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In situ oxidizable directing group-enabled enantioselective synthesis of chiral platform ferrocene formaldehydes†

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Herein, we have developed an efficient oxidatively removable directing group approach, enabling highly enantioselective PdII-catalyzed C-H activation. Successful rationalization of difficult C-H activation over the labile β-H oxidation step led to the direct synthesis of chiral 2alkenylated ferrocene formaldehydes with up to 71% yields and 98:2 er.

The integration of directing groups (DGs) into transition metalcatalysed C-H activation has revolutionized organic synthesis, as these directing groups not only lead to a new array of molecules but also stabilize the inherently unstable species. However, in situ transformation of the directing group into desired functionalities is always challenging and has not been fully addressed yet.¹

Planar chiral ferrocenes,² particularly ferrocene formaldehydes, serve as important platform building blocks for synthesizing various planar chiral catalysts and ligands, including industrially used Josiphos, Ugi's amines, PPFA, and PHOX-type ligands (Scheme 1).3 Synthesis of planar chiral ferrocene formaldehyde derivatives has always been challenging yet remains essential.4 The major limitations are the multistep conventional routes or expensive reagents for the very high enantioselective synthesis of platform ferrocene formaldehydes.⁴ Moreover, a Pd^{II}-enabled transient directing group approach⁵ for highly enantioselective C-H activation was unsuccessful for metallocenes as it led to C-H activation on the lower cp-ring.⁵

Our group is continuously working on TM-catalyzed directing group methodologies for diverse selective C-H activation in ferrocenes.⁶ Furthermore, we aim to develop a highly enantioselective and efficient methodology to construct important chiral platform ferrocene formaldehydes with high enantioselectivity. Consequently, a removable directing group strategy was envisioned, leading to enantioselective C-H activation and,

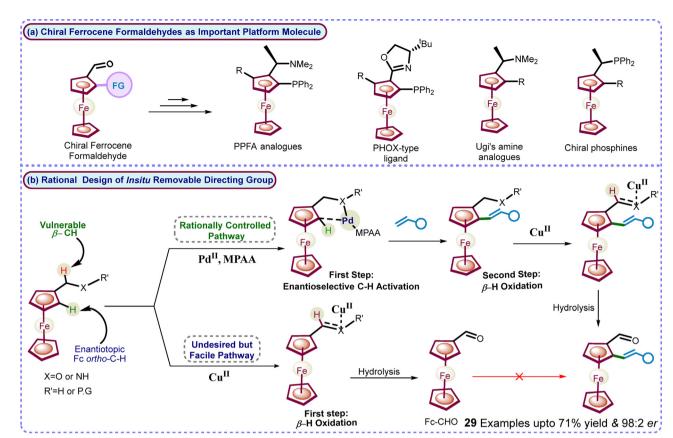
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subsequently, in situ transformation of the directing group into important platform chiral formaldehyde functionalities (Scheme 1). Herein, we have successfully developed an in situ oxidizable directing group methodology through a sequential rationalization of unreactive enantiotopic C-H bond activation over facile β -H oxidation of protic amines. The developed in situ oxidizable directing group methodology led to the efficient synthesis of diverse new alkenylated platform chiral ferrocene formaldehydes with up to 71% yield and 98:2 er in a stepeconomical manner (Scheme 1).

We commenced our investigation of ferrocenyl-methylamine 1a with a combination of Pd(OAc)2 as a catalyst and a recently reported chiral NOBINAc ligand^{6c} with acrylate 2a (Table 1). In addition, an oxidant, Cu(OAc)2, with the base Cs₂CO₃, was added to facilitate the subsequent oxidation of the catalyst as well as the directing group. Ferrocenylamine 1a produced the desired oxidized amine product - chiral 1,2alkenylated ferrocene formaldehyde 3a - in a poor yield of 20% with a moderate enantioselectivity of 90:10 er (Table 1, entry 1). Furthermore, various solvents were screened to control the excessive oxidation of amine 1a (Table 1, entries 2-4). Among the solvents screened, tert-amyl alcohol increased the yield of 3a to 32%, and undesirably the enantioselectivity of 3a was reduced to 70:30 er (Table 1, entry 4), which may be due to the incompatibility of the NOBINAc ligand with the polar protic tert-amyl alcohol. To circumvent the undesired oxidation of 3a to FcCHO and to further enhance the er, we screened a series of chiral mono-protected amino acid ligands (L2-L9; see Fig. S3 and Table S2, ESI†). To our delight, the screened MPAA ligands L2-L9 demonstrated notable efficacy, delivering yields ranging from 32% to 75% and er values from 87:13 to 98:2. Among all the ligands screened, Boc-1-tert-Leucine L2 provided the best results with amine 1a, achieving a 75% yield and 98:2 er of 3a (for details see Tables S1-S4, ESI†).

Next, a variety of ferrocenylamines 1b-1h were tested under enantioselective C-H activation followed by oxidative deamination conditions (Fig. 1). Other sulfonyl (SO₂R)-protected



Scheme 1 (a) Ferrocene formaldehyde as a valuable platform molecule and (b) rational design of the step-economical oxidizable directing group strategy and our work.

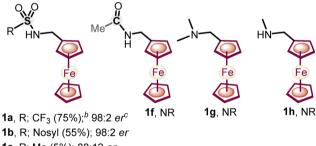
Table 1 Optimization of reaction conditions for the enantioselective in situ oxidizable directing group strategy

NI NI NI NI NI	OF.	Pd ^{II} (10 mol%) Ligand (40 mol%) Cs ₂ CO ₃ (2 equiv) Cu(OAc) ₂ (1.5 equiv) Solvent (1.0 mL), air 60°C, 24 h	FcCHO	Ligand NHAC OH L1 OH L1 OH L2	
Entrv ^a	Solvent	Ln	FcCHO (%)	$3a^{b}$ (%) er ^c (%)	

Entry ^a	Solvent	Ln	FcCHO (%)	$3a^b$ (%)	er ^c (%)
1	THF	L1	80	20	90:10
2	Toluene	L1	75	25	87:13
3	DMF	L1	88	12	76:24
4	^t Amyl alcohol	L1	68	32	70:30
5 6 ^d	^t Amyl alcohol	L2	35	65	96:4
6^d	^t Amyl alcohol	L2	25	75	98:2

^a Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), Pd(OAc)₂ (0.01 mmol), ligand (0.04 mmol), Cs₂CO₃ (0.2 mmol), Cu(OAc)₂ (0.15 mmol), DMSO (0.5 mmol), dry solvent (1 mL), air, 60 °C, 24 h. The crude yield of 3a was determined by ¹H NMR with CH₂Br₂ as an internal standard. ^c The enantiomeric ratio (er) of 3a was determined by HPLC analysis. ^d The reaction was stirred for 30 h at 55 °C. Ligand L1 = NOBINAc and L2 = Boc-L-tert-leucine.

ferrocenylamines 1b-1e also provided the chiral product 3a in 5-55% yields, with 88:12 to 98:2 er, whereas amines 1f-1h, lacking a coordinating SO₂R group, did not yield the desired

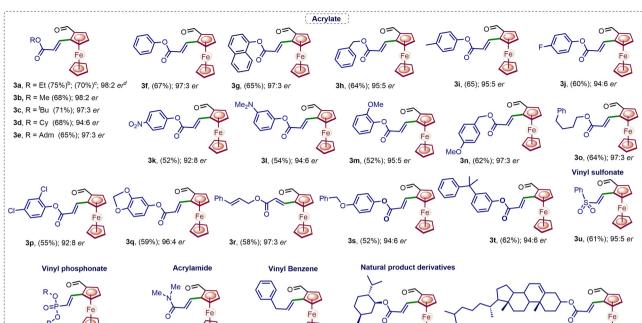


1c, R; Me (5%); 88:12 er 1d, R; 3,5-di-F-Ph (36%); 94:6 er

1e, R; Tosyl (25%); 97:3 er

Fig. 1 Screening of amines for enantioselective C-H activation and subsequent oxidative deamination. Reaction conditions: the same as those mentioned in Table 1, entry 6.

alkenylated formaldehyde 3a. The screening of the various amines suggests that the low pK_a of the methylene C-H bond, the coordinating ability of amine DGs, and the better leaving group ability of the -S(O)₂R substituent are needed for effective enantioselective C-H activation and in situ directing group removal.8 Furthermore, the substrate scope with regard to various olefins (2a-2aa) was explored. Acrylates 2a-2t with alkyl, electron-donating and electron-withdrawing groupsubstituted aryl, naphthyl, and benzyl substitution yielded an



Scheme 2 Substrate scope for enantioselective C-H alkenylation. ^a Reaction conditions are the same as those mentioned in Table 1, entry 6. ^b The crude yield of 3a was determined by ¹H NMR with CH₂Br₂ as an internal standard. ^c Isolated yields of 1,2-alkenylated ferrocene formaldehydes 3a-3aa. ^dThe er of **3a** was determined by HPLC. ^eThe dr ratio of the isolated product was determined by ¹H NMR.

3z. (51%): 7:1 dr

3v. R = H (48%): 98:2 er

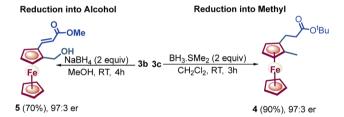
array of 1,2-alkenylated ferrocene formaldehydes 3a-3t in 52-71% yields and 92:8-98:2 er (Scheme 2). Moreover, other olefins, namely, vinyl sulfonate 2u, phosphonates 2v and 2w, acrylamide 2x, and vinyl benzene 2y, also showed the amenability to afford respective chiral 1,2-alkenylated ferrocene formaldehydes 3u-3y in 48-66% yields and 92:8-97:3 er (Scheme 2). Furthermore, olefins derived from natural products L-menthol and cholesterol 2z and 2aa were also coupled diastereoselectively to afford the respective menthol- and cholesterol-containing chiral ferrocene formaldehydes 3z and 3aa in 51% and 49% yields, with 7:1 to 10:1 dr, respectively (Scheme 2). Additionally, we performed a gram-scale reaction, achieving up to 50% yield of chiral 1,2-alkenylated ferrocene formaldehyde 3a with 95:5 er. Furthermore, chiral 1,2-alkenylated ferrocene formaldehydes 3c and 3b were reduced to their respective methyl and alcohol groups, leading to molecules 4 and 5 without any reduction in enantioselectivity (3c, 97:3 er versus 4, 97:3 er, and 3b, 97:3 er versus 5, 97:3 er, Scheme 3).

3x. (55%): 95:5 er

(65%): 92:8 et

Furthermore, to gain mechanistic insights into controlled amine oxidation versus enantioselective C-H activation pathways, a series of control experiments were performed (Scheme 4).

The failure to obtain product 3a from ferrocene formaldehyde under optimized conditions (Scheme 4, eqn (1)) rules out imine involvement in the enantioselective C-H activation. Furthermore, we examined the possibility of a radical-driven process where the radical quenchers (TEMPO and BHT) failed to prevent oxidation or to form any adducts as observed by mass spectrometry (Scheme 4, eqn (2)). Next, the role of Pd^{II} and CuII in the oxidation of amine was studied by selectively



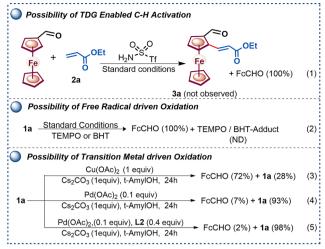
3aa. (49%): 10:1 dr

Scheme 3 Post-derivatization of aldehydes into methyl and alcohol functionalities.

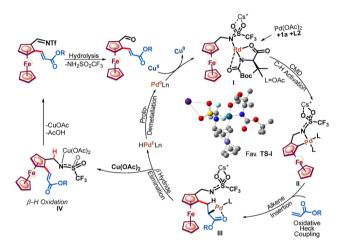
varying the metal salts involved in the reaction (Scheme 4, eqn (3)-(5)). The reaction outcomes indicate that both Cu(OAc)₂ and $Pd(OAc)_2$ are capable of facilitating the respective β -H oxidation, and the presence of the base Cs2CO3 significantly accelerates the oxidation.

Additionally, it was noted that the presence of an MPAA ligand slows the β-H oxidation driven by the Pd(OAc)₂ catalyst (Scheme 4, eqn (5)). Furthermore, the relative rates of C-H activation versus amine oxidation were rationalized by ¹H NMR experiments, suggesting that the rate of C-H activation is 1.76 times higher than the rate of amine oxidation (see Fig. S4-S9, ESI†). Further, a ligand acceleration experiment was conducted, which revealed that the presence of ligand L2 accelerates the reaction by 4.6-fold (see Fig. S8, ESI†). Furthermore, the DFT computational studies were performed to determine the relative enantiotopic C-H energy within CMD, which showed a 2.48 kcal mol⁻¹ lower energy for the favorable TS than for the unfavorable TS (see Fig. S10, ESI†). Based on control experiments, we have proposed a plausible catalytic cycle (Scheme 5). Initially, amine

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Mechanistic investigation of C-H activation versus deamination



Scheme 5 Plausible catalytic cycle. The favourable TS shown was obtained by DFT calculations.

1a, Pd(OAc)₂, and ligand L2 with a Cs⁺ cation form a Pd-aminate, I, as suggested by 19F NMR experiments (see Fig. S9, ESI†) and a previous report. 10 Furthermore, the Pd-aminate I undergoes enantioselective C-H activation to generate a chiral palladacycle, II. The chiral palladacycle **II** interacts with the olefin through π -bond interactions, leading to the formation of a Pd-alkyl intermediate, III. Consequently, intermediate III would undergo β-H elimination to afford chiral 2-alkenylated ferrocenylamine. The 2-alkenylated ferrocenylamine was then oxidized by Cu(OAc)2 through one-electron oxidation of triflamide to form copper-amidate IV, followed by hydrolysis, yielding chiral 2-alkenylated ferrocenyl formaldehydes.⁹

In summary, we have developed a mild in situ oxidizable directing group methodology for the highly enantioselective and monoselective synthesis of chiral platform ferrocene formaldehydes. The developed methodology effectively rationalizes the difficult enantioselective C-H activation step first and the facile β-H oxidation step later, which represents an efficient alternative to the transient directed strategy using a dual PdII/CuII cycle in stacked molecules.

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Conflicts of interest

There are no conflicts to declare.

Data availability

Detailed synthetic procedures, reaction condition optimization, data characterization, controlled experiments, and geometries and energies of theoretically investigated structures are provided in the ESI.†

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