Ligand-Dependent Regiodivergent Enantioselective Allylic Alkylation of α-Trifluoromethylated Ketones

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Article

**Keywords:** CF3, stereogenicity

**DOI:** https://doi.org/10.21203/rs.3.rs-110638/v1

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Abstract

The asymmetric introduction of CF₃ unit is a powerful tool for modifying pharmacokinetic properties and slowing metabolic degradation in medicinal chemistry. A catalytic and enantioselective addition of α-CF₃ enolates allows for expeditious access to functionalized chiral building blocks with CF₃-containing stereogenicity. The computational studies reveal that the choice of ligand in a designed palladium-complex system regulates the regioselectivity and stereoselectivity of the asymmetric allylic alkylation (AAA) of α-CF₃ ketones and Morita–Baylis–Hillman (MBH) adducts. Multiple C-H···F interactions are involved in the transition states.

Introduction

The wide application of fluorinated compounds in agrochemicals, pharmaceuticals and materials science has triggered every endeavor to develop efficient methods for selective incorporation of a trifluoromethyl group into organic molecules.¹⁻¹² The reliable methodology to access CF₃-containing stereogenicity is still underdeveloped in the context of matured asymmetric synthesis.¹³ The electrophilic trifluoromethylation of ketones has shown low reactivity and enantioselectivity, even with the aid of chiral auxiliary (Fig. 1a).¹⁴ Meanwhile, the exploitation of α-CF₃ enolate as an active nucleophile for enantioselective C−C bond-forming reactions is a viable strategy for pursuing this end, allowing rapid access to densely functionalized chiral building blocks.¹⁵,¹⁶ Despite the significant advances in enolate-based chemistry over the past decades,¹⁷⁻¹⁹ α-CF₃ enolates have only been scarcely explored because of the M-F elimination of their metal enolates.²⁰ Electrophilic alkylation of prefunctionalized α-CF₃ ketones provided remarkable outcomes by the use of chiral auxiliaries or directing groups (Fig. 1b).²¹⁻²⁴ In contrast, the direct asymmetric alkylation of naked α-CF₃ ketones represents unmet challenges in terms of reactivity and selectivity that has not been addressed.²⁵,²⁶

Despite the broad application of Morita–Baylis–Hillman (MBH) adducts as functionalized allylic synthons, good regio- and enantiocontrol of metal-catalyzed C1-selective adducts has not yet been realized.²⁷⁻³² The comprehensive studies on palladium-catalyzed AAA reactions by Trost and co-workers revealed that the regioselectivity can be modulated by both strics and electronics of the ligand.³³⁻³⁶ The nucleophilic attack of α-CF₃ enolate from Re/Si faces to either terminal of the π-allyl-metal complexes would result in a number of stereoisomers. To overcome the above issues, we have designed a regiodivergent enantioselective allylic alkylation of auxiliary-free α-CF₃ ketones with MBH adducts. By only switching the chiral ligands of the palladium complexes, excellent regio- and stereocontrol can be achieved on both C1 and C3 adducts for the construction of CF₃-bearing quaternary centers (Fig. 1c).

Results
Reaction optimization of the C1-selective reaction. To determine the suitable conditions for C1-selective allylic alkylation of α-CF₃ ketone 1, we first studied the reaction of dihydroindenone 1a and MBH ester 2a (1.2 equiv.) in the presence of Pd₂dba₃ (5 mol%) with a survey of chiral ligand (12 mol%) in THF at room temperature (Table 1). Spiro type ligand (L1) afforded the products in a total of 85% yield, in which the C1-adduct 3a was only 7% with 50% ee (entry 1). When using BINAP (L2) and Phosphos (L3-L5), low region- and enantioselectivities for 3a were obtained (entries 2-5). The reverse of the absolute configuration was obtained with L6 (entry 6). When switching to mono-dentate binaphthol-derived phosphoramidite L7, increased ratio of the C1 adduct 3a was observed (entry 7, 35:65). SIPHOS L8 resulted in a good regioselectivity (85:15) and 97% ee (entry 8).

### Table 1 Optimization of the C1-selective reaction conditions.

| entry | base | ligand | solvent | Yield | 3a:4a | d.r. | ee |
|-------|------|--------|---------|-------|-------|------|----|
| 1     | none | L1     | THF     | 85    | 7:93  | >20:1| 50 |
| 2     | none | L2     | THF     | 82    | 6:94  | >20:1| 25 |
| 3     | none | L3     | THF     | 75    | 12:88 | >20:1| 44 |
| 4     | none | L4     | THF     | 84    | 9:91  | >20:1| 51 |
| 5     | none | L5     | THF     | 93    | 4:96  | >20:1| 60 |
| 6     | none | L6     | THF     | 84    | 6:94  | >20:1| 90 |
| 7     | none | L7     | THF     | 87    | 35:65 | >20:1| 60 |
| 8     | none | L8     | THF     | 89    | 85:15 | >20:1| 97 |
| 9     | none | L8     | DCM     | 67    | 48:52 | >20:1| 85 |
| 10    | none | L8     | Toluene | 92    | 87:13 | >20:1| 98 |
| 11    | Et₃N | L8     | Toluene | 93    | 93:7  | >20:1| 99 |
| 12    | DIPA | L8     | Toluene | 96    | 95:5  | >20:1| 99 |

* Yield of isolated 3a and 4a;  
* The values of 3a:4a and distereomeric ratios of 3a were determined by 19F NMR analysis of the crude products;  
* The ee values of the major product were determined by chiral HPLC analysis.
Further optimization with L8 showed that using dichloromethane as the solvent did not improve the reaction yield (entry 9). With toluene, the yield increased to 92% (entry 10). By adding 2 equivalents of Et₃N, both reaction yields and selectivities were simultaneously (entry 11). The best results were obtained with DIPEA (entry 12, 96%, 95:5 for 3a, >20:1 d.r., 99% ee). Thus, the optimized conditions were selected for further investigation of the C1-selective AAA reaction.

**Table 2 C1-selective asymmetric allylic alkylation.**

Substrate scope of C1-alkylation. The reaction scope of C1-alkylation was explored using CF₃-ketones 1a and different MBH esters 2 (Table 2). Phenyls bearing both electron-withdrawing and electron-donating groups could be readily added to 1a to furnish the CF₃-ketones in high yields with excellent distereoselectivities and enantioselectivities (3b-3l). Furan, thiophene and naphthyl-derived MBH esters were tolerated (3n & 3o). Various substituted indenones on benzene ring could also afford the corresponding the C1-adducts (3p-3x).
Table 3 Optimization of the C3-selective reaction conditions.

| entry | ligand | base   | LG    | T(°C) | Yield | E/Z | ee\(^d\) |
|-------|--------|--------|-------|-------|-------|-----|--------|
| 1     | L1     | none   | OBoc  | 25    | 85    | 93:7| 8:1    | 10     |
| 2     | L3     | none   | OBoc  | 25    | 75    | 88:12| 10:1   | 44     |
| 3     | L4     | none   | OBoc  | 25    | 84    | 91:9| 8:1    | 0      |
| 4     | L5     | none   | OBoc  | 25    | 93    | 96:4| 13:1   | 60     |
| 5     | L7     | none   | OBoc  | 25    | 87    | 65:35| 1:6    | -40    |
| 6     | L5     | none   | OAc   | -30   | 40    | 92:8 | 15:1   | 85     |
| 7     | L5     | none   | OAc   | -30   | 27    | 95:5 | 13:1   | 95     |
| 8     | L5     | Na\(_3\)PO\(_4\) | OAc | -30   | 50    | 95:5 | 18:1   | 93     |
| 9     | L5     | K\(_2\)CO\(_3\) | OAc | -30   | 56    | 90:10| 16:1   | 85     |
| 10    | L5     | NaOAc  | OAc   | -30   | 37    | 92:8 | 16:1   | 94     |
| 11    | L5     | KOH    | OAc   | -30   | 25    | 90:10| 15:1   | 80     |

\(^a\) Yield of isolated 3 and 4. \(^d\) The ratios of 4:3 and E/Z ratio of 4 were determined by \(^{19}\)F NMR analysis of the crude products. \(^c\) The ee values of 4a were determined by chiral HPLC analysis.

**Reaction optimization of the C3-selective reaction.** For the optimization of C3-selective adduct, we slightly modified the reaction conditions for substrate 1a and MBH ester 2b (LG = OBoc). With L1 and L4, low ee's were obtained. For L3 and L7, moderate regioselectivity and distereoselectivity were achieved. L5 gave high regioselectivity (96:4) and 60% ee (entry 6). Switching the leaving to -10 °C and -30 °C further improved the distereoselectivity, affording the C3-selective adduct in 85% ee and 95% ee, respectively. However, the reaction yields decreased significantly (entries 8 & 9). By adding bases such as Na\(_3\)PO\(_4\), K\(_2\)CO\(_3\) and NaOAc, the reaction yields were improved and the enantioselectivities remain high. KOH is found to be detrimental both to the reaction efficiency and distereoselectivity.
**Substrate scope of C3-alkylation.** The reaction scope of asymmetric allylic alkylation is further extended to a range of MBH esters with L5 to generate C3-selective adducts (Scheme 2). MBH esters 2 with -OAc leaving group and phenyls bearing both electron-withdrawing and electron-donating groups could readily furnish the CF₃-ketones in good yields with high d.r. and ee's (4a-4j). Naphthalene-derived MBH esters were also tolerated (4k). Using CF₃-substituted tetralones, the corresponding adducts were also formed with equally high distereoselectivity (4l-4o).

**Theoretical calculation study.** To gain insight into the regioselectivity, DFT calculation was carried out with M06L/6-311++G(2d,p)-SDD-SMD(THF)//B3LYP/6-31G(d)-LANL2DZ-SMD (THF). For the Pd/L5 system, calculation suggests an outer-sphere SₐN₂ type attack is 3.6 kcal/mol lower than that for C1 attack, consistent with the experimental regioselectivity (Fig. 2a). Interestingly, the calculated ΔΔG‡ value of the nucleophilic addition TS parallels the calculated ΔΔG‡ of their corresponding π-allyl-Pd precursor (Fig. 2b) with 2.4 kcal/mol energy difference. Thus, the relative stability of the π-allyl-Pd complexes preserved in the subsequent nucleophilic addition TSs and thus dictates the regioselectivity of the Pd/L5 system. A closer look at Pd-allyl complexes reveals longer C-Pd distances in C1-attack precursor, indicating a looser Pd-allyl binding. This is likely the result of the trans-influence of phosphine on the PHOX ligand as well as the delocalization of positive charges on C1 by the conjugated phenyl group. As shown in Fig. 2c, the back-donation interaction involving d orbital of Pd-center and π-π orbital of allyl moiety favors C3-attack precursor (-5.90 eV vs -5.79 eV on HOMOs). In order to disclose the regio- and stereo-effects of the CF₃ group for the AAA reaction, further calculations on the trifluoromethyl and the methyl ester analogue have been performed. The free energy difference between C1 and C3 attack for the -CO₂Me substrate is only 1.3 kcal, much smaller than that of CF₃ substrate (3.6 kcal). Thus, poor regioselectivity is expected. The bond lengths between Pd center and allyl group in each transition state
for CF₃ and CO₂Me substituted ketones remain no change. For the three centers involved in SₐN₂ type reactions, there are obvious differences between the breaking Pd-C bond length and the forming C-C bond length. This is because trifluoromethyl group is close to a spherical structure compared with the planar structure of methyl ester. Therefore, the repulsion of allylic spherical hindrance and repulsion is greater than that of CO₂Me group, which makes the transition state C-C bond longer than that of CO₂Me in the reaction intermediate. Meanwhile, in the transition state of C3 attack, it was found that two substituents have obvious differences in the weak interaction between allylic group and ligands. For spherical trifluoromethyl moiety, multiple C-H···F interactions can be observed. This weak interaction can stabilize the transition state of C3 attack and reduce the energy of transition state, which enhances the reaction regioselectivity. While in the unfluorinated system, this effect was not identified (Fig. 3).

The plausible reaction pathways that based on previous reports⁴⁰-⁴² and computational studies are illustrated in Fig. 4. The AAA process was initiated by the coordination of Pd-L* complex to the MBH ester followed by oxidative addition to generate Pd-πallyl species. Subsequent nucleophilic addition of α-CF₃ enolate to Pd-π allyl species at C1 or C3-position afforded trifluoromethylated ketones depending on the ligand-regulated process. The final decomlexation releases the corresponding product 3/4 and regenerate palladium catalysts. The key selectivity deviation is originated from each catalytic pathway using bidentate or monodentate ligand. For the bidentate Phoxphos L⁵, complextion of A with MBH ester and oxidative addition generated Pd-π allyl specie B. Because B is stable enough and ligand exchange with L⁵ is not likely to occur. Hence, nucleophilic addition of CF₃-enolate to B from outer-sphere affords C3-selective intermediate D. For the monodentate SIPHOS ligand L⁸, only one phosphoramidite ligand can coordinate to the metal center of the allylpalladium complexes.⁴³-⁴⁵ Thus, similar oxidative addition process occurs first. The following decarboxylation of the Boc group releases tBuO and the Pd-tBuO²⁻ complex F is obtained.⁴⁶ Here, an equilibrium of ligand exchange between the CF₃-enolate and tBuO²⁻ controls the regioselectivity of the product. Configuration G with less steric hindrance against the Ar group of MBH ester is more favorable than H, which explains the C1 selectivity for SIPHOS L⁸.

Discussion

In summary, we have developed a highly-tunable ligand-regulated regiodivergent asymmetric allylic alkylation of fluorinated ketones with MBH adducts. The choices of ligand in the palladium catalytic systems turn out to be critical for both reactivity and selectivity for the construction of the CF₃-containing quaternary stereocenters. This protocol could access to a variety of fluorine-bearing motifs with high efficiency and selectivity.

Methods

General procedure for for C1-selective asymmetric allylic alkylation. (Conditions A) To a reaction tube with magnetic stirring bar were added the chiral ligand L⁸ (0.06 mmol), Pd₂(dba)₃ (0.0025 mmol) and Toluene (0.4 mL) under argon. The mixture was stirred for 30 minutes at room temperature. Then the
mixture was sequentially added trifluoromethylated ketones (0.05 mmol) and MBH adducts (0.06 mmol) and DIPEA (0.1 mmol). The resulting mixture was stirred for 12 h at room temperature. Then the solvent was removed in vacuo. The ratio of C1-selective/C3-selective product and the distereomeric ratios of the C1-selective product were determined by $^{19}$F NMR analysis of the crude mixture. The crude product was purified by flash chromatography on silica gel with ethyl acetate/petroleum ether (1/10) and then dichloromethane/petroleum ether (1:1) as the eluent to afford the corresponding product. The ee value of the C1-selective product was determined by HPLC analysis using a Chiralcel IG-3 column.

**General procedure for for C3-selective asymmetric allylic alkylation. (Conditions B)** To a 10-mL schlenk tube equipped with magnetic stirring bar were added the chiral ligand L5 (0.012 mmol), Pd$_2$(dba)$_3$ (0.005 mmol) and THF (0.4 mL) under argon. The mixture was stirred for 20 minutes at room temperature and another 20 minutes at -30 °C. Then the mixture was sequentially added trifluoromethylated ketones (0.05 mmol), Na$_3$PO$_4$ (0.15 mmol) and MBH adducts (0.06 mmol in 0.6 mL THF). The resulting mixture was stirred for 48 h at -30 °C. Then the reaction was quenched by addition of saturated ammonium chloride solution (2 mL) and water (10 mL), and the mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered, and the solvent was removed in vacuo. The ratio of C3-selective/C1-selective product and the E/Z value of C3-selective product were determined by $^{19}$F NMR analysis of the crude mixture. The crude product was purified by flash chromatography on silica gel with ethyl acetate/petroleum ether (1/10) as the eluent to afford the corresponding compound. The ee value of C3-selective product was determined by HPLC analysis using a Chiralcel IG-3 column.

**Data availability**

The authors declare that the main data supporting the findings of this study, including experimental procedures and compound characterization, are available within the article and its Supplementary Information files. X-ray structural data of compound 3i and 4n are available free of charge from the Cambridge Crystallographic Data Center under the deposition number CCDC 1911158 and 2009810. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

**Declarations**

**Acknowledgements**

This work was funded by the National Natural Science Foundation of China (Nos. 21772085, 21971107, 22071101) and the Fundamental Research Funds for the Central Universities (Nos. 020514380220, 020514380131, 020514913412, 020514913214). We also thank Jiangsu Provincial Key Laboratory of Photonic and Electronic Materials at Nanjing University for support. Professor Hon Wai Lam at University of Nottingham is gratefully acknowledged for helpful discussion.

**Author contributions**
Y.Z. designed and guided this project. Y.N. is responsible for the plan and implementation of the experimental work. C.L. and X.X. are responsible for the calculation studies. Y.W., X.W., X.X. and Y.P. co-wrote the manuscript, discussed the results and commented on the manuscript.

**Competing interests**

The authors declare no competing interests.

**Additional information**

**Supplementary information** accompanies this paper at https://doi.org/10.1038/xxxx.

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Figures
Figure 1

Overview of α-CF3 enolate chemistry.
Figure 2

(a) Transition states and their relative free energy of C1/C3 attack of the Pd/L5 system. (b) π-allyl-Pd precursors and their relative free energy. NBO charges on terminal carbons are marked in red. (c) HOMO of π-allyl-Pd precursors.
Figure 3

Weak interactions in C3 attack transition states of CF3 and COOMe substituents. Bond lengths are denoted in Å.
Figure 4
Proposed mechanism.

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