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Enantioselective Tsuji-Trost α-Fluoroallylation of Amino Acid Esters with *gem*-Difluorinated Cyclopropanes

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In memory of Professor Qing-Yun Chen

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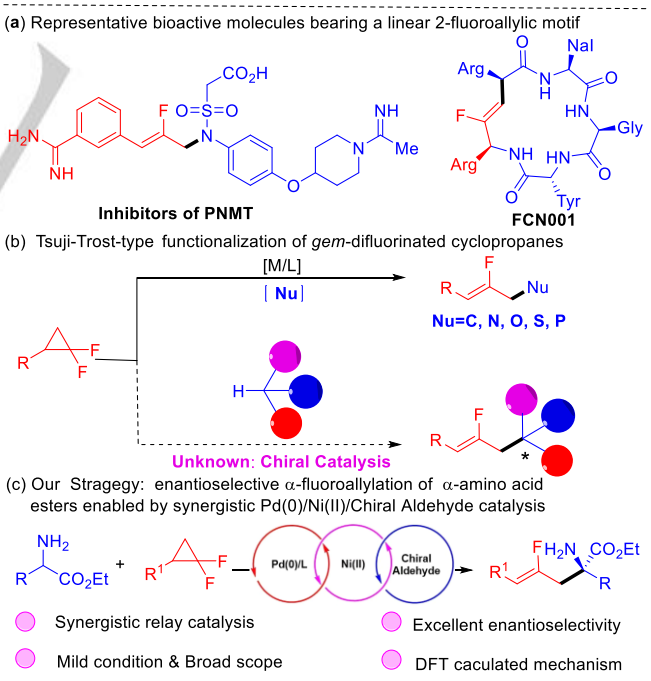
Abstract: A novel enantioselective Tsuji-Trost-type cross coupling reaction between *gem*-difluorinated cyclopropanes and *N*-unprotected amino acid esters enabled by synergistic Pd/Ni/chiral aldehyde catalysis is presented herein. This transformation streamlined the diversity-oriented synthesis (DOS) of optically active α-quaternary α-amino acid esters bearing a linear 2-fluoroallylic motif, which served as an appealing platform for the construction of other valuable enantioenriched compounds. The key intermediates were confirmed by HRMS detection, while DFT calculations revealed that the excellent enantioselectivity was attributed to the stabilizing non-covalent interactions between the Pd(II)-π-fluoroallyl species and the Ni(II)-Schiff base complex.

Enantioselective fluoroallylation is of great interest given that fluoroallylic scaffolds could work as competent enzyme inhibitors, amide bond isosteres or mimics of enols and are privileged structural units in many different bioactive molecules (**Scheme 1a**).[1] *gem*-Difluorinated cyclopropanes (*gem*-F_2CPs) which possess unique reactivity are specifically important fluorinated allyl surrogates in cross-coupling reactions.[2] Indeed, Fu group pioneeringly reported the first Pd-catalyzed ring-opening functionalization of *gem*-difluorinated cyclopropanes by employing various nucleophiles (e.g., N and O), sparking the intensive research interest in developing novel transformations in this field (**Scheme 1b**).[3] And recently, significant progress has been achieved in the alkylation of *gem*-F_2CPs.[4] Li group elegantly developed the Pd/NHC-catalyzed the ring-opening alkylation of *gem*-F_2CPs with simple hydrazones,[5] generating the



Scheme 1. Enantioselective ring-opening functionalization of *gem*-difluorinated cyclopropanes: The state of the art and our reaction design.

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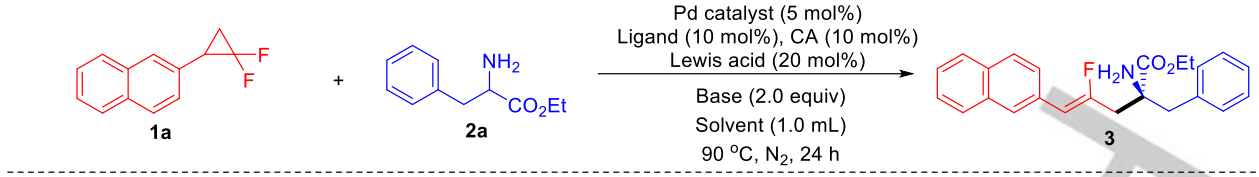
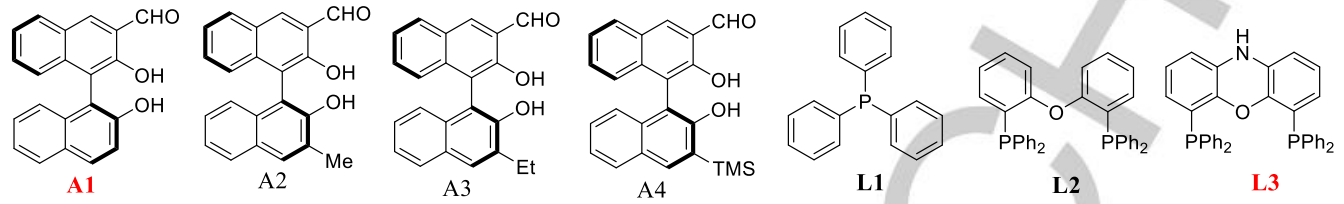
Table 1: Optimization of reaction conditions[a]





Entry	CA	Pd source	Ligand	Solvent	LA	Base	Yield[b]	Ee[c]
1	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhMe	$ZnCl_2$	Et_3N	0%	/
2	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhMe	$CuCl_2$	Et_3N	0%	/
3	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhMe	$CoBr_2$	Et_3N	31%	67%
4	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhMe	$NiBr_2$	Et_3N	19%	79%
5	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhMe	$NiCl_2$	Et_3N	42%	80%
6	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	$PhCF_3$	$NiCl_2$	Et_3N	15%	81%
7	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	PhCl	$NiCl_2$	Et_3N	12%	80%
8	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	Mesitylene	$NiCl_2$	Et_3N	43%	82%
9	**A2**	$[Pd(C_3H_5)Cl]_2$	**L1**	Mesitylene	$NiCl_2$	Et_3N	50%	73%
10	**A3**	$[Pd(C_3H_5)Cl]_2$	**L1**	Mesitylene	$NiCl_2$	Et_3N	45%	68%
11	**A4**	$[Pd(C_3H_5)Cl]_2$	**L1**	Mesitylene	$NiCl_2$	Et_3N	38%	77%
12[d]	**A1**	$[Pd(C_3H_5)Cl]_2$	**L1**	Mesitylene	$NiCl_2$	TMEDA	68%	90%
13[d][e]	**A1**	$Pd(Ph_3P)_4$	**L1**	Mesitylene	$NiCl_2$	TMEDA	trace	/
14[d]	**A1**	$[Pd(C_3H_5)Cl]_2$	**L2**	Mesitylene	$NiCl_2$	TMEDA	36%	77%
15[d]	**A1**	$[Pd(C_3H_5)Cl]_2$	**L3**	Mesitylene	$NiCl_2$	TMEDA	88%	90%
16[d][f]	**A1**	$[Pd(C_3H_5)Cl]_2$	**L3**	Mesitylene	$NiCl_2$	TMEDA	91%	93%

Conditions: [a] **1a** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv), $[Pd(C_3H_5)Cl]_2$ (5 mol%), ligand (10 mol%), **A1** (10 mol%), Lewis acid **(**20 mol%), base (2.0 equiv), solvent (1.0 mL, *c* 0.2 M), 90 °C under N_2 atmosphere for 24 h. [b] Isolated yields. [c] The enantiomeric excess was determined by chiral HPLC. [d] base (2.5 equiv). [e] $Pd(Ph_3P)_4$ (10 mol%). [f] $[Pd(C_3H_5)Cl]_2$ (6 mol%), and ligand (12 mol%) were used. CA=Chiral Aldehyde.

2-fluoroallylic alkanes with branched selectivity, while Gong[6] disclosed the first Pd-catalyzed cross coupling of *gem*-F_2CPs with *gem*-diborylalkanes to afford the 2-fluoroallyic alkylboronates. Particularly, the ring-opening alkylation of *gem*-F_2CPs could also be realized by the Pd/Cu dual-catalyzed three components coupling of *gem*-F_2CPs with alkenes and B_2pin_2.[7] Nevertheless, enantioselective ring-opening alkylation of *gem*-difluorinated cyclopropanes, to the best of our knowledge, remains a formidable challenge in organic synthesis.

α-Quaternary α-amino acids (α-AAs)[8] are the valuable scaffolds in a diverse of natural products and pharmaceuticals, and enantioselective Tsuji-Trost allylation has served as an efficient pathway to assemble the functionalized chiral α-quaternary α-AAs.[9] In this regard, dual transition-metal synergistic catalysis has been nicely developed for the stereodivergent synthesis of α-quaternary α-AAs by Wang[10], Zhang[11] and Zi[12] group.[13] Notably, carbonyl catalysts have been elegantly discovered for the functionalization of *N*-unprotected α-amino acid esters by Guo[14] and Zhao[15] group independently. Inspired by these achievements in synergistic relay catalysis and as a continuation of our interest in the functionalization of strained rings[16] and the construction of biorelevant molecular skeletons[17], we thus questioned the possibility of the enantioselective 2-fluoroallylation of α-amino acid esters with *gem*-difluorinated cyclopropanes, in which the *in-situ* generated chiral Ni(II)-Schiff base complexes derived from amino acid esters might efficiently trap the highly reactive Pd-fluoroallyl complex resulted from the activation of *gem*-difluorinated cyclopropanes (**Scheme 1c**). However, this proposal is novel yet pretty challenging, and the following key issues must be addressed: (1) the strong nucleophilicity of the amino group might be problematic, affording the 2-fluoroallylic amines as byproducts. (2) the enantioselectivities might be plagued by the high reaction temperature which is needed for the ring opening of

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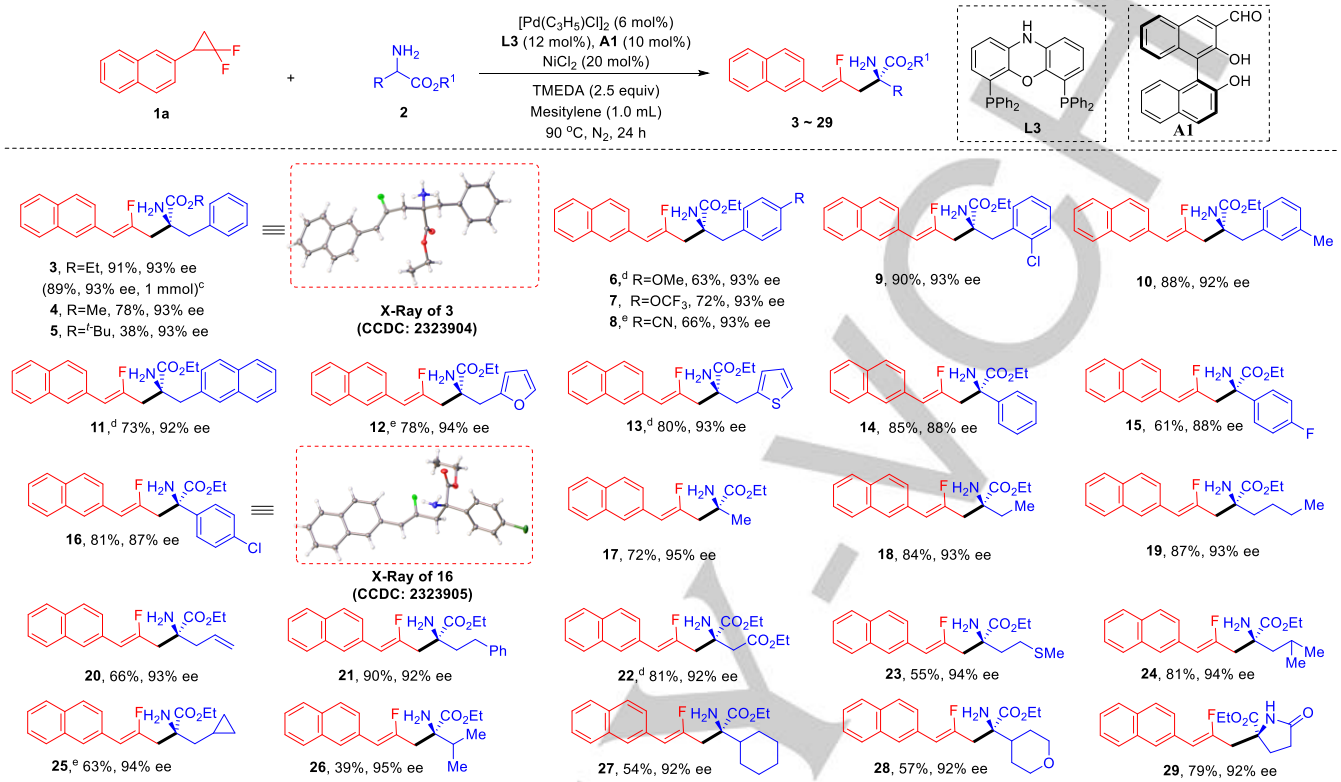
gem-difluorinated cyclopropanes. Herein, we report an unprecedented asymmetric Tsuji-Trost-type cross coupling reaction between *gem*-difluorinated cyclopropanes and *N*-unprotected amino acid esters enabled by the palladium/nickel/chiral aldehyde synergistic relay system, leading to the efficient construction of optically active nonproteinogenic α,α-disubstituted α-amino acids esters with a linear 2-fluoroallylic motif in a highly enantioselective manner.



Scheme 2. Scope with respect to amino acid ester structures **2**.[a], [b], [f] [a] 1a (0.2 mmol), 2 (0.4 mmol, 2.0 equiv), $[Pd(C_3H_5)Cl]_2$ (6 mol%), L3 (12 mol%), A1 (10 mol%), $NiCl_2$ (20 mol%), TMEDA (2.5 equiv), mesitylene (1.0 mL, *c* 0.2 M), 90 °C under N_2 atmosphere for 24 h. [b] Isolated yields. [c] 36 h. [d] Using *L*-amino ester 2 as reactant. [e] Using *D*-amino ester 2 as reactant. [f] The enantiomeric excess was determined by chiral HPLC.

To verify our hypothesis, the enantioselective ring-opening Tsuji-Trost-type reaction of *gem*-F_2CPs **1a** with racemic ethyl phenylalaninate **2a** was initially evaluated and the key results are summarized in Table 1 **(**see SI for details). The $ZnCl_2$ and $CuCl_2$ were firstly chosen as Lewis acids to stabilize the Schiff bases, however, no desired product could be detected by GC-MS (entry 1 and 2). Subsequently, more Lewis acids were carefully examined, and $NiCl_2$ turned out to be superior than other metal salts (entries 3-5).[18] Moreover, mesitylene stood out as the optimal solvent of choice among those screened (entries 6-8). Changing the chiral aldehyde has no positive effect (entries 9-11). The nature of bases and palladium sources significantly impacted both the enantioselectivity and yield, with a combination of $[Pd(C_3H_5)Cl]_2$ and TMEDA being the best (entries 12-13). A careful evaluation of ligands demonstrated that **L3** serves best in this transformation. The final optimization of the reaction parameters focused on varying the palladium loading, Pd/**L3** ratio, as well as reaction temperature (entries 14-16), and heating a mesitylene solution of **1a** and **2a** (c 0.2 M, N_2 atmosphere) in the presence of $[Pd(C_3H_5)Cl]_2$ (6 mol %), **L3** (12 mol %), **A1**(10 mol %), $NiCl_2$ (20 mol %) with TMEDA (2.5 equiv) as base at 90 °C for 24 h furnished the desired 2-fluoroallylation product **3** in 91% yield with 93% ee (entry 16). Control experiments showed that no reaction occurred in the absence of the Pd or Ni or chiral aldehyde catalysts. Moreover, when chiral **2a** and racemic **A1** were used in the reaction system, only racemic **3** was afforded, indicating the chiral aldehyde is the active species involved in the stereodetermining process.

With the optimized conditions established, we next sought to evaluate the generality of this protocol by exploring the scope of the reaction with respect to different amino acid esters. As outlined in Scheme 2, esters derived from both natural and non-natural α-AAs could function efficiently in this enantioselective ring-opening transformation platform. Changing the ester groups did not influence the enantioselectivity, but impacted the yields seriously. For example, the methyl and *tert*-butyl phenylalaninate delivered the desired products **4** and **5** in 78% and 38% yield respectively with both 93% ees. A series of ethyl phenylalaninates with both electron-donating and electron-withdrawing substituents at varying positions on the aryl units could be smoothly functionalized, producing the α-quaternary 2-fluoroallylic amino acid esters **6** - **10** with similar efficiency in term of absolute stereocontrol. Significantly, with respect to fused aromatics and heteroaromatics, naphthalene, furan and thiophene-substituted amino acid esters were competent coupling partners to afford the corresponding products **11** - **13** in good yields with excellent levels of enantioinduction. To our delight, this asymmetric fluoroallylation strategy is also viable for halide-substituted ethyl

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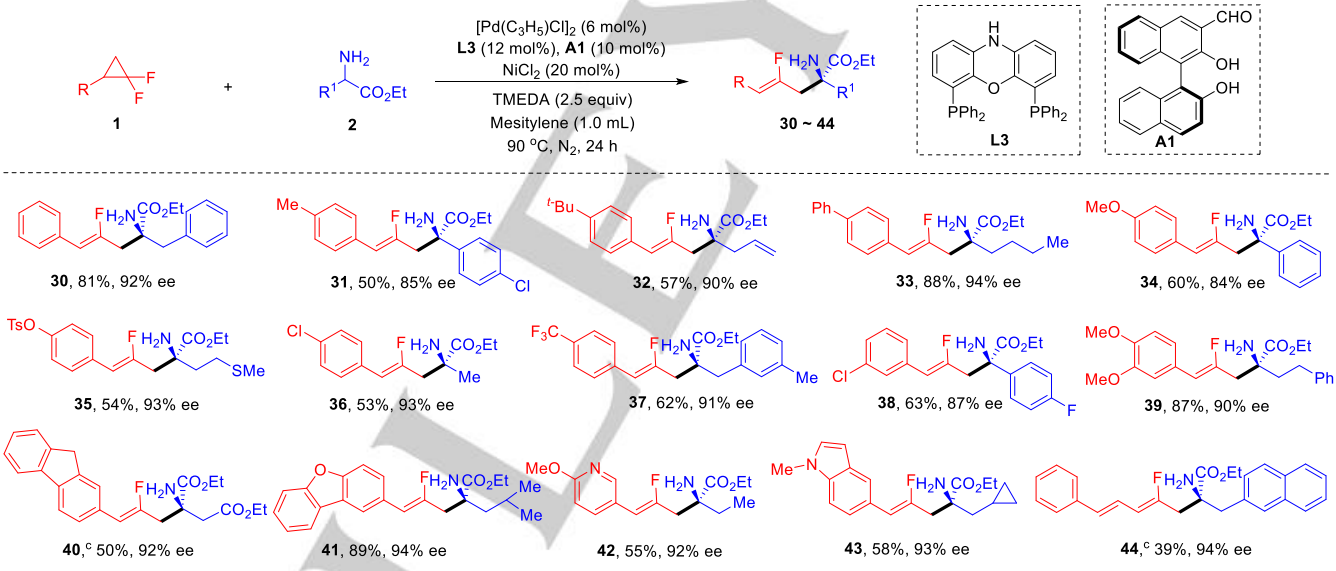
phenylglycinates, affording the enantioenriched target **14** - **16** with satisfactory results. Alkyl-substituted amino acid esters were then examined, and ethyl esters derived from alanine, 2-aminobutyric acid and norleucine could take part in the transformation nicely to deliver the corresponding **17** - **19** in high yields and excellent enantioselectivity. Remarkably, this synergistic relay catalysis platform is also amendable to a wide range of alkyl-substituted amino acid esters containing functional groups such as alkene, phenyl group, ester and thioether, as exemplified by the efficient synthesis of **20** - **23**. Moreover, alkyl-substituted amino acids with steric hindrance could also behave well to afford **24** - **28** in 92-95% ee with 39 - 81% yields. Particularly, when racemic diethyl glutamate was applied, the enantioenriched lactam **29** was furnished in 92% ee with 79% yield through a one-pot process involving the sequential 2-fluoroallylation, hydrolysis and lactamization. Excellent chemoselectivity could be clearly observed in this synergistic relay system, and the tolerance of various synthetically useful functional groups such as the ether (**6**, **28**), trifluoromethoxy (**7**), halides (**9**, **16**), alkene (**20**) and cyano group (**8**) provides a solid platform for the late-stage elaboration. In addition, **3** could be achieved in 89% yield with 93% ee at 1.0 mmol scale in a single batch, demonstrating the robust practicality of this Tsuji-Trost-type fluoroallylation protocol. Finally, the absolute configuration of **3** (CCDC: 2323904) and **16** (CCDC: 2323905) were confirmed by the X-ray crystallography analysis, and all other analogs were assigned accordingly. [19]

Various *gem*-difluorinated cyclopropanes were then interrogated with different amino acid esters to further evaluate the efficiency and diversity of this Tsuji-Trost-typed 2-fluoroallylation strategy. In general, *gem*-F_2CPs with different *para*-substituents on the aryl rings exhibited similar reactivity to furnish the target **30** - **37** in excellent levels of enantioinduction with good to excellent yields under the optimized conditions, implying that the electronic nature of aryl units does not seriously impact the reaction efficiency and stereocontrol. Moreover, *gem*-F_2CPs with *meta*-and di-substituted aryl rings were compatible with this triple catalytic system, and the products **38** and **39** were generated in 63% yield with 87% ee and 87% yield with 90% ee respectively. Particularly noteworthy is the product **40** in which the acidic protons of the fluorene could be kept intact under the basic conditions. Pleasingly, this enantioselective 2-fluoroallylation protocol could be efficiently expanded to *gem*-F_2CPs containing heterocycles such as dibenzofuran, pyridine as well as indole, delivering **41** - **43** in 92%-94% ee and 55%-89% yields. Furthermore, vinyl substituted difluorocyclopropane was also a competitive reaction partner to give the corresponding chiral fluorodiene-substituted α-quaternary α-amino acid **44** in 94% ee and 39% yield, which outstandingly enriches the diversity of the product scaffolds.



Scheme 3. Scope with respect to *gem*-difluorocyclopropane structures **1**. [a], [b], [d] [a] **1a** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv), $[Pd(C_3H_5)Cl]_2$ (6 mol%), **L3** (12 mol%), **A1** (10 mol%), $NiCl_2$ (20 mol%), TMEDA (2.5 equiv), mesitylene (1.0 mL, *c* 0.2 M), 90 °C under N_2 atmosphere for 24 h. [b] Isolated yields. [c] Using *L*-amino ester **2** as reactant. [d] The enantiomeric excess was determined by chiral HPLC.

The high functional-group compatibility of this methodology promoted us to transform the natural product-derived *gem*-F_2CPs to exemplify the power of this enantioselective ring-opening coupling paradigm (Scheme 4). Reaction of the γ-tocopherol-derived *gem*-difluorinated cyclopropane with the ethyl cyclohexylglycinate furnished the corresponding **45** in 47% yield with 94% *de* under standard reaction conditions, while the *gem*-difluorinated cyclopropane derived from estrone was similarly converted to the desired **46** in excellent diastereocontrol with high efficiency, as shown in Scheme 4a. Subsequently, more manipulations were conducted to demonstrate the synthetic value of this asymmetric Tsuji-Trost-typed fluoroallylation protocol. Reduction of **3** with $LiAlH_4$ in THF furnished the β-amino alcohol **47** in 90% yield with 93% ee, which could further react with picolinonitrile to afford the chiral fluoroallylic pyridine-oxazoline-type ligand **48** (Scheme 4b). Additionally, the quaternary amino acid ester **3** could be transformed to the dipeptide **49** smoothly by reacting with Boc-*L*-Leucine (Path I, Scheme 4c). In particular,

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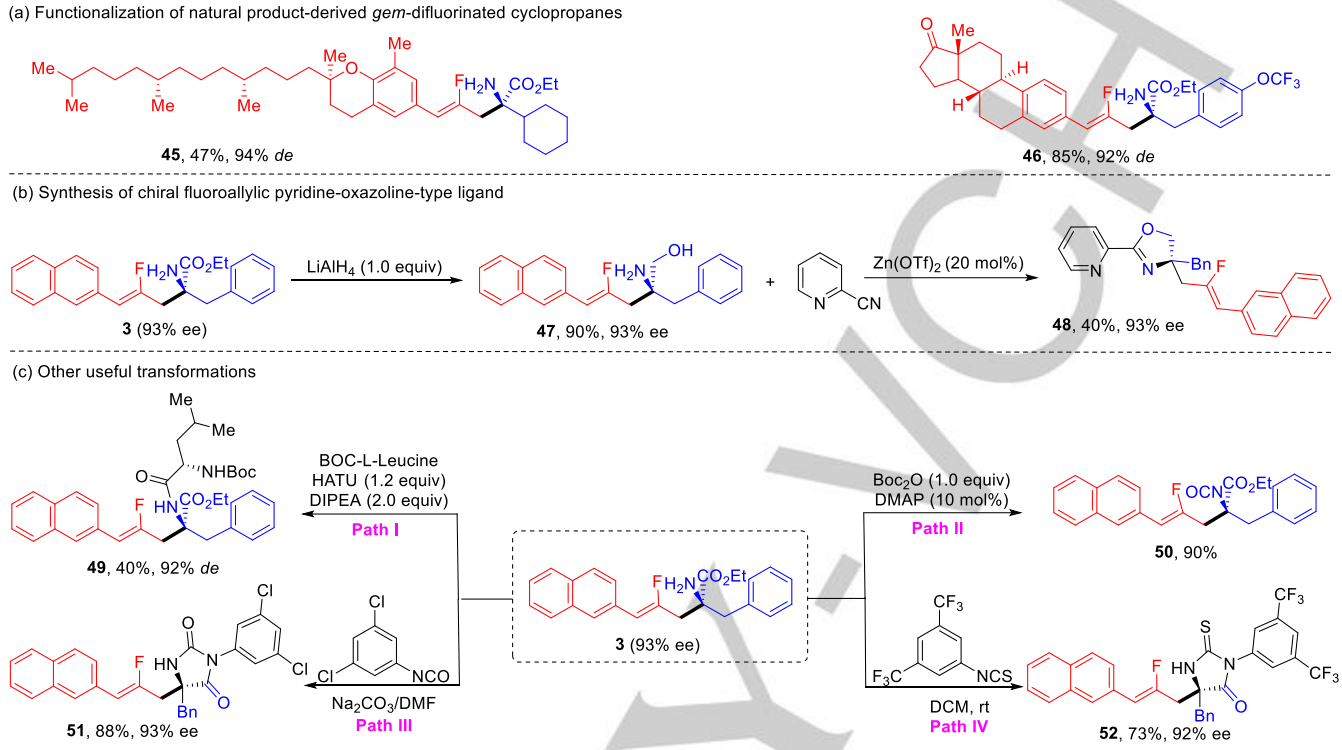
combination of **3** with Boc_2O and DMAP produced the synthetically useful isocyanate synthon **50** in 90% yield (Path II, Scheme 4c). And treatment of **3** with 3,5-dichlorophenyl isocyanate in the presence of Na_2CO_3 in DMF furnished the 2-fluoroallylic hydantoin **51** in 88% yield with 93% ee (Path III, Scheme 4b). Finally, 2-fluoroallylic 2-thiohydantoin **52** could be obtained in 73% yield with 92% ee by reacting **3** with 3,5-ditrifluorophenyl isothiocyanate (Path IV, Scheme 4b).



Scheme 4. Synthetic applications and transformations. a) Functionalization of natural product-derived *gem*-F_2CPs; b) Synthesis of chiral fluoroallylic pyridine-oxazoline-type ligand. c) Other useful transformations.

To gain insight into the potential mechanism, High Resolution Mass Spectrometry (HRMS) in negative ion mode was used to characterize the key intermediates *in situ* involved in this proposed mechanism (Scheme 5a). The Schiff bases **B** (m/z =488.1886, M-H) could be detected directly in the reaction system. Due to the activation of $NiCl_2$, the key intermediates **C** and **D** were not stable enough for HRMS detection. Nevertheless, comparing the isotopic distribution with theoretical data, fragment **C1** (m/z =516.0772, M-H) and **D1** (m/z =700.1441, M-H) resulted from intermediates **C** and **D** via the cleavage of ethyl group could be detected and confirmed. The existence of fragments **C1** and **D1** demonstrated the formation of Schiff base-Ni complexes in the reaction system. Furthermore, a set of experiments with ee-varied chiral aldehyde catalyst **A1** under the standard conditions were conducted. As depicted in Scheme 5b (see SI for details), a linear relationship between the ee values of the chiral aldehyde catalyst **A1** and fluoroallylation product **3** could be observed, implying that the enantio-determining step involves one molecule of chiral aldehyde catalyst **A1**.

Based on these results, a possible catalytic cycle was proposed, and DFT calculations were performed to understand the detailed enantio-determining transition states, as shown in Scheme 5c and 5d. The reaction is proposed to initiate with the coordination of *gem*-difluorinated cyclopropane **1a** to Pd(0) center to form the stable intermediate **Int1**, followed by the ring opening transition state **TS1** to afford the Pd(II) intermediate **Int2**. A free energy barrier of 17.7 kcal/mol is needed for this process. Then, the β-F elimination via transition state **TS2** takes place with a reaction barrier of 22.6 kcal/mol to give intermediate **Int3**, where the F-transfers to $HTMEDA^+$, generating the cation fluoroallyl complex **Int4**. Meanwhile, in the Ni-catalyzed cycle, the reaction starts with the coordination of **A1** and **2** with Ni center, releasing HCl to form the stable intermediate **Int5**, which is a downhill process of 49.9 kcal/mol. Subsequently, the Schiff base reaction occurs to afford **Int6**, followed with the coordinate of TMEDA and release of HCl to form **Int7**. Subsequently, the Tsuji-Trost-typed alkylation process involving a bimetallic cooperatively catalyzed transition state **TS3** (-65.5 kcal/mol) is located, which needs a reaction barrier of 8.8 kcal/mol. In addition, transition state **TS3'**(-63.0 kcal/mol) leading to the formation of enantiomer product was also calculated. Finally, the target product could be achieved by hydrolysis via **TS4** and **TS5**. Our DFT calculation also reveals that the water molecules play a crucial role as effective proton shuttle to promote the hydrolysis process (see more details in Supporting Information, Figure S9 and S10). With the increase of water molecules, the reaction barrier decreases dramatically from 45.2 kcal/mol to 28.4 kcal/mol, indicating that the water hydrogen-bond network in the real system could accelerate and stabilize this process.

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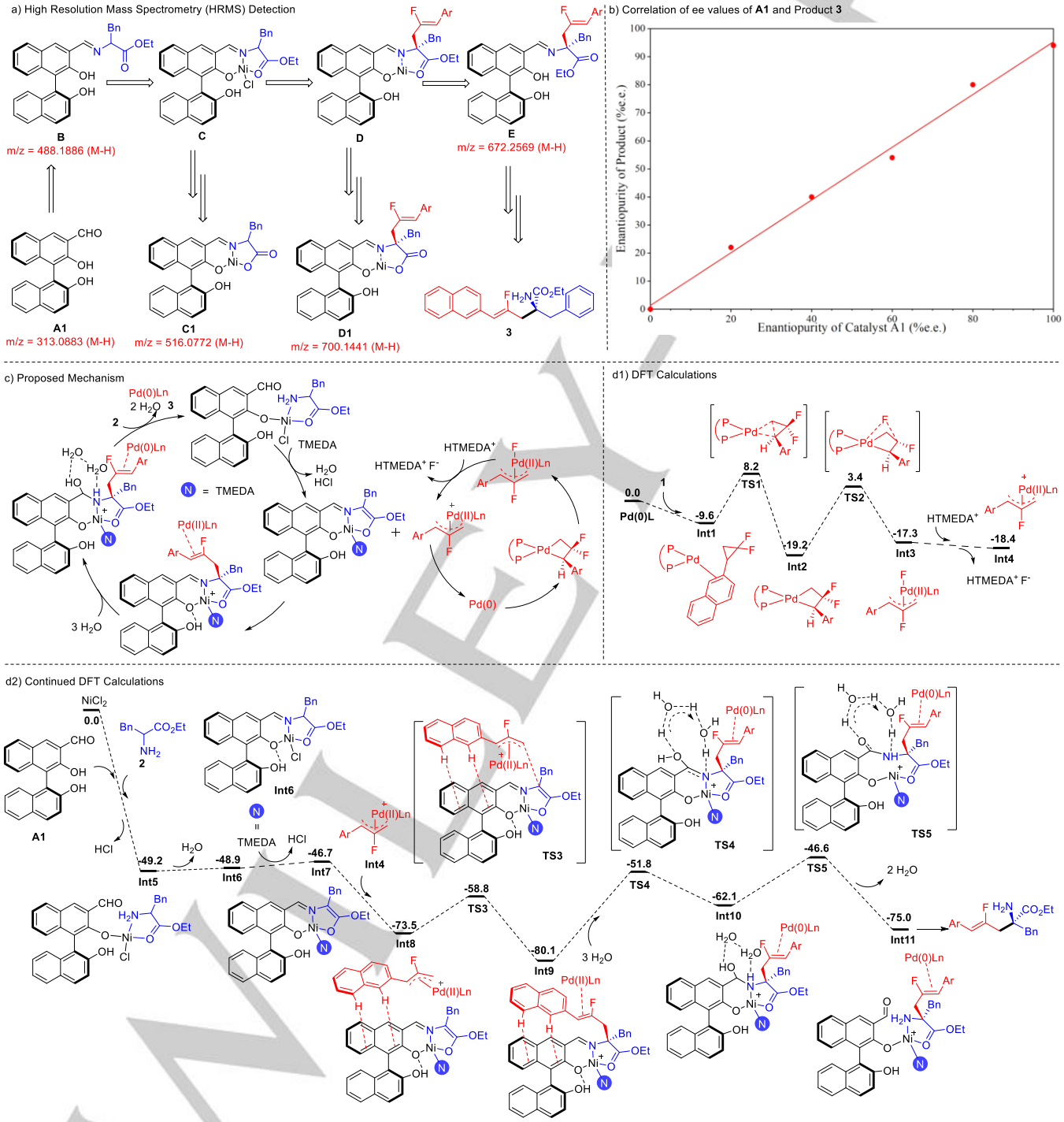
To better elucidate the origin of the 2.5 kcal/mol energy difference between **TS3** and **TS3'**, the energy decomposition analysis was performed. As shown in Figure1a, the energy difference between **TS3** and **TS3'** mainly comes from the difference of interaction energies (6.8 kcal/mol) between Pd(II)-π-fluoroallyl species and the Ni(II)-Schiff base complex.[20] Structural analysis reveals the presence of three CH···π[21] (b1=3.334Å, b2=2.980Å, b3=2.820Å) interactions and one π···π (b4=3.002Å) interaction between the Pd(II)-π-fluoroallyl species and the Ni-Schiff base complex in the favoured transition state **TS3** (Figure1b). However, only three weak π···π interactions are formed in **TS3'** (b1=3.307Å, b2=3.429Å, b3=3.123Å). The distance of these non-covalent interactions in **TS3** are shorter than those in **TS3'**, implying the existence of stronger interactions in **TS3**. In addition, these non-covalent interactions could be further confirmed by the NCI analysis in Figure1c.



Scheme 5. Mechanistic investigations. a) HRMS detection of key intermediates. b) Correlation of ee values of **A1** and product **3**. c) Proposed mechanism. d) DFT calculated Gibbs free energy profiles for the reaction (in kcal/mol).

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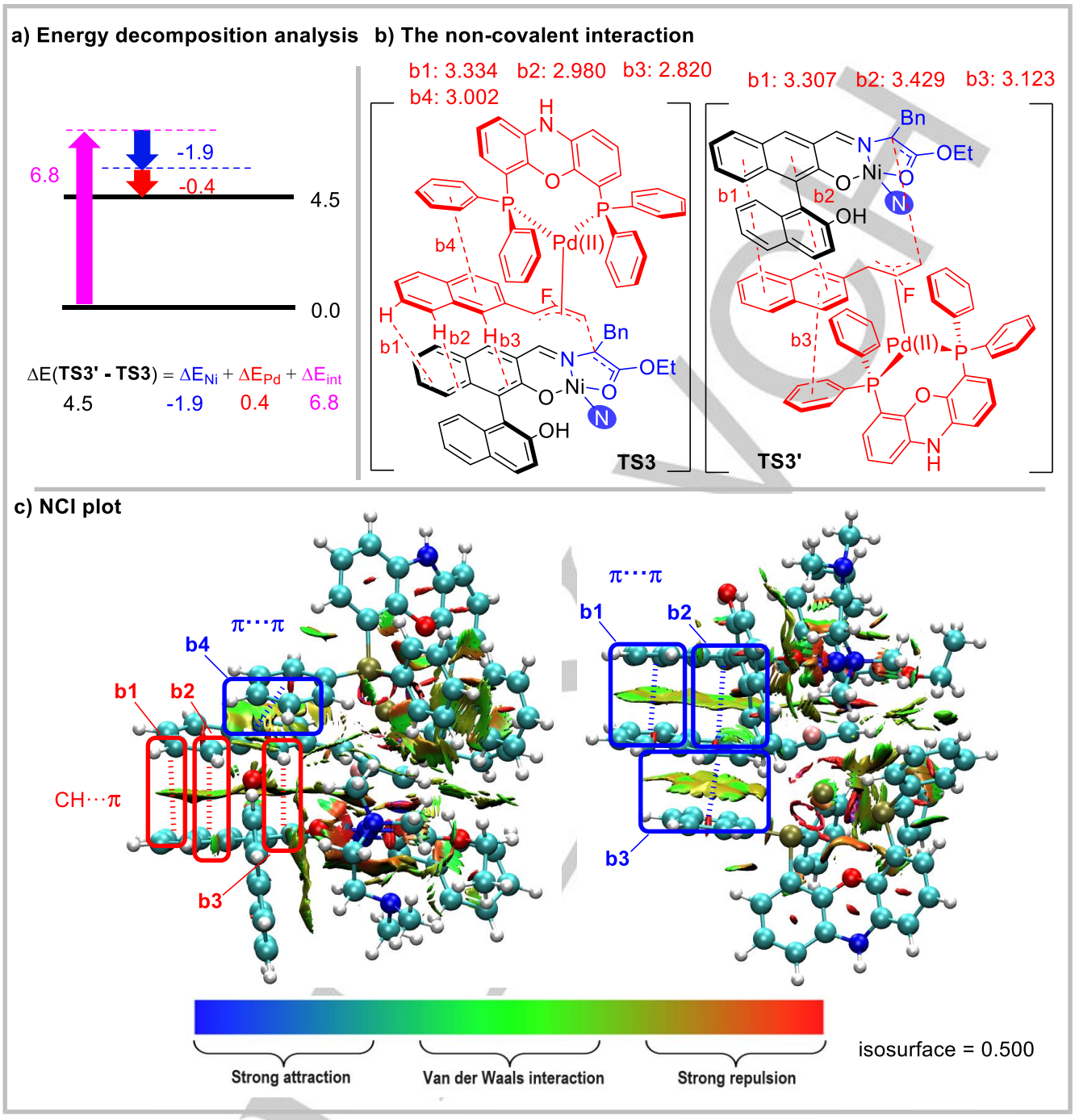

Figure 1. The Wheeler's energy decomposition analysis and NCI plot for the enantio-determining transition states.

In conclusion, a robust ternary Pd/Ni/chiral aldehyde synergistic relay catalysis system has successfully been developed for the enantioselective ring-opening cross coupling of *gem*-difluorinated cyclopropanes with *N*-unprotected amino acid esters. This operationally simple Tsuji-Trost-type 2-fluoroallylation strategy, with a feature of broad scope and excellent enantioinduction, streamlines the rapid access to the diversity-oriented synthesis (DOS) of optically active α-quaternary α-amino acid esters bearing a linear 2-fluoroallylic motif in good to excellent yields. The synthetic utility of this protocol was further demonstrated by late-stage modification of complex biorelevant molecules and the synthesis of various enantioenriched α-quaternary α-amino acid derivatives. The key intermediates were confirmed by HRMS detection, and DFT calculations revealed that the observed enantioselectivity originated from the stabilizing non-covalent interactions between the Pd(II)-π-fluoroallyl species and the Ni(II)-Schiff base complex.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorine • amino acid esters • palladium • nickel • asymmetric synthesis

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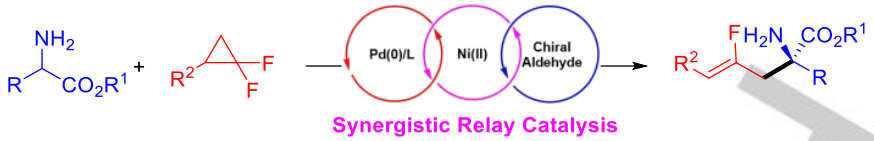

A robust palladium/nickel/chiral aldehyde synergistic relay system was developed for the enantioselective ring-opening functionalization of gem-difluorinated cyclopropanes with N-unprotected amino acid esters, enabling the efficient assembly of α-quaternary α-amino acid esters bearing a linear 2-fluoroallylic motif in a highly enantioselective manner.