excess (*ee*) of the desired product **14t** or **14u** could not be determined because of the failure in purification of corresponding product. The preliminary study could be an indication that it is quite challenging to prepare mono-substituted fluorine-containing β-ketoamides.



Scheme 4. Enantioselective salan-Cu -catalyzed fluorination: Substrate scope

On the basis of the above results and on spectral analysis from UV-vis, fluorescence emission spectra (FL), electrospray ionization mass spectrometry (ESI-MS), we propose a plausible mechanistic pathway to explain the observed reactivity. As illustrated in Figure 2, the salan-Cu catalyst may be initially generated in a first step as confirmed by ESI-MS (m/z = 942.26: [Cu(salan **L1f**)Na]$^+$). The formation of catalyst-substrate complex (intermediate **I**) derived from the salan-Cu catalyst and β-ketoamide would occur quickly. Then it binds the cationic fluorine from NFSI (intermediate **II**), which would be trapped by β-excess



Scheme 5. Enantioselective salan-Cu -catalyzed fluorination: aromatic β-ketoamide with tertiary amide and acylic β-ketoamides

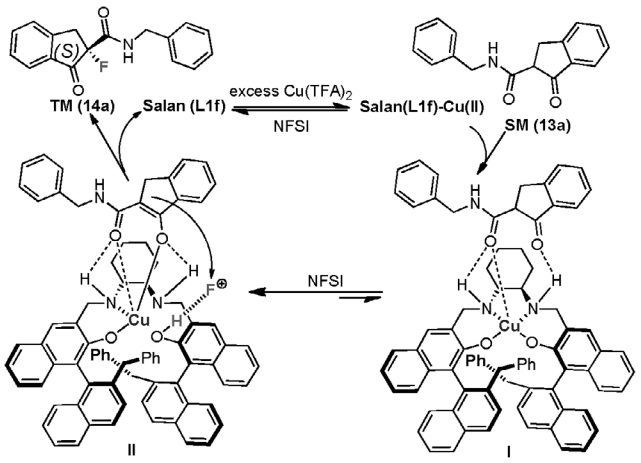


Figure 2. Proposed mechanism of the salan-Cu catalyzed fluorination reaction.

amount of copper salt to set up an intramolecular nucleophilic attack step. The key catalytic model with intermediate **II**, as supported by SI-MS studies (Figure S1-S7 of Supporting Information), involves the two-point binding and nonconvalent interaction of salan-Cu catalyst with both β-ketoamide and NFSI, including the hydrogen bonding of secondary amine, aromatic interaction induced from benzyl moiety.[19] On the basis of experimental results, UV-vis absorption, fluorescent spectra (FL), and HOMO–LUMO calculation of β-ketoamide (see Figure S8-S12 of Supporting Information), the role of the amide-group on β-ketoamide is suggested to be the enhancement of catalyst-substrate interaction. For FL spectra of salan ligand **L1 f** (1.0×10^{-5} mol/L) in the presence of β-ketoester **11** at various concentrations in DCM, as shown in Figure S11, the change of fluorescence emission upon addition of substrate (β-ketoester **11**) showed that the nonconvalent interaction between salan-Cu and β-ketoester **11** is weak in comparison to that of the formation of catalyst-ketoamide **13 a** complex. According to the calculated results (Figure S12 of Supporting Information), the lower-energy bands of β-ketoamide **13 a** showed a preferential interaction with salan-copper complex, which would be crucial to the achievement of a high level of enantioselectivity in this fluorination reaction. Notably in the last, excess amount of copper salt guaranteed the rapid formation of salan-Cu complex and avoided the decomposition of this catalyst in the presence of NSFI or under the reaction conditions (see Figure S7 of Supporting Information).

In summary, we have developed a facile enantioselective construction of C–F containing molecules through catalytic asymmetric fluorination, in which the chiral fluorine-containing β-ketoamides would be a type of important fluorine/amides-based candidates for drug development. The Ar-BINMOL-derived salan-copper complex was firstly to be demonstrated as a highly efficient macromolecular catalyst in the fluorination of β-ketoamides (up to 99% *ee* and 99% yields). And this approach featured experimental simplicity and low catalyst loadings, in which the amount of salan ligand could reduced to the level of 0.4 mol% (TON = 248). To our knowledge, the Ar-BINMOL-derived salan ligand-based copper catalyst system exhibits the highest level of catalytic performance in term of stereoselectivity and conversion reported to date in the fluorination of carbonyl compounds. In addition, the consequence of the enzyme-like behavior of Ar-BINMOL-derived salan-Cu complex allowed us to get indirect evidence by spectra analysis for the great potential of non-covalent interactions arise from the macromolecular salan-Cu catalyst and substrates, which would be useful for the exploration of the multiple non-covalent interaction-activated transformations in the near future.

Experimental Section

General Remarks

All reagents were used as purchased unless noted otherwise. β-Ketoamides **13 a-r** were prepared according to literature methods.[20] Ar-BINMOL-derived Salan Ligand **L1 a/L1 f**, **L3, L4, L5, L6 a-b, L7, L8, L9, L10** were prepared according to literature methods,[11] and the detailed experimental procedures were provided in the Supporting Information (SI). Toluene was dried and distilled over CaH_2; and THF were distilled from sodium and benzophenone. Flash column chromatography was performed over silica (200–300 mesh). ^{1}H NMR, ^{13}C NMR, ^{19}F NMR were respectively recorded at 400 or 500 MHz, 101 or 126 MHz and 376 or 471 MHz respectively on Advance (Brucker) 400 or 500 MHz Nuclear Magnetic Resonance Spectrometer, and were referenced to

the internal solvent signals. Thin layer chromatography was performed using silica gel; F_{254} TLC plates and visualized with ultraviolet light. HPLC was carried out with a Agilent Technologies 1260 Infinity system equipped with a photodiode array detector. ESI mass spectra were performed on a Trace DSQ GC/MS spectrometer. Data are reported in the form of (*m*/*z*). High Resolution Mass Spectra (ESI-HRMS) were operated on a micro TOF-Q II (Bruker). IR spectra were recorded using a FTIR apparatus (Nicolot 5700). Melting point was recorded by X-4 Optimelt (Shanghai optical instrument factory). Optical rotation was determined by SGW-3 Digital Automatic Polarimeter (Shanghai INESA Physico Optical instrument Co., Ltd). The absolute configuration was determined by single-crystal X- ray. X-ray diffraction: Data sets were collected with Bruker APEX DUO and Bruker APEX-II CCD diffractometers. Programs used: data collection Bruker APEX2,[21a] data reduction Bruker SAINT, absorption correction for multi-scan, structure solution SHELX-97,[21b] structure refinement SHELXL-97,[21b] graphics Bruker SHELXTL.[21b]

General Procedures for the Asymmetric Fluorination of β-Ketoamides 13

To a flask charged with $Cu(OOCCF_3)_2{\cdot}H_2O$ (0.01 mmol, 2.9 mg) and (*R,R,R,R*)- **L1 f** (0.005 mmol, 4.3 mg) in solution (DCM/xylene = 2:1, 0.6 mL) was stirred at room temperature until the mixture turn from blue to brown. Then the β-ketoamide **13** (0.20 mmol in 0.4 mL DCM) was added, then 0.4 mL xylene was added and stirred 5 min at room temperature. After the reaction was cooled to −40 °C, NFSI (0.22 mmol, 69.3 mg) was added in a portion. Then the reaction was stirred for 12 h until completion (monitored by TLC, PE/AcOEt = 4:1). The solvent was removed under vacuum and the product **14** was isolated by flash chromatography (PE/AcOEt 5:1 to 4:1). The absolute configuration of compounds **14** was assigned to be (*S*) by analogy to the structure determined by single-crystal X-ray analysis performed on compound **14a** (see the X- ray analysis section). All the products are confirmed by GC-MS, NMR, and IR, and representative characterization data for **14** are listed in the Supporting Information (SI).

Acknowledgements

Support for this Project was by the National Natural Science Founder of China (No. 21173064, 51303043, and 21472031), and Zhejiang Provincial Natural Science Foundation of China (LR14B030001) is appreciated. XLW thank Dr. Zheng Xu for her help in the calculation of the HOMO–LUMO of the substrate. XLW also thank Prof. M. Kanai (The University of Tokyo), Prof. Y. Lu (The National University of Singapore), Prof. M. Shibasaki (The University of Tokyo and Institute of Microbial Chemistry, Tokyo), and Prof. C. G. Xia (Lanzhou Institute of Chemical Physics, CAS) for their help in the past years.

References

[1] a) J. A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119 and J. A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1; b) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708; c) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214.

[2] a) M. G. Campbell, T. Ritter, *Org. Process Res. Dev.* **2014**, *18*, 474; b) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305; c) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C. H. Wong, *Angew. Chem.* **2005**, *117*, 196; *Angew. Chem. Int. Ed.* **2005**, *44*, 192.

[3] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

[4] For selected reviews, see: a) M. Ueda, T. Kano, K. Maruoka, *Org. Biomol. Chem.* **2009**, *7*, 2005; b) C. Bobbio, V. Gouverneur, *Org. Biomol. Chem.* **2006**, *4*, 2065; c) N. Shibata, T. Ishimaru, S. Nakamura, T. Toru, *J. Fluor. Chem.* **2007**, *128*, 469; d) A. M. R. Smith, K. K. Hii, *Chem. Rev.* **2011**, *111*, 1637.

[5] a) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4350; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359; b) S. Piana, I. Devillers, A. Togni, U. Rothlisberger, *Angew. Chem.* **2002**, *114*, 1021; *Angew. Chem. Int. Ed.* **2002**, *41*, 979; c) L. Hintermann, M. Perseghini, A. Togni, *Beilstein J. Org. Chem.* **2011**, *7*, 1421; d) A. Bertogg, L. Hintermann, D. P. Huber, M. Perseghini, M. Sanna, A. Togni, *Helv. Chim Acta* **2012**, *95*, 353.

[6] For recent examples, see: a) S. Shirakawa, T. Tokuda, A. Kasai, K. Maruoka, *Org. Lett.* **2013**, *15*, 3350; b) J. Luo, W. Wu, L. W. Xu, Y. Meng, Y. Lu, *Tetrahedron Lett.* **2013**, *54*, 2623; c) V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681; d) F. Li, J. Nie, J. W. Wu, Y. Zheng, J. A. Ma, *J. Org. Chem.* **2012**, *77*, 2398; e) R. J. Phipps, K. Hiramatsu, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 8376; f) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2012**, *14*, 2726; g) J. Li, Y. Cai, W. Chen, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2012**, *77*, 9148; h) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738; i) X. Y. Yang, R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5225.

[7] For palladium and nickel catalysis, see: a) S. H. Kang, D. Y. Kim, *Adv. Synth. Catal.* **2010**, *352*, 2783; b) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164; c) H. R. Kim, D. Y. Kim, *Tetrahedron Lett.* **2005**, *46*, 3115; d) S. M. Kim, H. R. Kim, D. Y. Kim, *Org. Lett.* **2005**, *7*, 2309; e) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 3769; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; f) T. Suzuki, T. Goto, Y. Hamashima, M. Sodeoka, *J. Org. Chem.* **2007**, *72*, 246.

[8] a) J. A. Ma, D. Cahard, *Tetrahedron: Asymmetry* **2004**, *15*, 1007; b) A. Narayama, K. Shibatomi, Y. Soga, T. Muto, S. Iwasa, *Synlett* **2013**, *24*, 375; c) M. Frings, C. Bolm, *Eur. J. Org. Chem.* **2009**, 4085; d) K. Shibatomi, A. Narayama, Y. Soga, T. Muto, S. Iwasa, *Org. Lett.* **2013**, *13*, 2944; e) N. Shibata, T. Ishimaru, T. Nagai, J.

Kohno, T. Toru, *Synlett* **2004**, 1703; f) N. Shibata, H. Yasui, S. Nakamura, T. Toru, *Synlett* **2007**, 1153; g) K. Balaraman, R. Vasanthan, V. Kesavan, *Tetrahedron: Asymmetry* **2013**, *24*, 919.

[9] J. Peng, D. M. Du, *RSC Adv.* **2014**, *4*, 2061.

[10] The enantioselective construction of chiral molecules having a quaternary stereogenic center still represents a much more challenging area. For recent examples, see: a) K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa, S. Iwasa, *J. Am. Chem. Soc.* **2012**, *134*, 9836; b) J. A. Dabrowski, M. T. Villaume, A. H. Hoveyda, *Angew. Chem.* **2013**, *125*, 8314; *Angew. Chem. Int. Ed.* **2013**, *52*, 8156; c) R. Kastl, H. Wennemers, *Angew. Chem.* **2013**, *125*, 7369; *Angew. Chem. Int. Ed.* **2013**, *52*, 7228; d) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik, J. P. Das, *J. Am. Chem. Soc.* **2014**, *136*, 2682.

[11] a) F. Li, Z. J. Zheng, J. Y. Shang, K. Z. Jiang, G. Q. Lai, J. X. Jiang, L. W. Xu, *Chem. Asian J.* **2012**, *7*, 2008; b) F. Li, L. Li, W. Yang, L. S. Zheng, Z. J. Zheng, K. Jiang, Y. Lu, L. W. Xu, *Tetrahedron Lett.* **2013**, *54*, 1584.

[12] a) G. Gao, F. L. Gu, J. X. Jiang, K. Jiang, C. Q. Sheng, G. Q. Lai, L. W. Xu, *Chem. Eur. J.* **2011**, *17*, 2698; b) L. S. Zheng, S. Tao, L. W. Xu, *Chin. J. Org. Chem.* **2014**, *34*, 1255.

[13] L. S. Zheng, K. Z. Jiang, Y. Deng, X. F. Bai, G. Gao, F. L. Gu, L. W. Xu, *Eur. J. Org. Chem.* **2013**, 748.

[14] H. Sasaki, R. Irie, T. Hamada, K. Suzuki, T. Tsutomu, *Tetrahedron* **1994**, *50*, 11827.

[15] For recent examples, see: a) S. Koya, Y. Nishioka, H. Mizoguchi, T. Ychida, T. Katsuki, *Angew. Chem.* **2012**, *124*, 8368; *Angew. Chem. Int. Ed.* **2012**, *51*, 8243; b) T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017; c) Y. Nishioka, T. Uchida, T. Katsuki, *Angew. Chem.* **2013**, *125*, 1783; *Angew. Chem. Int. Ed.* **2013**, *52*, 1739.

[16] List and coworkers have ever found that a SPINOL-derived chiral phosphoric acid with potential π-π stacking interaction enable long-range control to induce enantioselectivity on the nanoscale or macromolecular size: L. Kötzner, M. J. Webber, A. Martínez, C. D. Fusco, B. List, *Angew. Chem.* **2014**, *126*, 5303; *Angew. Chem. Int. Ed.* **2014**, *53*, 5202.

[17] The crystal structure of **14a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 1002368). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data request/cif.

[18] During the preparation of this manuscript, Che and coworkers reported the Iron(III)-salan complexes-catalyzed fluorination of β-ketoesters (46–97% *ee*) that has been widely investigated in the past decade and also found that the structures of β-ketoesters were crucial to the enantioselective fluorination: X. Gu, Y. Zhang, Z. J. Xu, C. M. Che, *Chem. Commun.* **2014**, *50*, 7870.

[19] The noncovalent interaction of aromatic rings with functional groups can control and influence the stereoselectivity in many reactions, including asymmetric dihydroxylations, hetero-Dields-Alder reactions, transfer hydrogenations, acyl transfers, and Claisen rearrangements. For selected review, see: a) E. H. Krenske, K. N. Houk, *Acc. Chem. Res.* **2013**, *46*, 979; For recent examples, see: b) V. B. Birman, E. W. Uffman, H. Jiang, X. Li, C. J. Kilbane, J. *Am. Chem. Soc.* **2004**, *126*, 12226; c) D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2004**, *116*, 6916; *Angew. Chem. Int. Ed.* **2004**, *43*, 6748–6751; d) S. Hiraoka, K. Harano, M. Shiro, M. Shionoya, *Angew. Chem.* **2005**, *117*, 2787; *Angew. Chem. Int. Ed.* **2005**, *44*, 2727; e) R. J. Hooley, S. M. Biros, J. R. Rebek, *Angew. Chem.* **2006**, *118*, 3597; *Angew. Chem. Int. Ed.* **2006**, *45*, 3517; f) H. Nakajima, M. Yasuda, R. Takeda, A. Baba, *Angew. Chem.* **2012**, *124*, 3933; *Angew. Chem. Int. Ed.* **2012**, *51*, 3867.

[20] a) C. D. Fusco, S. Meninno, C. Tedescoa, A. Lattanzi, *Org. Biomol. Chem.* **2013**, *11*, 896; b) T. A. Moss, A. Alba, D. Hepworth, D. J. Dixon, *Chem. Commun.* **2008**, 2474; c) A. Russo, G. Galdi, G. Croce, A. Lattanzi, *Chem. Eur. J.* **2012**, *18*, 6152.

[21] a) *Bruker, APEX and SAINT. Bruker AXS inc.,* Madison, Wisconsin, USA; b) G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.