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Enantio- and Site-selective α-Fluorination of *N*-Acyl-3,5-dimethylpyrazoles Catalyzed by Chiral π–Cu(II) Complexes

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Dedication ((optional))

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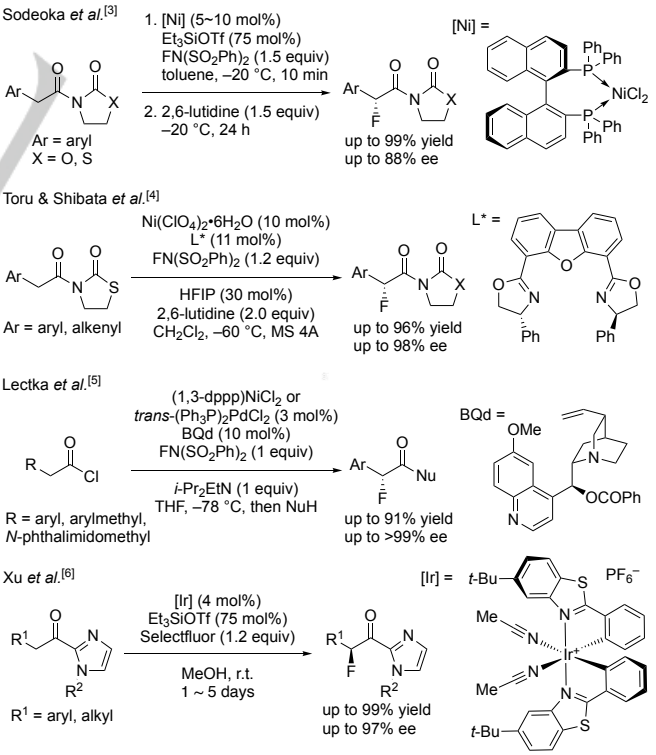
Abstract: Catalytic enantioselective α-fluorination reactions of carbonyl compounds are among the most powerful and efficient synthetic methods for constructing optically active α-fluorinated carbonyl compounds. Nevertheless, α-fluorination of α-nonbranched carboxylic acid derivatives is still a big challenge because of relatively high pK_a values of their α-hydrogen atoms and difficulty of subsequent synthetic transformation without epimerization. Here we show that chiral Cu(II)–3-(2-naphthyl)-L-alanine-derived amide complexes are highly effective catalysts for the enantio- and site-selective α-fluorination of *N*-(α-arylacetyl)- and *N*-(α-alkylacetyl)-3,5-dimethylpyrazoles. The substrate scope has been widely broadened (25 examples including quaternary α-fluorinated α-amino acid derivative). α-Fluorinated products are converted to the corresponding esters, secondary amides, tertiary amides, ketones, and alcohols with almost no epimerization in quantitative yield.

Introduction

Optically active α-fluorinated carbonyl compounds have received increased attention due to their widespread biological and therapeutic properties.[1] Enantioselective α-fluorination reactions of carbonyl compounds are among the most powerful and efficient synthetic methods for constructing optically active target molecules, and great effort has been devoted to the development of their catalytic versions.[8–12] The carbonyl substrates for these are limited to aldehydes, ketones, 1,3-dicarbonyl compounds, and 3-substituted oxindoles that have relatively low pK_a values associated with the α-hydrogen atoms.[2]

In contrast, α-fluorination of α-nonbranched carboxylic acid derivatives is still a big challenge because of relatively high pK_a values of their α-hydrogen atoms and difficulty of a synthetic transformation of α-fluorinated products without epimerization. To the best of our knowledge, only a few successful examples of catalytic enantioselective α-fluorination of carboxylic acid derivatives have been reported (Scheme 1).[3–6] In 2007, Sodeoka *et al.* developed the nickel(II)-catalyzed enantioselective fluorination of *N*-arylacetylthiaoxazolidin-2-ones.[3] In this pioneering work, the substrates are limited to arylacetyl derivatives. In 2008 and 2009, Toru and Shibata *et al.* also reported a similar nickel(II)-catalyzed reaction.[4] In 2008, Lectka *et al.* reported nickel(II) or palladium(II) and chiral Lewis base-cocatalyzed enantioselective α-fluorination of highly reactive acid chlorides.[5] In 2016, Xu *et al.* reported the iridium(III)-catalyzed enantioselective α-fluorination of 2-acylimidazoles.[6] Although the substrate scope is broadened to include aliphatic acyl derivatives, the reaction is very slow (reaction time: 1~5 days), and the removability of the imidazole moiety without epimerization has not been ascertained.[6] In view of these limitations, there has been a need for the development of a more efficient and practical asymmetric catalytic system. Very recently, Maulide *et al.* developed chemoselective fluorination to enolonium species generated from tertiary amides with nucleophilic fluorinating agents, but its asymmetric version has not been developed.[7]



Scheme 1. Previous examples of catalytic enantioselective α-fluorination of carboxylic acid derivatives.

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Our attention is focused on the use of π–Cu(II) complexes of CuX_2 with 3-aryl-L-alanine-derived amides as asymmetric catalysts. Since 2006, we have reported several π–Cu(II) complex-catalyzed enantioselective nucleophilic addition reactions to α,β-unsaturated *N*-acylpyrazoles, which are appropriate as electrophiles because of the relatively low pK_a values of *N*-acylpyrazoles[8,9] due to the electron-deficiency of the pyrazole moiety.[10–16] In addition, several groups have reported that *N*-acylpyrazoles are useful as amide pronucleophiles for the same reason.[17–20] Against this background, here we describe the development of a highly efficient enantioselective α-fluorination of *N*-acyl-3,5-dimethylpyrazoles catalyzed by chiral π–Cu(II) complexes.

Results and Discussion

Initially, to clarify the acidity of *N*-acylpyrazoles, we estimated the pK_a value of *N*-acetyl-3,5-dimethylpyrazole (**1a**) based on its molecular electrostatic potential (MEP), because a linear relationship between MEP and pK_a values had been established (Figure 1).[21] The resonance and inductive effects from the pyrazole moiety to the *N*-acetyl moiety should be influenced by the difference in the rotational conformation of the amidyl C–N bond. Although the most stable conformer of **1a** is pseudo-*E*

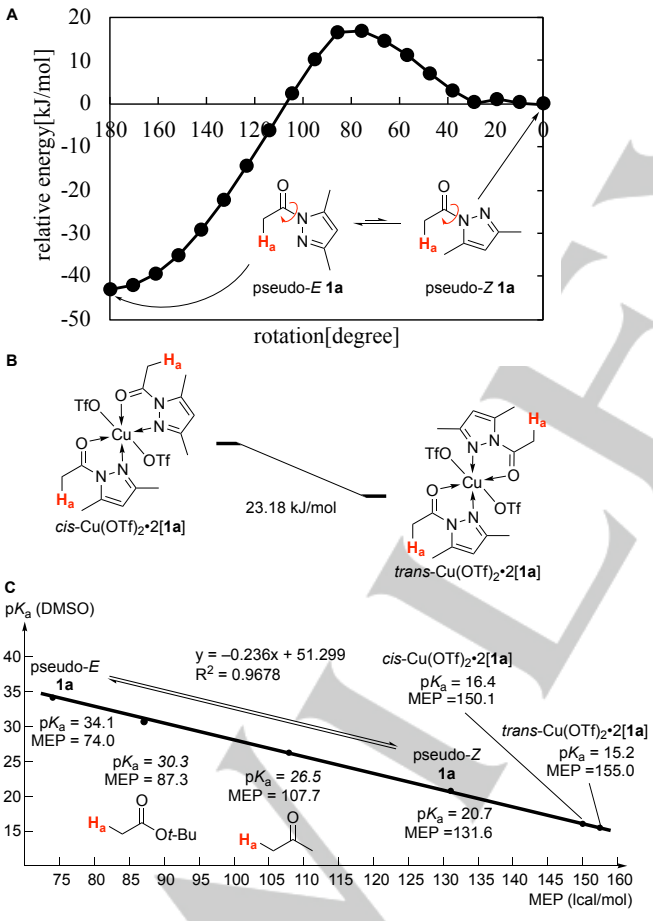
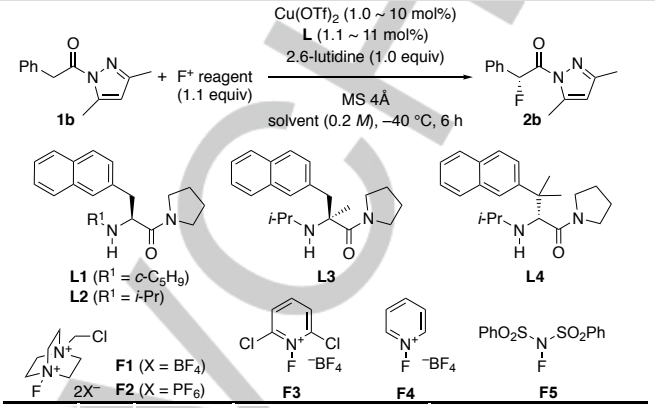


Figure 1. The pK_a values of **1a** and $Cu(OTf)_2$•2[**1a**] Complexes.[21] (**A**) Relationship between relative energy and dihedral angle (N–N–C=O) of **1a**. Plotted dihedral angle (°) = 0.00, 9.47, 18.95, 28.42, 37.89, 47.37, 56.84, 66.32, 75.79, 85.26, 94.74, 104.21, 113.68, 123.16, 132.63, 142.11, 151.58, 161.05, 170.53, 180.00. (**B**) The thermal stability of $Cu(OTf)_2$•2[**1a**]. (**C**) The linear relationship between pK_a (DMSO) and MEP values. Calculated pK_a values: plain numbers. Measured pK_a values: Italic numbers. The equation (y = –0.236x + 51.299) was calculated based on the pK_a of known compounds and MEP values of these compounds calculated by us.

Table 1: Optimization for the enantioselective α-fluorination of **1b**[a]



Entry	L	F⁺ reagent	Solvent	2b	
				Yield [%]	Ee [%]
1[b]	**L1**	**F1**	MeCN	96	88
2[c]	**L1**	**F1**	MeCN	24[d]	87
3	**L1**	**F1**	EtCN	24	78
4	**L1**	**F1**	Acetone	87	85
5	**L1**	**F1**	THF	14	–
6	**L1**	**F2**	MeCN	85	90
7	**L1**	**F3**, **F4**	MeCN	0	–
8	**L1**	**F5**	MeCN	68	89
9	**L2**	**F1**	MeCN	91	89
10	**L2**	**F1**	PhCl[e]	<5[d]	–
11	**L2**	**F1**	PhCl[e]/MeCN (1:2)	60	79
12	**L2**	**F1**	PhMe[e]/MeCN (1:2)	42	80
13	**L2**	**F2**	MeCN	99 (98)[f]	91 (89)[f]
14[g]	**L2**	**F2**	MeCN	97	91
15[h]	**L2**	**F2**	MeCN	38[i]	81
16	**L3**	**F2**	MeCN	>99	94
17[j]	**L4**	**F2**	MeCN	93	–96

[a] Unless otherwise noted, **1b** (0.3 mmol), F⁺ reagent (1.1 equiv), $Cu(OTf)_2$ (10 mol%), **L** (11 mol%), 2,6-lutidine (1.0 equiv), and MS 4Å (powder, 100 mg) were added in solvent (1.5 mL). [b] When $Cu(NTf_2)_2$ was used, the same results were obtained (96% yield, 88% ee). [c] Without 2,6-lutidine. [d] Any products except for **2b** were not observed. [e] **F1** did not dissolve in less polar solvents like chlorobenznene and toluene. [f] The results when the reaction was quenched after 1 h. [g] **1b** (6.0 mmol) was used in the presence of $Cu(OTf)_2$ (1.0 mol%), **L2** (1.1 mol%), and MS 4Å (powder, 1.5 g). [h] **1b'** was used in place of **1b**. Yield and ee of **2b'** are shown. [i] **1b** was not recovered. [j] $Cu(OTf)_2$ (5 mol%) and **L4** (5.5 mol%) were used.

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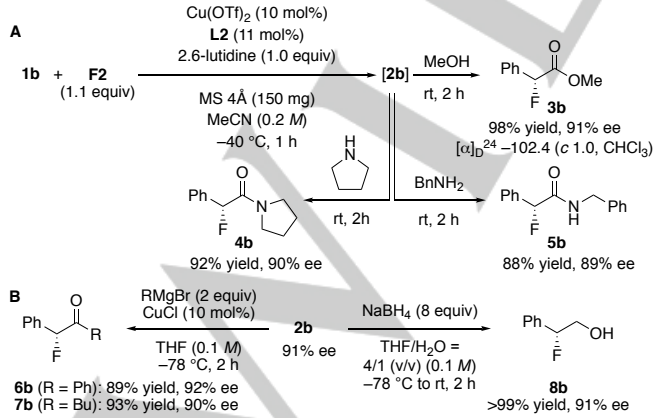
according to our theoretical calculation (Figure 1A), the chelation of $Cu(OTf)_2$ to **1a** fixes the rotational conformation to pseudo-*Z* (Figure 1B): *trans*-$Cu(OTf)_2$•2[**1a**] is 23.18 kJ/mol more stable than *cis*-$Cu(OTf)_2$•2[**1a**]. Thus, we realized that this chelation was highly significant for increasing the acidity of H_a: pK_a of *cis*-$Cu(OTf)_2$)•2[**1a**] = 15.2; pK_a of *trans*-$Cu(OTf)_2$•2[**1a**] = 16.4 (Figure 1C). This is one of the reasons why *N*-acetylpyrazole is more reactive than other esters and amides.

Next, we examined the enantioselective fluorination of **1b** in the presence of 10 mol% of $Cu(OTf)_2$•3-aryl-L-alanine-derived amide **L** under various conditions (Table 1). As expected, fluorinated product **2b** was obtained in 96% yield with 88% ee using Selectfluor **F1** in the presence of 10 mol% of $Cu(OTf)_2$•3-(2-naphthyl)-L-alanine-derived *N*-cyclopentylamide **L1**[13] and 2,6-lutidine in acetonitrile at –40 °C for 6 h (entry 1). The addition of 1 equivalent of 2,6-lutidine was required to neutralize *in situ*-generated HX (entry 1 versus entry 2). Although $Cu(NTf_2)_2$ was also examined in place of $Cu(OTf)_2$, no difference was observed probably because of anion-exchange with BF_4^- of **F1** (footnote b, entry 1). Acetonitrile gave the best results as a solvent (entry 1 versus entries 3~5; entry 9 versus entries 10~12). Selectfluor analogue **F2** gave slightly higher enantioselectivity than **F1** (entry 1 versus entry 6). Although **F5** was also usable (entry 8), other fluorinating reagents **F3** and **F4** were inert (entry 7). *N*-Isopropylamide **L2** as well as **L1** were also effective as chiral ligands (entry 9). Thus, **2a** was obtained in 99% yield with 91% ee (entry 13). Surprisingly, this reaction completed within 1 h (footnote d). $Cu(OTf)_2$ and **L2** could be reduced to 1.0 mol% and 1.1 mol%, respectively, at a 20-times scale (6.0 mmol) of **1b** (entry 14). When *N*-(phenylacetyl)pyrazole (**1b'**) was used in place of **1b**, fluorinated product **2b'** was obtained in 38% yield with 81% ee because of the instability of amide bond of **1b'** and **2b'** (entry 15). When α-methyl analogue **L3** was used in place of **L2**, **2b** was obtained in quantitative yield with 94% ee (entry 16). Furthermore, when 3,3-dimethyl analogue **L4** (5.5 mol%) was used, the enantioselectivity was increased to 96% ee (entry 17). Methyl substituents of **L3** and **L4** may sterically stabilize transition-state assemblies folded by π–Cu(II)-interaction due to the Ingold-Thorpe effect.[22–25]

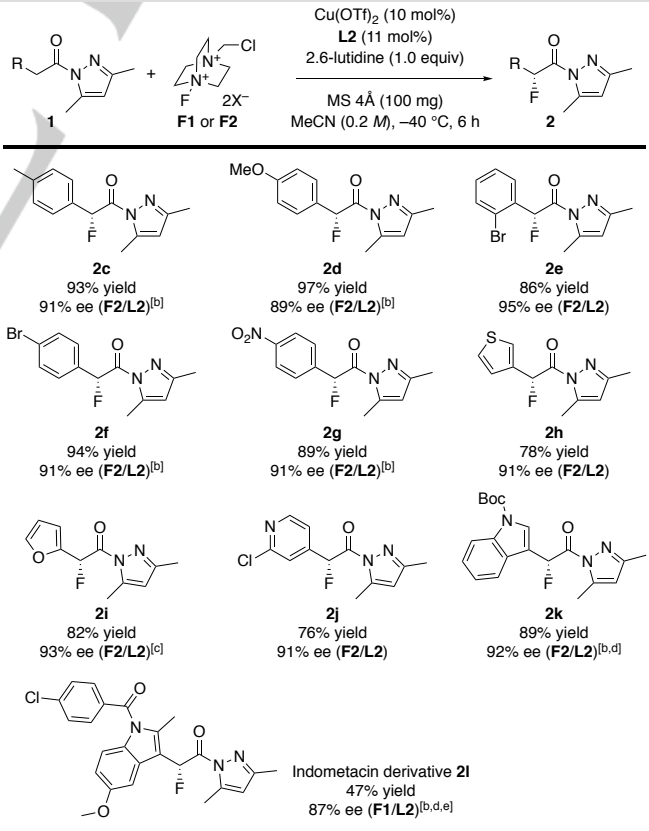
The absolute configuration of **2b** (entry 13, Table 1) was determined by comparison of the optical rotation with that of known methyl ester **3b**,[26] suggesting an *R* configuration (Scheme 2A). The transformation from **1b** to **3b** could be carried out by a one-pot procedure (Scheme 2A). In a similar manner, the corresponding tertiary amide **4b** and secondary amide **5b** were obtained with almost no epimerization.[27] Furthermore, transformations from **2b** to ketones **6b** and **7b** and alcohol **8b** also proceeded in good yield without epimerization (Scheme 2B).[11,19,27]

With the optimized reaction conditions in hand, we decided to explore the utility and applicability of our strategy by using differently substituted carboxamides **1** in the reaction with catalyst $Cu(OTf)_2$•**L2** (Tables 2–4). A variety of electron-withdrawing and electron-donating substituents were tolerated, independently of their position in the aromatic rings of α-aryl- and α-heteroarylacetamides **1c**–**1l** (Table 2). Interestingly, site- and enantioselective α-fluorination of β,γ-unsaturated carboxamides **1m** and **1n** proceeded in reasonable yield with good enantioselectivity, and no γ-fluorinated products were observed (Table 3). The ee values of **2m** and **2n** were increased to 93 and 94 % by the use of **L4** (5 mol%). Saturated or γ,δ-unsaturated carboxamides like **1o**–**1t** were also applicable as substrates, and highly enantioselective fluorination occurred at –20 °C or –40 °C in good yield (Table 3). The enantioselectivitity was also increased by the use of **L3** (**1q**–**1s**). Lewis basic *N*-Boc, thioacetyl and acetyl substituents of **1** were tolerated (**1k** in Table 2, **1q** in Table 3, **1u** and **1v** in Table 4). The site- and enantioselective α-fluorination of **1u**, **1v** and **1w**



Scheme 2. Transformation of α-fluorinated carboxamide **2b** (**A**) One-pot reaction from carboxamide **1b** to α-fluorinated carboxylic ester **3b** and amides **4b** and **5b**. (**B**) Synthetic transformations from α-fluorinated carboxamide **2b** to α-fluoroalkanones **6b** and **7b** and α-fluoroalkanol **8b**.

Table 2: The enantioselective α-fluorination of α-aryl- and α-heteroarylacetamides [a]



[a] Unless otherwise noted, the reaction was carried out under the same conditions as for entry 13 in Table 1. [b] Solvent (0.1 *M* for **1**) was used. [c] Shortened to 1 h. [d] Acetone was used. [e] Shortened to 3 h.

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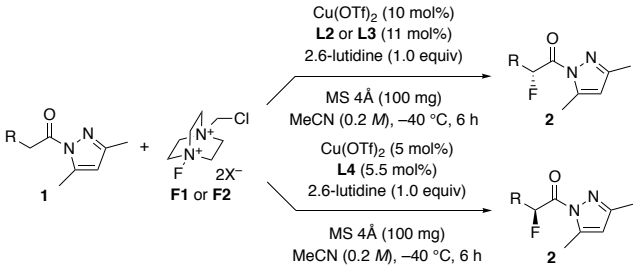
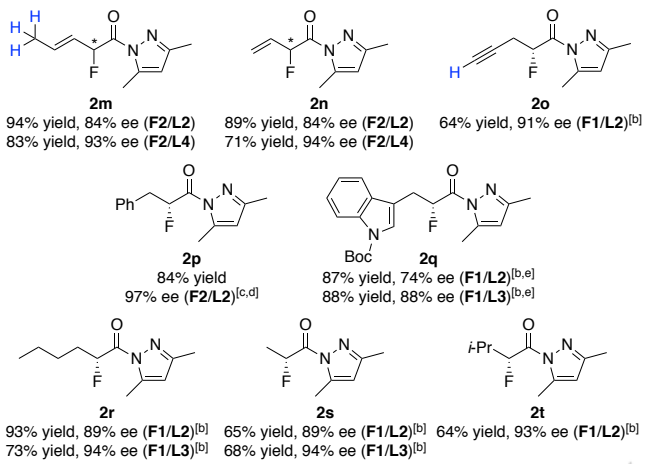
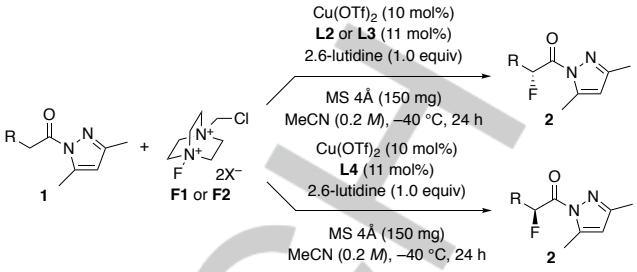
Table 3: The site- and enantioselective α-fluorination of β,γ- or γ,δ-unsaturated carboxamides and saturated carboxamides[a]

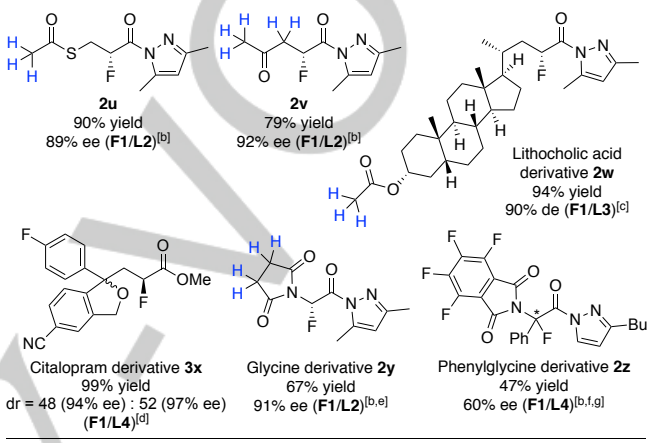




[a] Unless otherwise noted, the reaction was carried out under the same conditions as for entry 13 in Table 1. [b] 150 mg of MS 4Å (powder) was used. Changed to –20 °C. Extended to 24 h. [c] Solvent (0.1 *M* for **1**) was used. [d] Extended to 24 h. [e] Acetone was used.

Table 4: The site- and enantioselective α-fluorination of functionalized carboxamides[a]



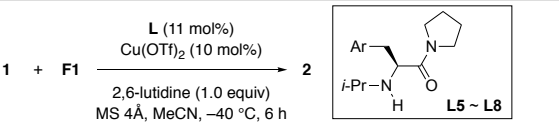


[a] Unless otherwise noted, the reaction was carried out under the same conditions as for entry 13 in Table 1. 150 mg of MS 4Å (powder) was used. Extended to 24 h. [b] Changed to –20 °C. [c] Changed to –20 °C, and then elevated to 0 °C. [d] **3x** was produced through one-pot procedure of enantioselective fluorination of **1x** and subsequent transeterification of **2x** (see Scheme 1A). [e] Solvent (0.3 *M* for 1) was used. [f] Acetone was used. [g] Racemic 2-(2-(3-butyl-1*H*-pyrazol-1-yl)-2-oxo-1-phenylethyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione **1z** was used in place of **1**.

proceeded without α-fluorination of their acetyl moieties (Table 4). In addition, dried molecular sieves 4Å (powder) were effective for maintaining the catalytic activity, in particular, in the reaction of substrates with relatively low reactivities (**1o** and **1q**–**1t** in Table 3, **1u**–**1z** in Table 4). It is noteworthy that α-fluorination of biologically important substrates such as indometacin, lithocholic acid, citalopram,[7] and glycine derivative proceeded with high enantioselectivity (**1l** in Table 2, **1w**–**1y** in Table 4). This method was applicable for enantioselective synthesis of quaternary α-fluorinated α-amino acid derivative **2z**, which is the first example of asymmetric catalysis to the best of our knowledge (Table 4).[28,29]

Finally, we turn our attention to mechanistic aspects. To ascertain the π–Cu(II) interaction of $Cu(OTf)_2$•**L2**, several aryl- and cyclohexyl-L-alanine amides **L5**–**L8** were examined for the enantioselective α-fluorination of **1b** and **1p** under the same conditions using **L2** (Table 5). The use of **L6** gave **2b** in 91% yield with 55% ee while the use of **L5** gave **2b** in 43% yield with 30% ee. These results could be explained by assuming a folded cationic intermediate [**L6**•$Cu^+(OTf)$•**1b**][$^-$OTf] and an extended neutral intermediate [**L5**•$Cu(OTf)_2$•**1b**], respectively. The π–Cu(II) interaction between 3-phenyl moiety of **L6** and Cu(II) prefers the formation of a more active folded cationic intermediate [**L6**•$Cu(II)^+(OTf)$•**1b**][$^-$OTf], which promotes enolization and induces high enantioselectivity on α-fluorination. In contrast, a nonpreferred extended complex [**L6**•$Cu(OTf)_2$•**1b**] is a resting state. In a similar way, although **L2**•$Cu(OTf)_2$ was quite effective

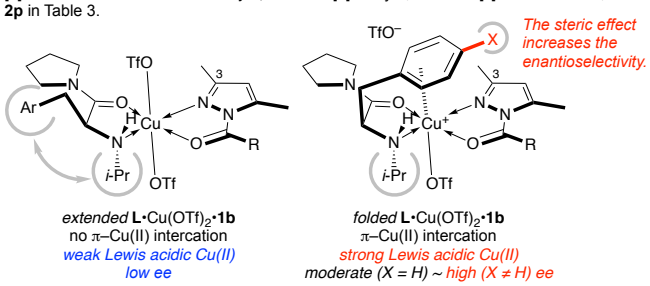
Table 5: Ligand effect on the enantioselectivity and reactivity



L: yield and ee of **2b**[a]	L•$Cu(OTf)_2$•**1b** *preferred conformation (extended/folded)*
L5 (Ar = *c*-C_6H_{11}): 42% yield, 30% ee	extended
L6 (Ar = Ph): 91% yield, 55% ee	
L7 (Ar =4-CF_3-C_6H_4): 72% yield, 65% ee	
L8 (Ar = 4-MeO-C_6H_4): 95% yield, 69% ee	
cf. **L2** (Ar = 2-naphthtyl):[b] 91% yield, 89% ee	folded

L: yield and ee of **2p**[c]	L•$Cu(OTf)_2$•**1p** *preferred conformation (extended/folded)*
L5 (Ar = *c*-C_6H_{11}): <5% yield, –	extended
cf. **L2** (Ar = 2-naphthtyl): 84% yield, 97% ee	folded

[a] The same conditions with entry 9, Table 1. [b] Entry 9, Table 1. [c] For conditions, see: **2p** in Table 3.



for the enantioselective α-fluorination of **1p**, **L5**•Cu(OTf)$_2$ was almost inert. The use of π-electron poor **L7** decreased the reactivity (to 72% yield) but the enantioselectivity was still 65% ee. This lower reactivity could be explained by relatively weak π–Cu(II) interaction. The steric effect of *p*-trifluoromethyl group of **L7** might contribute to increase the enantioselectivity. In contrast, the use of π-electron rich **L8** increased the reactivity (95% yield) and the enantioselectivity (69% ee). These results could be explained by stabilization of π–Cu(II) interaction and steric effect by *p*-methoxy group of **L8**. Ultimately, the use of **L2** increased the reactivity (91% yield) and the enantioselectivity (89% ee) by a synergistic effect of the π–Cu(II) interaction and steric effect of the 2-naphthyl group of **L2**.

The reactivity and the enantioselectivity in the α-fluorination catalyzed by **L2**•Cu(OTf)$_2$ were somewhat decreased in mixed solvents of acetonitrile and aromatic solvents like chlorobenzene and toluene (entry 9 versus entries 10~12 in Table 1). These results also suggest the existence of the π–Cu(II) interaction.

Furthermore, we succeeded in X-ray single-crystal diffraction analysis of the single-crystal structure of **L2**•Cu(OTf)$_2$•**1a** as shown in Figure 2. The distance between C(33) of the 2- naphthyl moiety of **L2** and Cu(II) was 3.131Å.[30–33] This result shows the π–cation interaction in the solid state of this complex. The pseudo-trans chelation of **1a** was preferred to avoid steric hindrance between the *N*-isopropyl group of **L2** and the 3-methyl group of **1a**. These results suggest that not only π–Cu(II) interaction but also the steric hindrance of *N*-isopropyl, pyrrolidinyl, 2-methyl, and 3-methyl groups for the 2-naphthylmethyl group of might be contributed to stabilizing its conformational folding.

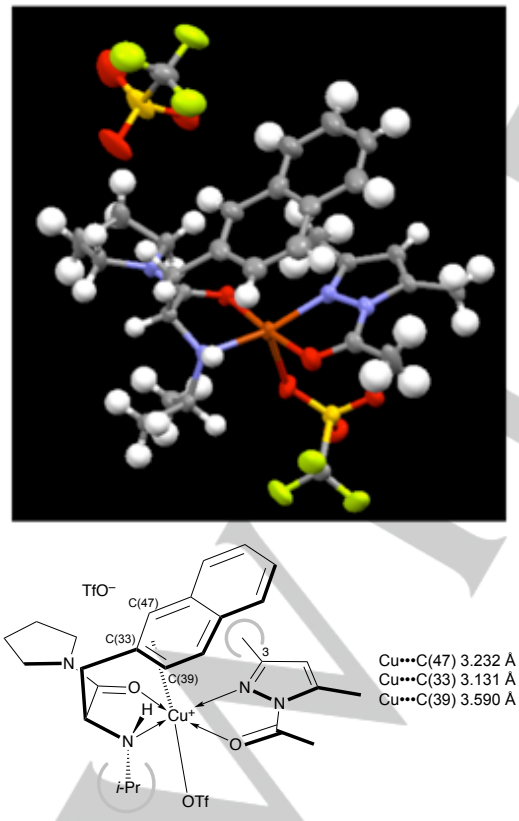


Figure 2. X-ray single-crystal diffraction analysis of a 1:1:1 complex of **L2**•Cu(OTf)$_2$•**1a**.

In 2008, Takeuchi *et al.* reported the first UV spectral evidence for the π–cation interaction between the indolyl group of Tryptophan in peptides and Cu^{2+}.[30] Based on Takeuchi's method,[30] the UV absorption difference spectrum between "a 1:1:1 complex of *N*-isopropyl-L-tryptophan pyrrolidine amide **L9**•Cu(OTf)$_2$•**1a**" and "**L9** and Cu(OTf)$_2$•**1a**" in acetonitrile also exhibited a negative band at 226 nm and a weak positive band at 240 nm attributable to an indolyl π–Cu(II) interaction (Figure 3). The enantioselective α-fluorination of **1b** using **L9** under the same conditions as for entry 13 in Table 1 gave **2b** with 58% ee in 70% yield. These results suggest the possibility of π–Cu(II) interaction of catalysts in an acetonitrile solution.

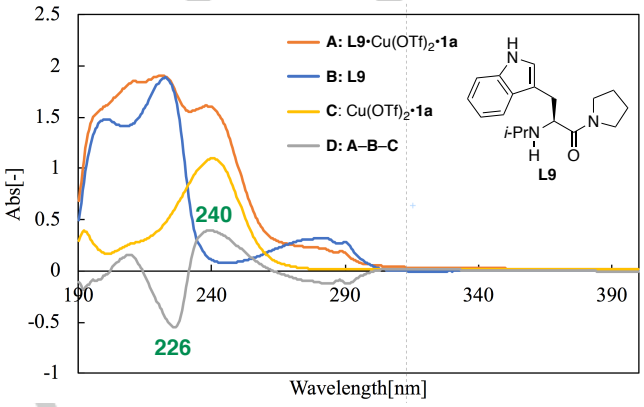


Figure 3. UV Absorption spectra of **L9**, **1a**, and a 1:1:1 complex of **L9**•Cu(OTf)$_2$•**1a**.

In addition, the difference of ESR spectra of **L2**•Cu(OTf)$_2$•**1a** and **L5**•Cu(OTf)$_2$•**1a** complexes mainly comes from the difference in the number of coordinated $^{-}$OTf group (Figure 4). When doubly coordinated $^{-}$OTf groups reduced to single, distribution of unpaired electron on Cu(II) *d*-orbital should be changed with the changes of *g* tensors and hyperfine coupling constants of Cu(II).

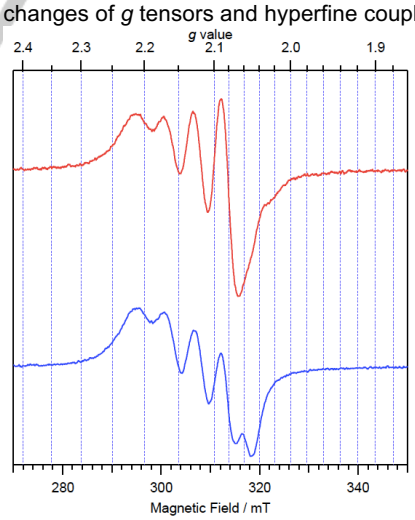
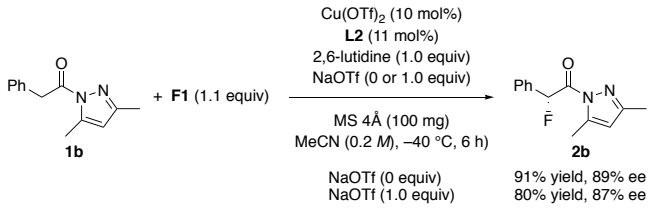


Figure 4. ESR spectra of **L2**•Cu(OTf)$_2$•**1a** (red) and **L5**•Cu(OTf)$_2$•**1a** (blue) at room temperature. The ESR sample tubes were set to an *X*-band ESR spectrometer (JEOL JES-RE1X). ESR parameters for the measurements at room temperature were microwave power of 1 mW, field modulation width of 0.1 mT at 100 kHz, the static magnetic field of 310 ± 40 mT. Microwave frequency and magnetic field of the spectrometer were monitored using a microwave frequency counter (Hewlett-Packard, 53150A) and an NMR field meter (Echo Electronics Co. Ltd., EFM-2000AX), respectively.

Although there is no definite evidences of a very small electron donation from the naphthalene to Cu(II) *d*-orbital, the small donation may induce the distribution change of the unpaired electron in the Cu(II) *d*-orbital. These results may also suggest the possibility of the ligand exchange between a triflate anion and the 2-naphthyl moiety of **L2** at the apical position of **L2**•$Cu(OTf)_2$•**1a** in a solution state.[34]

The enantioselectivity was not influenced by the presence of excess NaOTf (Scheme 3). This result suggests that the π–Cu(II) interaction was stable even in the presence of NaOTf. The bent conformation of **L2** might be stabilized by the π–Cu(II) electronic interaction and the steric effect of **L2**. The Lewis acidity of Cu(II) decreases due to strong π–Cu(II) electronic interaction but increases due to the release of its counter anion ($^-$OTf). Therefore, appropriate π–Cu(II) electronic interaction and the steric effect is important to appear Lewis acidity of Cu(II).



Scheme 3. The influence of sodium triflate on the enantioselective α-fluorination of **1b**

Based on these evidences of the π–Cu(II) interaction, the proposed (*Z*)-enol-type transition state assembly is shown in Figure 5. The 2-naphthalene ring of **L2** may effectively shield the *re*-face of the (*Z*)-enol form of **1b** through π–Cu(II) interaction. Thus, F^+ reagent can approach the *si*-face of the (*Z*)-enol form of **1b** to give (*R*)-**2b**. In contrast, an (*E*)-enol-type transition state is disfavored due to the steric hindrance between the 5-methyl group and phenyl group. In this α-fluorination, HX was produced together with (*R*)-**2b**, and was neutralized with 2,6-lutidine.

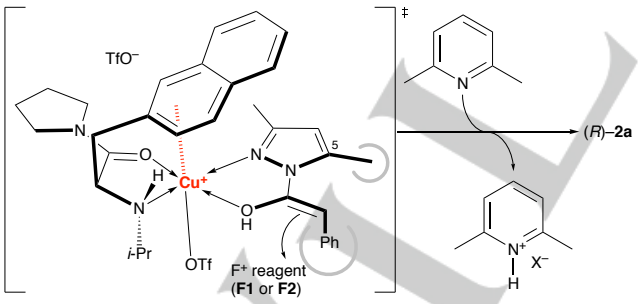


Figure 5. Proposed transition-state assembly.

Conclusion

In summary, we have developed a highly enantio-, and site-selective α-fluorination of *N*-acyl-3,5-dimethylpyrazoles catalyzed by chiral π–Cu(II) catalysts. This new catalytic method is highly useful even compared to those described in previous reports:[10–16] (1) new chiral ligands **L3** and **L4** have been developed, (2) the pseudo-*Z* conformation of *N*-acylpyrazoles increases the acidity of α-hydrogen atoms, (3) the substrate scope has been widely broadened, (4) the catalyst loading is reduced to 1.0~10 mol%, (5) the reaction is fast (1~24 h) and scalable (0.3~6.0 mmol), and (6) α-fluorinated products are converted to the corresponding esters, secondary amides, tertiary amides, ketones, and alcohols with almost no epimerization. In addition, the π–Cu(II) interaction between 3-aryl-L-alanine amide and CuX_2 has been clarified by X-ray single-crystal analysis, the UV absorption difference spectral analysis, and ESR analysis.[10–16,30–33] The further application of these catalysts in other asymmetric reactions is underway. Acknowledgements

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Keywords: π–cation • enantioselective • asymmetric catalysis • α-fluorination • pyrazole

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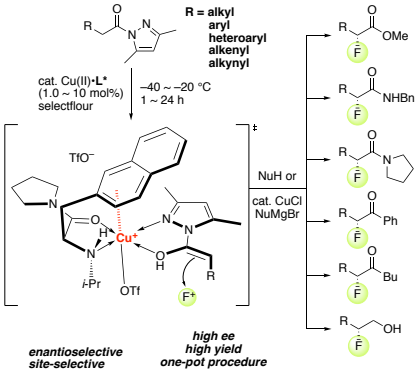

Chiral π–Cu(II) complex-catalyzed enantio-, and site-selective α-fluorination of *N*-acyl-3,5-dimethylpyrazoles has been achieved based on our finding that the pseudo-*Z* conformation of *N*-acylpyrazoles increases the acidity of their α-hydrogen atoms: (1) the substrate scope is wide (25 examples), (2) the reaction is fast and scalable, and (3) α-fluorinated products are converted to the esters, amides, ketones and alcohols without epimerization.

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