A General and Modular Access to Enantioenriched α-Trifluoromethyl Ketones via Nickel-Catalyzed Reductive Cross-Coupling

Dengkai Lin, Yongzhi Chen, Zhan Dong, Pan Pei, Haiting Ji, Lanzhu Tai, Liang-An Chen*
School of Chemistry and Materials Science, Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing Normal University, Nanjing 210023, People's Republic of China; E-mail: lachen@njnu.edu.cn

Abstract: The development of new catalytic enantioselective access to CF_3-containing stereogenicity is of great interest for the expediting discovery of lead compounds yet remains challenging. We devised a general and modular approach to facilely access enantioenriched α-CF_3 ketones via nickel-catalyzed reductive cross-coupling of readily available acid chlorides and racemic α-CF_3 alkyl bromides in an enantioconvergent fashion under mild conditions. This protocol featured neighboring directing group-free, high chemoselectivity, excellent functional group tolerance, facile scale-up, and notable amenability to straightforward downstream elaboration toward molecule complexity, thus constituting a reliable, direct, practical, and efficient synthetic alternative to furnish enantiopure α-CF_3 carbonyls. Interestingly, an appropriate choice of the phosphine ligand as co-ligand plays an important role in high efficiency and asymmetric induction. Mechanistic studies suggest a radical chain pathway.

Introduction: Fluorine-containing compounds play an important role in pharmaceuticals, agrochemicals, and advanced functional materials due to their unique biological, chemical, and physical properties.[1] In particular, the trifluoromethyl group is broadly employed as a valuable and privileged structural motif in medicinal chemistry because it can substantially impact solubility, lipophilicity, metabolic stability, bioavailability, and binding affinity of lead drug candidates.[2] Thus, significant endeavors have been devoted to incorporating the CF_3 groups into organic molecules over recent decades.[3] However, compared to the booming synthesis of trifluoromethylated aromatic compounds, the methods for installing molecules bearing Csp^3-CF_3, particularly the enantioenriched variants, still remain limited.[4] Although not abundant compared with other versions, likely due to a dearth of effective asymmetric assembly methods, CF_3-containing stereogenic centers are still present in many lead compounds and marketed drugs, and not surprisingly, are ever-growing (Figure 1a).[4f,4g] Therefore, the quest to develop general and efficient strategies for asymmetric setting the trifluoromethylated stereocenters into molecules, especially along with synthetically

versatile functionalized molecular architectures, is of great importance and highly sought after. In this context, the enantiopure α-CF_3 carbonyl compounds have gained considerable attention because they bear both a valuable chiral trifluomethylated stereocenter for pursuing the clinical success of drug candidates and an easily derivatized carbonyl group for further rapid elaboration of molecular complexity and diversity, thus potentially offering numerous application opportunities to furnish diverse molecules of biological interest (Figure 1).[5] However, the ability to craft these chiral functionalized building blocks with CF_3-containing stereogenicity remains challenging and limited to date. Generally, the strategies for accessing optically pure α-CF_3 carbonyl compounds can be divided into two categories based on enolate chemistry. The first strategy involves asymmetric electrophilic α-trifluoromethylation of carbonyl-derived enolate or enolate equivalent, often utilizing specially tailored CF_3-delivery reagents (Figure 1b).[6] In addition, most successful examples in achieving good enantioselectivity typically proceeded with stoichiometric chiral auxiliary-derived imides and tertiary α-alkyl β-ketoesters/amides.[6a-f] Remarkably, in terms of step-economy, an elegant approach to catalytic enantioselective α-trifluoromethylation of aldehyde was achieved employing enamine-based organocatalysis in combination with Lewis acid or Photoredox catalysis.[6h,6i] The second strategy relies on asymmetric α-functionalization of a prochiral CF_3-containing substrate through an intermediacy of α-CF_3 enolate under basic conditions (Figure 1c).[7,8] However, the stoichiometric chiral Evans-auxiliaries or complex amide-based directing groups with two-point coordination sites are strictly employed to dictate the enantioselectivity, thus leading to frustrated atom- and step-economy. Despite these efforts, it is important to emphasize that, to the best of our knowledge, there remains a paucity of highly enantioselective catalytic methods for constructing valuable ketones featuring α-trifluoromethylated stereocenter without the aid of neighboring coordination groups,[8] presumably due to the inherent difficulty in site-selective formation of ketone enolate and controlling the stereochemistry during the bond formation from enolate intermediates. Additionally, owing to the salient electron-withdrawing nature of the CF_3 substituent, a daunting challenge to be addressed is to prevent the potential racemization of the newly formed labile α-tertiary CF_3-containing stereogenicity of carbonyl compounds, particularly in the case of ketones and aldehydes that exhibit lower pKa for α-hydrogens because of their stronger resonance stabilization in comparison to amides and esters. In this vein, it is highly desirable to develop a new simple, mild, and general method for asymmetric catalytic preparation of this class of chiral CF_3-containing ketone compounds, especially their tertiary enantiomerically enriched variants.

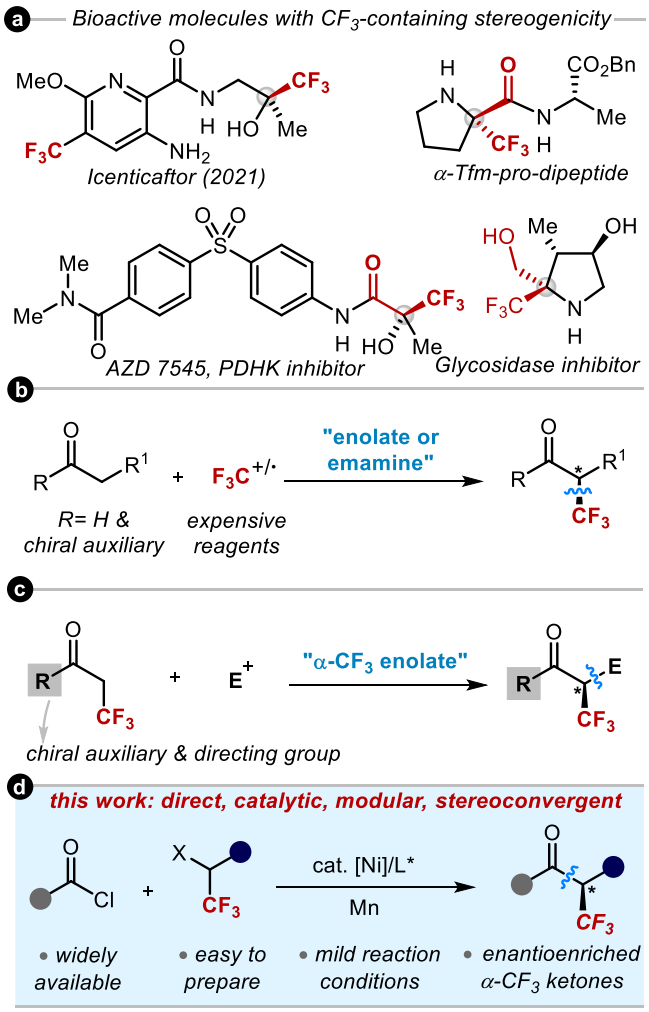


Figure 1. Strategies for Asymmetric Synthesis of Enantiomerically Pure *α*-CF_3 Carbonyl Compounds.

Nickel catalysis has garnered significant interest in the context of reductive cross-coupling reactions because it opens up a general and powerful paradigm for utilizing alkyl electrophiles to furnish Csp^3-enriched centers through a single-electron oxidative addition pathway[9,10] as well as typically features atom- and step-economical profiles, mild (less basic) reaction conditions, and broad functional group compatibility.[11] Accordingly, the effort toward developing enantioselective catalytic forms is a preeminent goal of this great synthetic promise yet remains a tedious exercise partially due to highly reactive radical species.[12] Pioneeringly, the Reisman group has accomplished a chiral nickel-catalyzed enantioselective reductive cross-coupling reaction of acyl chlorides with commonly used racemic benzylic chlorides as stabilized radical coupling partners to afford enantiopure α-aryl-α-alkyl ketones.[13] Inspired by this elegant enantioselective event, we herein described an enantioselective nickel-catalyzed reductive cross-coupling between acyl chlorides and electronically unactivated racemic α-trifluoroalkyl bromides to facilely access

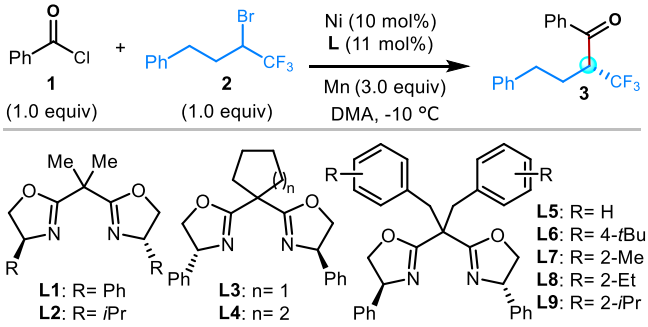
enantioenriched α-CF_3 ketones in an enantioconvergent fashion under mild conditions (Figure 1d). In this context, the two kinds of employed electrophiles are highly appealing, mainly due to their convenience of use and relatively inexpensive. Additionally, a vast majority of acid chlorides are commercially available or can be readily prepared from cheap carboxylic acid in an operationally simple reaction. A variety of widely available fluoroalkyl bromides and acyl chlorides with various functional groups are eligible for direct coupling in good to high yields and good enantioselectivity without using heteroatom-containing directing groups. Interestingly, it was found that an appropriate choice of the phosphine ligand as a co-ligand plays an important role in the high efficiency and asymmetric induction. This protocol constitutes a reliable, direct, and efficient synthetic alternative to the existing strategies for preparing enantiopure α-CF_3 carbonyl compounds.

Optimization of Reaction Conditions: The development of this direct reductive cross-coupling reaction to achieve an enantioselective variant was accomplished using model substrates benzoyl chloride **1** and α-CF_3 alkyl bromide **2** as outlined in Table 1. To our delight, the reaction was carried out at room temperature in the presence of $NiCl_2$(DME), **L1**, and Mn^0, allowing the formation of the coupling product **3** in 56% yield and 36% ee of trifluoromethylated stereogenic center (entry 1). Meanwhile, substantially related hydrodebrominated and β-fluorine eliminated byproducts from substrate **2** were observed. The lower reaction temperature was found to be helpful for both the yield and selectivity (entries 2). After many evaluations of the reaction temperature, -10 °C was identified as the optimal temperature for the formation of the chiral trifluoromethylated product (entry 3, also see the SI). Subsequently, various chiral bis-oxazoline ligands were evaluated, it was found that **L5** with geminal diaryl substituents could increase the selectivity (entries 4-7).

Interestingly, in our efforts to investigate the influence of varieties of nickel catalysts on the enantioselectivity, we surprisingly found that nickel catalyst bearing phosphine ligands were capable of vastly improving the enantiomeric ratio, albeit with a slightly decreased yield (entries 8-10). In this regard, we deem it possible that an additional phosphine ligand might serve as an ancillary ligand to the nickel complex and accordingly play an important role in the enantiocontrol. Gratifyingly, the further augmented yield and enantioselectivity were observed by adding a catalytic amount of PPh_3 as a co-ligand with the combination of $Ni(COD)_2$ (entries 8-10 vs entry 11).[14] At this stage, a different phosphine ligands screen was performed (see the SI), and we found that P(*p*-$CF_3C_6H_4)_3$ enabled the supportive formation of **3** in 81% yield and 80% ee. We then turned our attention to sequentially fine-

tuning the steric hindrance on geminal diaryl substituents based on **L5** in the presence of 20 mol% P(*p*-$CF_3C_6H_4)_3$. Delightedly, it was found that the enantioselectivity of the related product was improved with increasing the steric hindrance at the ortho position of diaryl substituents (entries 16-19). The reaction was performed with the increased amount of alkyl bromide, which facilitated the formation of the targeted product in an improved yield (entry 19). Astonishingly, the comparable yields and enantioselectivity could be reached even at a lower P(*p*-$CF_3C_6H_4)_3$ loading of just 5 mol% (entries 18 and 20). Finally, increasing the amount of ligand **L9** loading to 15 mol% would result in a slightly improved stereoinduction outcome (entry 21). As anticipated, control experiments further revealed that the reaction components, such as nickel catalyst, reductant, and ligand, proved to be crucial for success (See the SI).

Table 1. Optimization of Reaction Conditions.[a]



Entry	[Ni] 10 mol%	L	P	Yield (%)[b]	er[c]
1[d]	$NiCl_2$(DME)	**L1**	-	56	68:32
2[e]	$NiCl_2$(DME)	**L1**	-	73	72:28
3	$NiCl_2$(DME)	**L1**	-	61	74:26
4	$NiCl_2$(DME)	**L2**	-	49	65:35
5	$NiCl_2$(DME)	**L3**	-	39	-73:27
6	$NiCl_2$(DME)	**L4**	-	21	-67:33
7	$NiCl_2$(DME)	**L5**	-	46	75:25
8	$Ni(COD)_2$	**L5**	-	30	76:24
9	Ni(DPPF)Cl_2	**L5**	-	32	86:14
10	$Ni(PPh_3)_2Cl_2$	**L5**	-	24	88:12
11	$Ni(COD)_2$	**L5**	PPh_3	51	90:10
12[f]	$Ni(COD)_2$	**L5**	PPh_3	64	90:10
13[f]	$Ni(COD)_2$	**L5**	P(2-furyl)$_3$	85	89:11
14[f]	$Ni(COD)_2$	**L5**	P(*p*-$CF_3C_6H_4)_3$	81	90:10
15[f]	$Ni(COD)_2$	**L6**	P(*p*-$CF_3C_6H_4)_3$	83	89:11
16[f]	$Ni(COD)_2$	**L7**	P(*p*-$CF_3C_6H_4)_3$	82	94:6
17[f]	$Ni(COD)_2$	**L8**	P(*p*-$CF_3C_6H_4)_3$	74	94.5:5.5
18[f]	$Ni(COD)_2$	**L9**	P(*p*-$CF_3C_6H_4)_3$	80	94.5:5.5
19[f,g]	$Ni(COD)_2$	**L9**	P(*p*-$CF_3C_6H_4)_3$	88	94.5:5.5
20[f,g]	$Ni(COD)_2$	**L9**	P(*p*-$CF_3C_6H_4)_3$	96 (90)[j]	94.5:5.5
21[f,g,h,i]	$Ni(COD)_2$	**L9**	P(*p*-$CF_3C_6H_4)_3$	89 (**84**)[j]	**95:5**

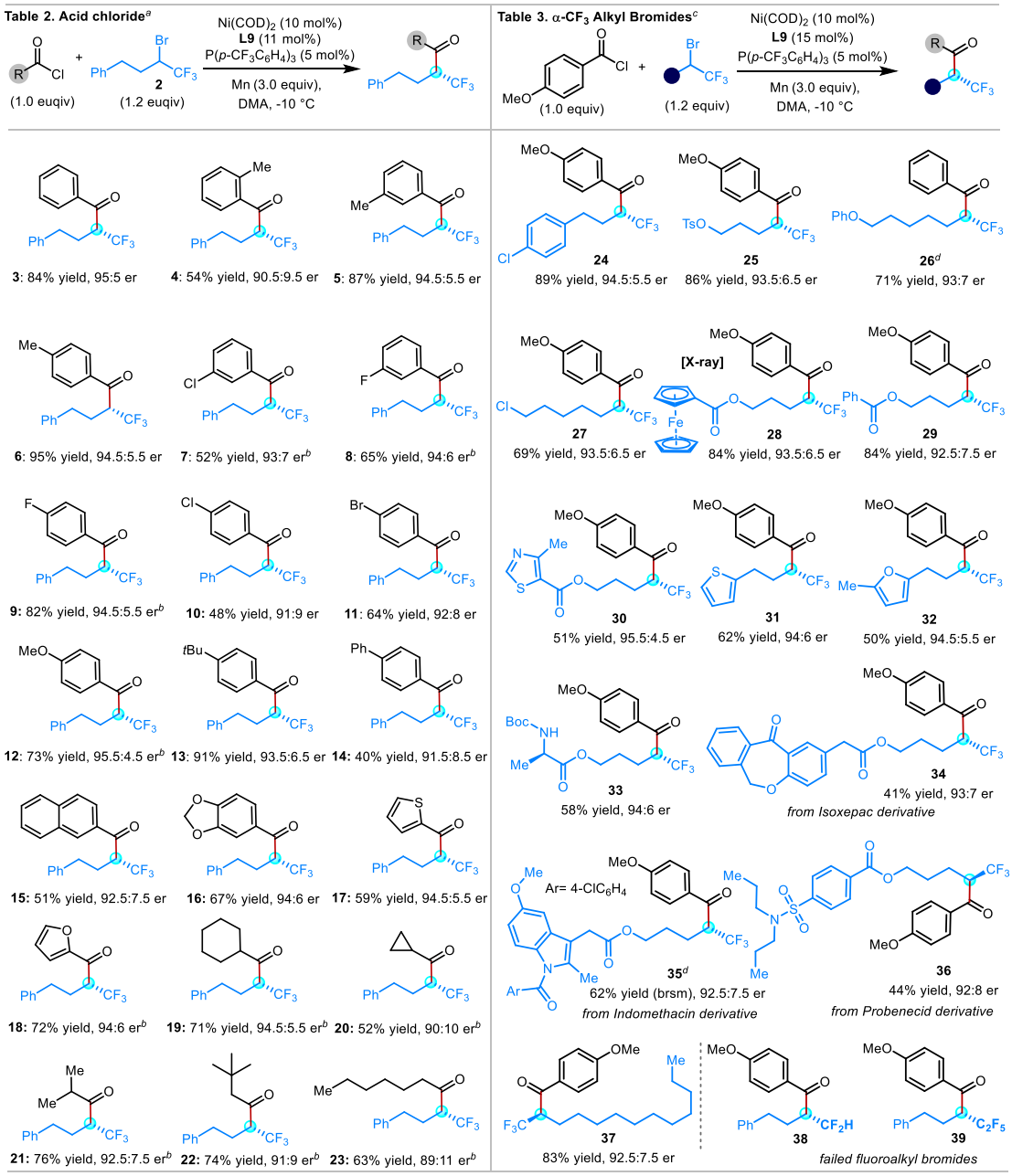
[a]**1** (0.10 mmol), **2** (0.10 mmol), 10 mol% nickel catalyst, 11 mol% ligand, Mn (0.30 mmol) in 2.0 mL of DMA at -10 °C. [b]Yields were determined by GC analysis with a calibrated internal standard. [c]Enantiomeric excess determined by HPLC on a chiral stationary phase. [d]Performed at room temperature. [e]Performed at 0 °C. [f]1.0 mL DMA was used. [g]1.2 equiv **2**

was used. [h]15 mol% **L9** was used. [i]5 mol% P(*p*-$CF_3C_6H_4)_3$ was used. [j]The yields in the parentheses were isolated.

Substrates Scope: With the optimized conditions in hand, we subsequently evaluated the generality of the developed protocol (Table 2). With respect to acid chloride coupling partners, aroyl chlorides bearing electron-donating (**4**-**6**, **9**, **12**, **13**, **16**), electron-withdrawing (**7**-**11**), and sterically demanding substituents (**4**, **15**, **16**) were suitable for the reductive coupling. Furthermore, various functional groups on aromatic rings such as fluoride, chloride, and bromide could be coupled with complete chemoselectivity (**7**, **8**, **10**-**12**), providing useful synthetic outlets for further elaboration. The catalytic coupling reactions with heteroaromatic acyl chlorides delivered the corresponding CF_3-containing product in good yields and enantioselectivities (**16**-**18**). It is worth emphasizing that the alkyl acid chloridescould be applied to smoothly forge the enantioenriched α-CF_3 substituted dialkyl ketones in good yields and enantiomeric excess (**19**-**23**). However, to our knowledge, this class of α-substituted chiral dialkyl ketones is highly challenging to access through classic enolate chemistry, mainly arising from the unpredictable site-selective enolization and mixed *E*/*Z* enolate formation.[15]

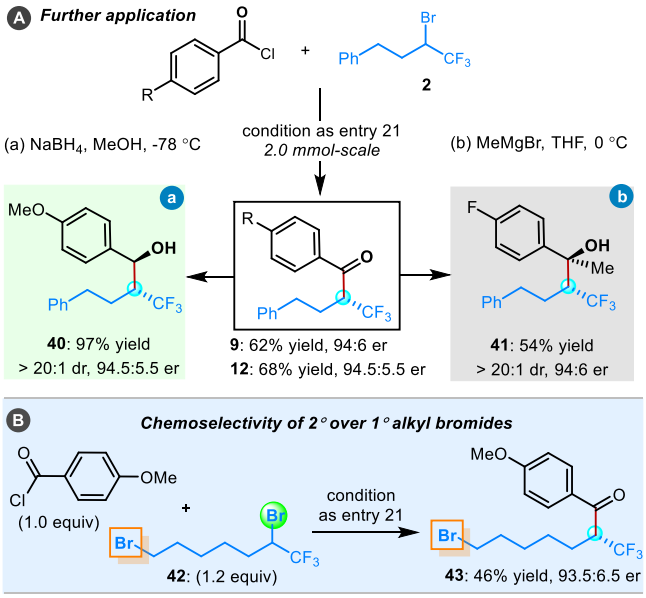
Next, the scope of the developed protocol was investigated against a broad range of α-trifluoromethylated alkyl bromides (Table 3). The alkyl bromides were functionalized with an array of valuable functional groups such as tosylate (**25**), ether (**26**), chloride (**27**), ester (**28**-**30**), and amino acid derivative (**31**), which were ideally compatible with the catalytic enantioselective coupling protocol. Notably, the heterocycles having potentially coordinating atoms furnished the desired α-CF_3 substituted ketones smoothly with a good enantiomeric excess (**30**-**32**). Finally, encouraged by the broad generality of this method, we envisioned that our developed asymmetric protocol might not only greatly simplify the synthesis of the simple enantiopure α-trifluoromethylated ketone building blocks but also be amenable to late-stage stereoselective modification of natural products, drug molecules, and amino acid derivatives. For example, α-CF_3 substituted alkyl bromides tethered to *D*-alanine, Isoxepac, Indomethacin, and Probenecid containing many functional groups (ketone, ester, amide, and sulfamide) could successfully give rise to chiral trifluoromethylated products in synthetically useful yields and good enantioselectivity (**33**-**36**). This protocol exhibits excellent chemoselectivity toward trifluoroalkyl bromide, whereas substrates with CF_2H and C_2F_5 groups failed to deliver the coupling products (**38** and **39**) under titled conditions.[16]

Table 2 and 3. Substrate Scope of Acid Chlorides and α-CF_3 Alkyl Bromides.



[a]Reaction conditions: acyl chloride (0.20 mmol), **2** (0.24 mmol), 10 mol% $Ni(COD)_2$, 11 mol% **L9**, 5 mol% P(*p*-$CF_3C_6H_4)_3$, Mn (0.60 mmol) in 2.0 mL of DMA at -10 °C for 10 hours under nitrogen. [b]15 mol% **L9** was used. [c]Reaction conditions: acyl chloride (0.20 mmol), **2** (0.24 mmol), 10 mol% $Ni(COD)_2$, 15 mol% **L9**, 5 mol% P(*p*-$CF_3C_6H_4)_3$, Mn (0.60 mmol) in 2.0 mL of DMA at -10 °C for 10 hours under nitrogen. [d]The reaction performed with benzoyl chloride using 20 mol% P(*p*-$CF_3C_6H_4)_3$ at 0 °C. [e]brsm: based on recovery of starting material trifluoroalkyl bromide (26%).

Figure 2: (A) Preparative-Scale Synthesis and Further Synthetic Transformations. (B) Example of Chemoselectivity Between 2° and 1° Alkyl Bromides.



To further showcase the synthetic utility of this coupling method, two examples of preparative-scale synthesis were conducted under the developed conditions in Figure 2, resulting in the formation of products **9** (R= F) and **12** (R= OMe) with good yields and enantioselectivity, respectively (Figure 2A). Furthermore, one of the notable features of the enantioenriched α-trifluoromethyl ketones is amenable to subsequent various practical synthetic transformations. Representatively, diastereoselective reduction by $NaBH_4$ and nucleophilic addition reactions of ketone with CH_3MgBr were separately performed in a single-step operation with ease, leading to the pharmaceutically useful enantioenriched β-trifluoromethylated secondary and tertiary alcohol (**40** and **41**) in good yields and excellent diastereoselectivity (dr > 20:1), and more notably, without any detectable erosion of enantiopurity in both courses. Of particular note is that this protocol displays excellent chemoselectivity of secondary alkyl bromide over primary alkyl bromide in C-C coupling under our developed conditions. A stunning example illustrates the notable chemoselectivity of this coupling method in Figure 2B (**42**→**43**). To summarize this part, this protocol is characterized by facile scale-up, exceptional chemoselectivity, and easily downstream chemistry towards the valuable chiral CF_3-containing products with structural complexity and diversity, thus enriching the chemical space and the alternative medicinal toolbox.

Mechanistic Studies: Next, we launched some control experiments to gain some insights into the reaction mechanism. Firstly, the radical inhibition experiment was performed to probe for the intermediacy of radical species through the treatment of **1** and **2** with an addition of TEMPO (2.0 equiv) under the conditions as entry 20. It was found that the reaction completely shut down the delivery of the desired product **3**, yet only gave rise to the TEMPO trapping adduct benzoyl-TEMPO **44** in 46% isolated yield (Figure 3a),[17] suggesting an alkyl radical might be highly involved in the catalytic cycle. Furthermore, the radical clock experiment was conducted upon the addition of α-cyclopropyl styrene (2.0 equiv) to the reaction of **1** and **2**, leading to the ring-opening expansion product **45** in 21% yield and 43% yield of coupling product **3** (Figure 3b). To summarize, these findings demonstrate that the catalytic cycle likely involves a radical pathway, and the oxidative addition of acid chlorides to the nickel(0) complex exists.[18] Additionally, The control coupling reaction of **1** and **2** under the conditions as entry 20 ($Ni(COD)_2$ as the catalyst) without using Mn reductant was carried out, yet failed to deliver the desired product **3**. Whereas the stoichiometric reaction of **1** and **2** with $Ni(COD)_2$ (1.0 equiv), **L8** (1.0 equiv), and P(*p*-$CF_3C_6H_4)_3$ (0.5 equiv) in the absence of Mn, smoothly furnishing the desired product **3** in 81% yield and 88% ee (Figure 3c). Taken together, these results indicated that 1) the Ni(0) species likely act as the actively competent catalyst and participate in the oxidation addition to acid chloride (also evidenced by the results in Figure 3a); 2) the reductant Mn was not necessary for reduction of alkyl bromides to generate alkyl radicals; however, 3) Mn was essential for the regeneration of catalytically active low valent nickel species from the related high valent nickel complex; 4) the generation of alkyl radicals likely proceeds by reducing alkyl bromides with low valent nickel.[10a,10b,18c] Although further studies are needed for understanding the details, at this stage, our findings support this coupling reaction would likely occur through a radical chain pathway involving the addition of alkyl radical to acyl-Ni(II) complex rather than a sequential reduction mechanism.[10b,12a]

Based on our mechanistic investigations and the precedent mechanistic understanding of the evoking open-shell species from the racemic alkyl halides in nickel catalysis.[10-13,19] A radical chain catalytic cycle for this asymmetric reaction was proposed, as depicted in Figure 4. The catalytic cycle initiates with selective oxidative addition of acid chloride to chiral bis-oxazoline ligated Ni(0) complex **I**, affording the resulting Ni(II)-acyl complex **II.** Subsequently, the generation of pentacoordinated high-valent nickel(III) complex **III** occurs by combining the cage-escaped secondary alkyl radical **VI** and a Ni(II)-acyl complex **II** through a radical addition pathway without the need for Mn reductant.[10a,20] Meanwhile, to account for (*R*)-

CF_3-containing stereogenicity formation, we proposed the stereoinduction model for the two equilibrating diastereomeric pentacoordinated nickel(III) complex **III** (Figure 5). The nickel catalyst complex Ni(**L9**)Br_2 was assigned by X-ray diffraction analysis. Rationally, compared to relatively smaller CF_3, the bulkier alkyl group would favorably point away from the phenyl substituent (red) on the chiral bis-oxazoline **L9** due to the reduced steric impulsion. On the other hand, due to diminished sterical hindrance between the hydrogen and Phenyl group (red), the smaller α-hydrogen of the CF_3 group would be preferentially located close to the phenyl substitute (red) after the sequential dissociation and recombination courses. Subsequently, this conformationally preferred nickel(III) complex **III** undergoes fast reductive elimination to furnish the experimentally observed (*R*)-**28** in a stereoconvergent manner,[20] as well as to release a corresponding nickel(I) complex **IV** that can engage the reduction of alkyl bromides to give rise to the secondary alkyl radical **VI** via halogen-atom abstraction or single-electron transfer.[10b,10e] Ultimately, the resulting Ni(II)BrCl complex **V** would be reduced to nickel(0) intermediate **I** by the Mn reductant, closing the catalytic cycle.[10a] The absolute configuration of the enantiomerically enriched product (*R*)-**28** was established via X-ray crystallographic analysis (Figure 5, right) that proved to be consistent with the proposed stereoinduction model under the chiral ligand **L9**, and the configurations of all other examples were assigned analogously.

Figure 3. Mechanistic Studies

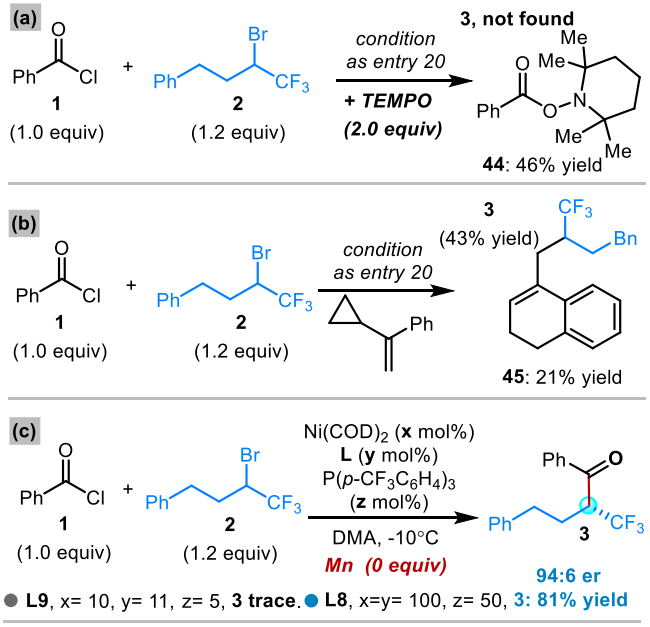


Figure 4. Proposed Radical Chain Mechanism.

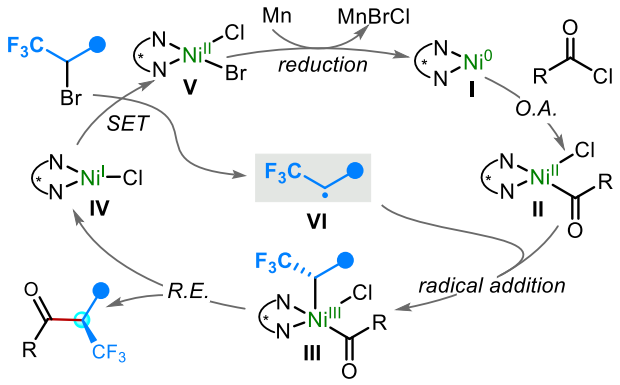
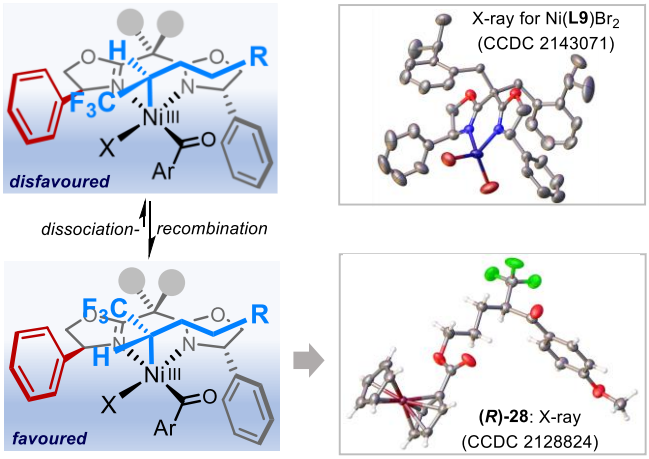


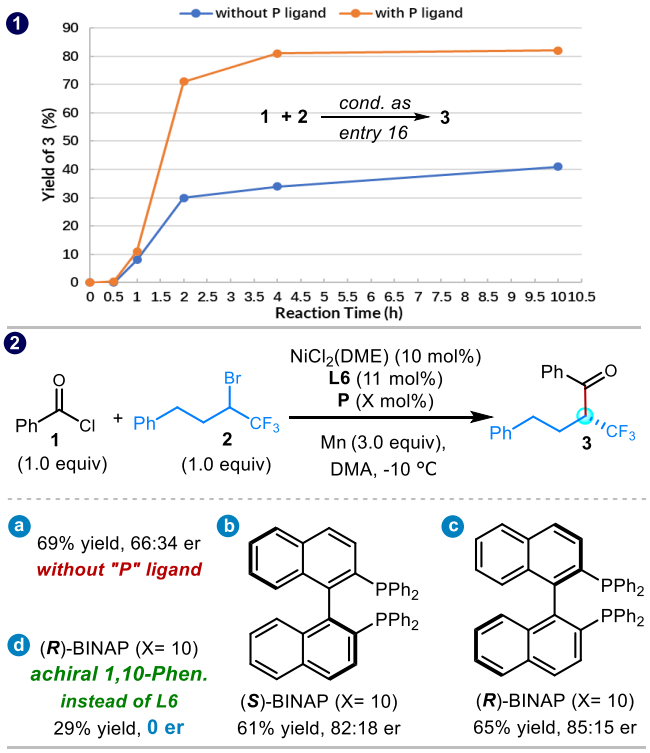
Figure 5. Stereochemical Model and X-Ray for the Products (*R*)-28 and Ni(L9)Br$_2$.



Given the important improvement of phosphine co-ligand for efficiency and enantiocontrol in this scenario, we conducted some control experiments to detail the investigations. Firstly, a series of chiral bis-oxazoline ligands (**L5-9**) were evaluated in the coupling reaction of **1** and **2** with and without phosphine ligand (PPh_3 or P(*p*-$CF_3C_6H_4)_3$), respectively (See the SI). And as expected, in all the cases, the reactions with a phosphine co-ligand indeed led to CF_3-containing products **3** with increased yields and improved enantiomeric ratios compared with that obtained without phosphine ligands under otherwise identical conditions. To further understand the positive effect of phosphine co-ligand, we conducted a collection of time-course reactions in the presence and absence of P(*p*-$CF_3C_6H_4)_3$, respectively (Figure 6.1). Astonishingly, the use of P(*p*-$CF_3C_6H_4)_3$ could not only sharply accelerate the reaction rate for generation of desired product **3** but also could vastly augment the yield and complete the catalytic cycle in a very short time (81% vs 34% yield for 4 hours). In this regard, we deep it possible that the suitable phosphine ligand may be acting as an ancillary ligand to the nickel complex and benefits the oxidative addition of acid chloride to the phosphine-ligated Ni(0) complex to generate sufficient Ni(II)-acyl

complex for the subsequent fast capture of the unstabilized *sec*-alkyl radical (Figure 4, **II** to **III**). This process is well-precedent to be highly critical for the radical chain mechanism in nickel catalysis.[10a,10b,18c] To probe the effect of phosphine co-ligand on the stereochemistry for the asymmetric reaction, the chiral phosphine ligands were evaluated in the reaction (Figure 6.2). For example, when the reactions, respectively, were subjected to the two opposite enantiomers (*S*/*R*) of chiral BINAP in the presence of chiral **L6**, both delivered product **3** with the identical absolute configuration (Figure 6.2a-c), thus indicating the phosphine ligands might not influence the absolute stereochemistry of the product during the catalytic process. Furthermore, upon treatment of the reaction using achiral 1,10-phenanthroline in combination with optically pure (*R*)-BINAP led to completely racemic product **3** (Figure 6.2d). Altogether, these results clearly demonstrated that the absolute stereochemistry over the coupling reaction was exclusively dictated by the chiral bis-oxazoline ligand but did not involve the engagement of the phosphine ligands. Even so, at this time, the exact role of the phosphine ligands in improving the yields and enantioselectivity still needs further clarification.[14] Nevertheless, the appropriately combinational use of the simple chiral ligand and readily available achiral ligand is of synthetically operational interest and accordingly unlocked an alternative technology for those challenging events in improving catalytic activity and asymmetric induction.

Figure 6. (1) Kinetic Studies: Time-Course Reactions. (2) Use of Chiral Phosphine Ligand in Combination with Chiral or Achiral N, N' Ligand.



Conclusion: In summary, a new general and modular entry to craft enantioenriched *α*-trifluoromethylated ketones by a nickel-catalyzed reductive cross-electrophile coupling in a stereoconvergent fashion has been established. The two employed electrophiles are easy-to-handle, readily available, and alternatively prepared from inexpensive precursors in simple operations. Notably, this protocol, without the assistance of directing group or stoichiometric chiral auxiliary, enables straightforward access to a variety of enantiopure α-CF_3 ketones under mild conditions, particularly α-CF_3 substituted dialkyl ketones that are admittedly difficult to access by conventional enolate chemistry. Moreover, the versatile ketone motif endows a robust handle for further structural elaborations with molecular complexity and diversity has been demonstrated. Interestingly, an appropriate choice of the phosphine ligand as a co-ligand plays an important role in the high efficiency and asymmetric induction, and preliminary mechanism investigations have demonstrated a radical chain mechanism for this coupling. Ultimately, we believe this powerful synthetic method will not only streamline the synthesis of enantioenriched α-CF_3 carbonyl compounds in a complementary new way but also stimulate and expedite the broad application in the discovery of new pharmaceuticals and agrochemicals because of the unique properties of alkyl-CF_3.[21]

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TOC Graphic: