Enantioselective Nickel-Catalyzed Reductive Decarboxylative C(sp^3)-C(sp^2) Cross-Coupling of Malonic Acid Derivatives

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Supporting Information Placeholder

ABSTRACT: The first enantioselective reductive decarboxylative C(sp^3)-C(sp^2) cross-coupling of malonic acid derivatives are reported via the intermediacy of redox-active esters (RAEs). A newly modified chiral bis-imidazoline ligand was identified as the optimal ligand to enable this reaction, providing direct access to valuable chiral α–aryl esters with high efficiency and excellent enantioselectivity. Our protocol is featured by its broad scope and exceptional compatibility with a variety of functional groups, even in the context of late-stage functionalization. In addition, C(sp^2)–I could be selectively functionalized with bromo(iodo)arene. The detailed mechanistic studies supported a radical based cross-coupling mechanism.

Malonic acid derivatives are ubiquitous in a myriad of biologically active natural products and pharmaceuticals, exemplified by L-γ-Carboxyglutamic acid, enloplatin, moxalactam, etc (Figure 1a).[1] Moreover, due to the high acidity of the α-protons in malonic acid or malonates, a variety of substitution reactions can be carried out, making it easy to obtain mono- or di-substituted malonic acid derivatives, as featured in the classic malonic ester synthesis.[2] Driven by these findings, chemists have recently been challenged to transform malonic acid derivatives into value-added enantioenriched compounds via asymmetric catalysis.[3] As such, the asymmetric decarboxylation of malonic acid derivates has emerged as a powerful tool for constructing chiral carbonyl compounds with stereogenic centers on either pronucleophiles or electrophiles, inspired by nature's biosynthesis of polyketides and fatty acids. A variety of chiral organocatalysts including thioureas, cinchona alkaloids, phosphoric acids, binaphthyl-based chiral amino ester, etc have been demonstrated to be highly stereoselective for a series of decarboxylative reactions such as protonation, aldol reaction, Mannich reaction , Michael addition and amination (Figure 1b).[4] There have also been reports of enantioselective decarboxylative nucleophilic addition reactions (e.g. aldol, 1,4-addition), in which chiral metal enolate intermediates have been generated by the extrusion of CO_2 from malonic acid derivatives (Figure 1b).[5] In addition, recent studies by the Huang group have shown that the chiral dinuclear zinc complex catalyzed desymmetrization of mono- and di-substituted malonic esters enable the construction of both quaternary and tertiary stereocenters with high enantioselectivity.[6] Despite these advances, practical asymmetric reactions with high levels of stereo-control on malonic acid derivatives substrates are still very rare, and a wide range of reactants remains to be explored.

This study was motivated by the recent explosion in transition metal-catalyzed decarboxylative cross-coupling reactions involving redox-active esters (RAEs) pioneered by Baran et al[7] and we aimed to devise a radical-based decarboxylation approach for the asymmetric transformation of malonic acid derivatives (Figure 1c). Contrary to the 2-e ionic approach (vide supra), the 1-e approach may allow access to a new chiral chemical space distinct from those previously reported. Despite this, the enantioselective control of the highly reactive carbon radical species remains a significant challenge.[8]

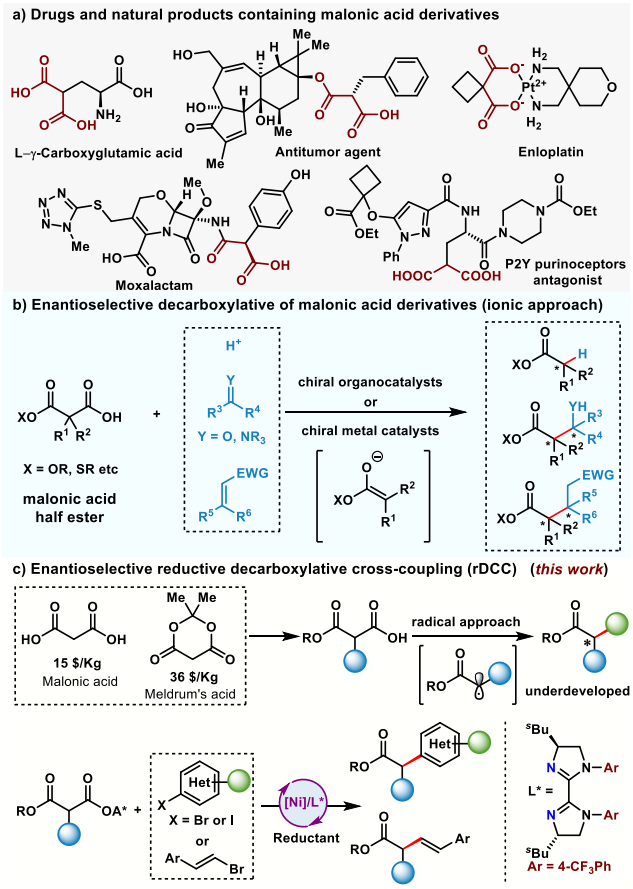


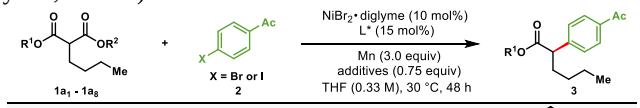
Figure 1. Enantioselective Decarboxylative Reaction of Malonic Acid Derivatives.

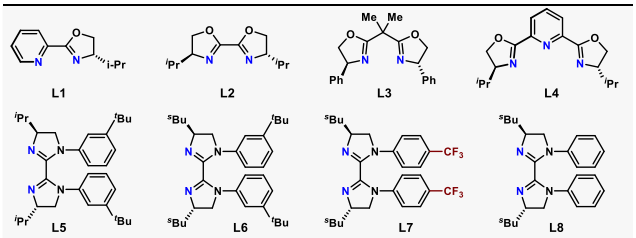
Among different conceivable scenarios, we envisioned that we could employ aryl/alkenyl halides as coupling partners to react with malonic acid-derived RAEs for forging sp^3–sp^2 architectures in an enantioselective manner. Compared to the traditional cross-coupling reactions using highly reactive organometallic reagents[9], this reductive cross-coupling strategy has many advantages due to its mild reaction conditions and compatibility with complex functionalized molecules.[10] Herein, we disclosed a nickel catalyzed reductive decarboxylative arylation/ alkenylation of malonic acid-derived RAEs that are easily prepared from feedstocks (malonic acid, ~15$/Kg and Meldrum's acid, ~36$/Kg) using a newly modified 4-CF_3-phenyl substituted chiral bis-imidazoline ligand (Figure 1c).

We commenced our study by evaluating the enantioselective reductive decarboxylative cross-coupling (rDCC) reaction of *n*-butyl substituted malonic acid-derived RAE (**1a**$_1$) with 4-acyl aryl bromide (**2a)** in the presence of Ni(II) catalyst and Mn reductant (Table 1). Extensive screening of various reaction parameters revealed that the nature and substitution pattern of the ligand backbone were critical for both reactivity and stereoselectivity. Specifically, while Pyrox (**L1**) gave the desired product in a promising yield (37%), the product was almost racemic (entry 1). To our delight, the BiOX (**L2**) ligand which was developed by Reisman group and phenyl substituted BOX (**L3**) ligand could significantly improve the enantioselectivity, furnishing the product in both 85:15 er although the yields decreased to 16% and 6% respectively (entry 2, 3). Tridentate chiral ligand (**L4**) proved to be much less effective (entry 4). Then we switch to chiral bis-imidazoline (BiIM) ligand scaffolds given their nature of electron-rich and easy modification on both electronics and sterics. Gratifyingly, when N-3-^{t}BuPh-^{i}PrBiIM (**L5**) was used as ligand, the desired product **3** was obtained in 23% yield with 82:18 er. More steric hindered ligand (**L6**) gave a better yield and enantioselectivity. After a careful survey of the substituents on the phenyl ring (see SI for a full listing of chiral ligands), we found electron-withdrawing group CF_3 to be optimal, affording **3** in 36% yield and 86:14 er (entry 7, 8).

With the optimal chiral ligand in hand, we started the extensive screening of other reaction parameters. Remarkably, when changing the ester OR^1 substituent from Et to ^{t}Bu (**1a**$_2$), the enantioselectivity was increased to 96:4, but unfortunately the yield was only 6%. We speculated that the main hydrodecarboxylation byproduct might be attributed to the reactivity of RAEs. After evaluating various NHP esters (**1a**$_3$-**1a**$_8$), we were pleased to find that 2,3-naphthalimide substituted NHP ester (**1a**$_7$) improved the yield to 25% without affecting the enantioselectivity (entry 10-15). Among different additives that we screened (entry 16-19), KI gave the best result (82% yield, 96:4 er). Control experiments indicated that nickel catalyst and Mn reductant were both crucial to promote this reaction (entry 20, 21). Finally, the 4-acyl aryl iodide could also participate in this reaction when employing TBAI as additives, giving the same product in 76% yield, 96:4 er (entry 22).

Encouraged by these findings, we next turned our attention to exploring the scope of this enantioconvergent rDCC reaction with a variety of malonic acid-derived RAEs (Table 2). To our delight, this reaction was found to be compatible with many RAEs bearing different α–substituents. For example, the α–methyl and α–3-phenylpropyl substituted malonic acid derivates underwent the reaction smoothly, providing the desired products in good yields and high ers (**4**, **5**). The α–benzyls (**6**-**8**), naphthyl (**9**) and heterocyclic substituents (**10**, **11**) were also tolerated despite diminished yields and ers were obtained for these products (**6**-**11**). The absolute configuration of **8** was unambiguously confirmed by X-ray crystallographic analysis. The compatibility of naphthyl and heterocycles is a valuable feature that remains problematic for enantioselective reductive cross-coupling reactions.[10p] More importantly, labile functional groups such as OBz, Cl, CN, terminal and internal alkenes did not affect the reaction and moderate to good yields and high ers were observed (**12**-**16**). Moreover, our enantioselective rDCC reaction could be extended to α–secondary substituents including isopropyl, cyclobutyl, N-Boc-3-azetidinyl and cyclopentyl with equal ease (**17**-**20**), enabling the formation of chiral ester products containing secondary-secondary sp^3 C–C linkages with excellent enantioselectivities. Finally, switching ester OR group from ^{t}Bu to 1-methylcyclohexyl, the reaction still proceeded well (**21**, 68% yield, 97:3 er).





Entry	1a	Ligand	Additive	Yield (%)[b]	Er (%)[b]
1	1a$_1$	**L1**	$MgCl_2$	37	51:49
2	1a$_1$	**L2**	$MgCl_2$	16	85:15
3	1a$_1$	**L3**	$MgCl_2$	6	85:15
4	1a$_1$	**L4**	$MgCl_2$	8	64:36
5	1a$_1$	**L5**	$MgCl_2$	23	82:18
6	1a$_1$	**L6**	$MgCl_2$	30	84:16
7	1a$_1$	**L7**	$MgCl_2$	36	86:14
8	1a$_1$	**L8**	$MgCl_2$	32	81:19
9	1a$_2$	**L7**	$MgCl_2$	6	96:4
10	1a$_3$	**L7**	$MgCl_2$	10	95:5
11	1a$_4$	**L7**	$MgCl_2$	10	91:9
12	1a$_5$	**L7**	$MgCl_2$	6	95:5
13	1a$_6$	**L7**	$MgCl_2$	5	95:5
14	1a$_7$	**L7**	$MgCl_2$	25	96:4
15	1a$_8$	**L7**	$MgCl_2$	n.d.	--
16	1a$_7$	**L7**	TMSCl	30	87:13
17	1a$_7$	**L7**	TBAI	<5	--
18	**1a$_7$**	**L7**	**KI**	**82**	**96:4**
19	1a$_7$	**L7**	-	20	95:5
20[c]	1a$_7$	**L7**	KI	n.d.	--
21[d]	1a$_7$	**L7**	KI	30	94:6
22[e]	1a$_7$	**L8**	TBAI	76	96:4

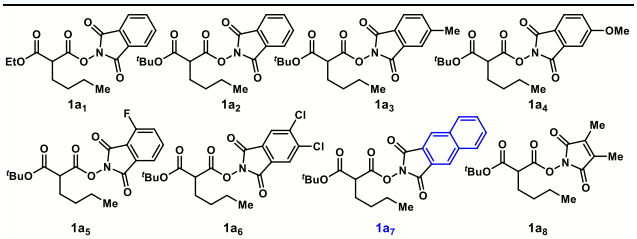
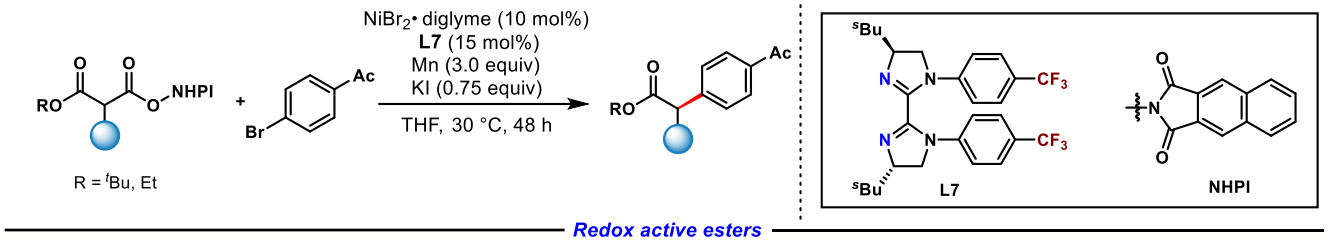
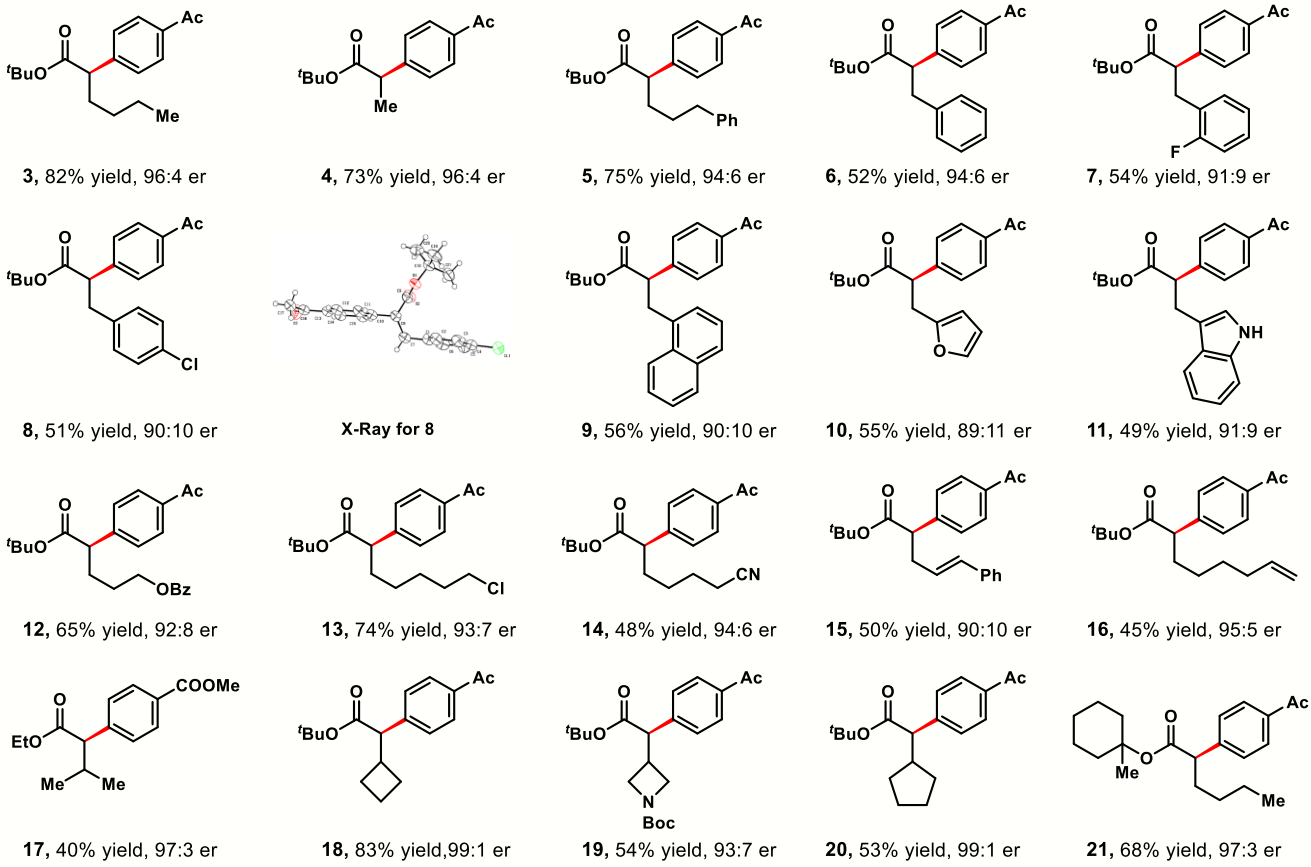


Table 1. Optimization of the Reaction Conditions.[a,b]
Reaction conditions: [a]**1** (0.25 mmol), **2** (0.1 mmol), $NiBr_2$·diglyme (10 mol%), **L** (15 mol%), Mn (3.0 equiv), additives (0.75 equiv), THF (0.33 M), 30 °C, 48 h. [b]Isolated yields, er values were determined by HPLC analysis. [c]No Ni catalyst. [d]Zn instead of Mn. [e]$NiCl_2$·DME (10 mol%), **L8** (15 mol%), TBAI (2.0 equiv) instead of KI.

Table 2. Scope of Malonic Acid Derivatives. [a]



Redox active esters



[a] Yields of isolated products are indicated in each case; reaction conditions: redox active esters (0.25 mmol, 2.5 equiv), aryl bromide (0.1 mmol, 1.0 equiv), $NiBr_2$·diglyme (10 mol%), **L7** (15 mol%), Mn (0.3 mmol, 3.0 equiv), KI (0.075 mmol, 0.75 equiv), THF (0.33 M), 30 °C, 48 h.

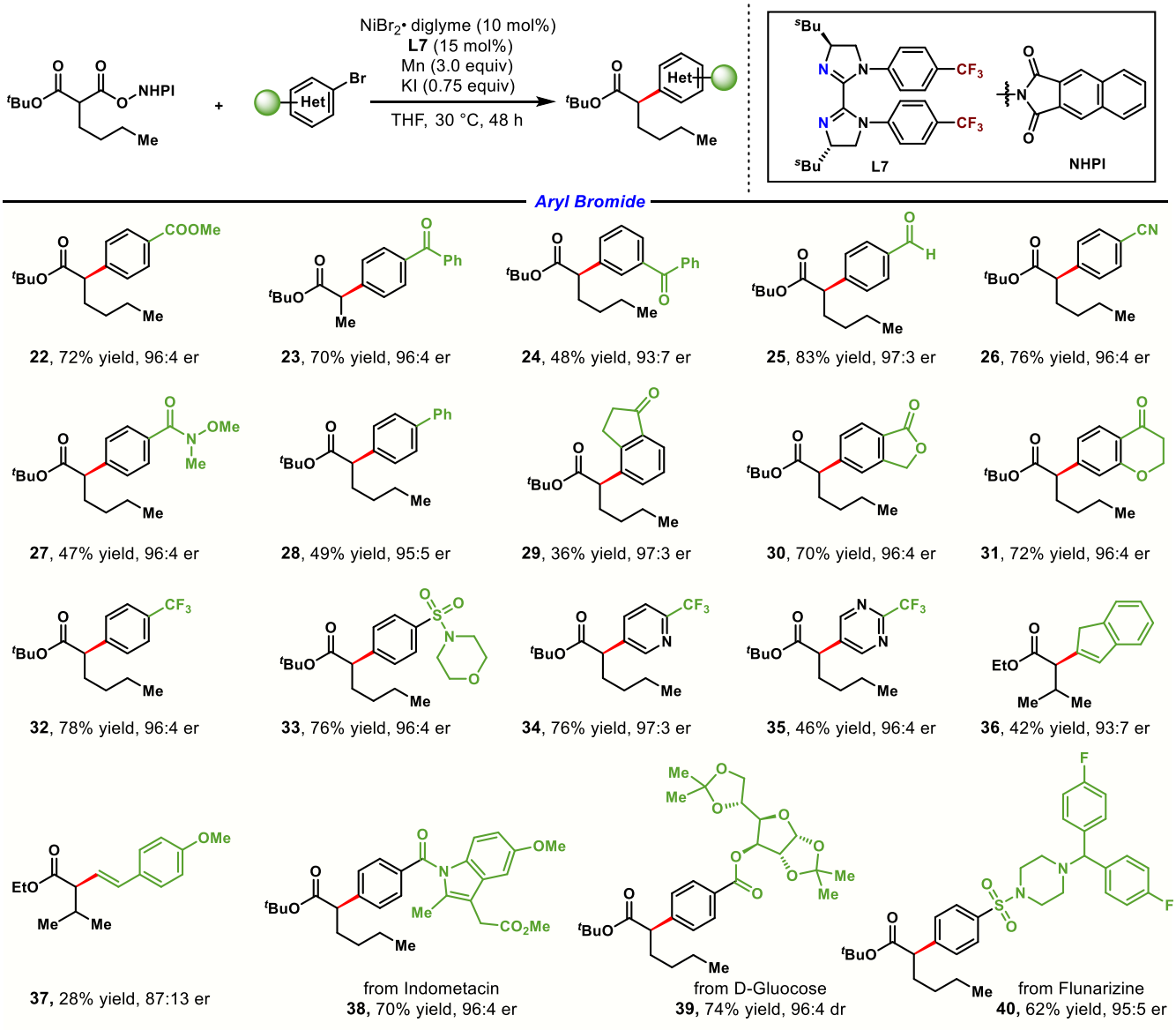
Next, we evaluated the scope of the aryl bromide coupling partners (Table 3). Aryl bromides with electron-withdrawing groups such as ester (**22**), ketones (**23, 24, 29, 31**), aldehyde (**25**), cyanide (**26**), Weinreb amide (**27**), phenyl (**28**), lactone (**30**), trifluoromethyl (**32**), sulfonamide (**33**) and even heteroaryl bromides (**34, 35**) exhibited good enantioselectivities (93:7 to 97:3 er). Notably, alkenyl bromides could also be coupled with α–isopropyl substituted ethyl malonate derived RAE, affording the corresponding products in synthetically useful yields and ers (**36**, **37**). To further demonstrate the potential utility of our method in complex settings, we applied this reaction to the derivatization of complex drug molecules, providing chiral esters in 62-74% yield and 95:5-96:4 ers (**38-40**). Aryl iodides exhibited broader scope than the aryl bromide congeners as both electron-deficient and electron-rich functional groups were all well-accommodated, furnishing the decarboxylative arylation products in good yields and high levels of enantioselectivities (Table 4). The electron rich drug fragment from Empagliflozin and Gemfibrozil could be incorporated into the chiral ester products as well (**51**, **52**).

In order to understand the nature of the reactive intermediate and elucidate the possible mechanism, detailed mechanistic studies were undertaken. Firstly, the target reaction was completely inhibited by TEMPO and the TEMPO adduct was detected by HRMS (Figure 2a). Moreover, the radical probe experiment with 1,1-diphenylethylene was conducted where the yield of **3** was decreased to 37% and the radical-trapped adduct was observed by HRMS as well (Figure 2b). In addition, when **2a** was reacted with radical clock substrate **1f**, cyclized product **55** was obtained as in mixture of diastereomers (20% yield, 1.6:1 dr) (Figure 2c). These results indicate that a radical intermediate is likely involved in this enantioselective cross-coupling process. Competing experiments between electron-poor and electron-rich aryl iodides were also carried out. Both 4-acyl and 4-SMe aryl iodides could participate in this reaction and the ratio of the product distribution was 2.3:1 with **3** as the major product (Figure 2c). The precatalyst **[Ni complex]-1** was prepared by mixing **L7** with $NiBr_2$·glyme in THF at room temperature and it was characterized by X-Ray crystallography analysis. The X-ray structure confirms that **[Ni complex]-1** is a

neutral octahedral mono-nuclear Ni^{II} complex consisting of two bis-imidazoline ligands. The reaction using **[Ni complex]-1** as catalyst could afford **3** in 67% yield, 96:4 er (Figure 2d). Although **[Ni complex]-1** shows both good reactivity and high enantioselectivity for this reaction, a linear relation-ship between the enantiomeric excess of chiral ligand and enantiomeric excess of product (**3**) was observed, suggesting that the catalytic active species might be a monomeric Ni complex bearing a single chiral ligand (Figure 2e).

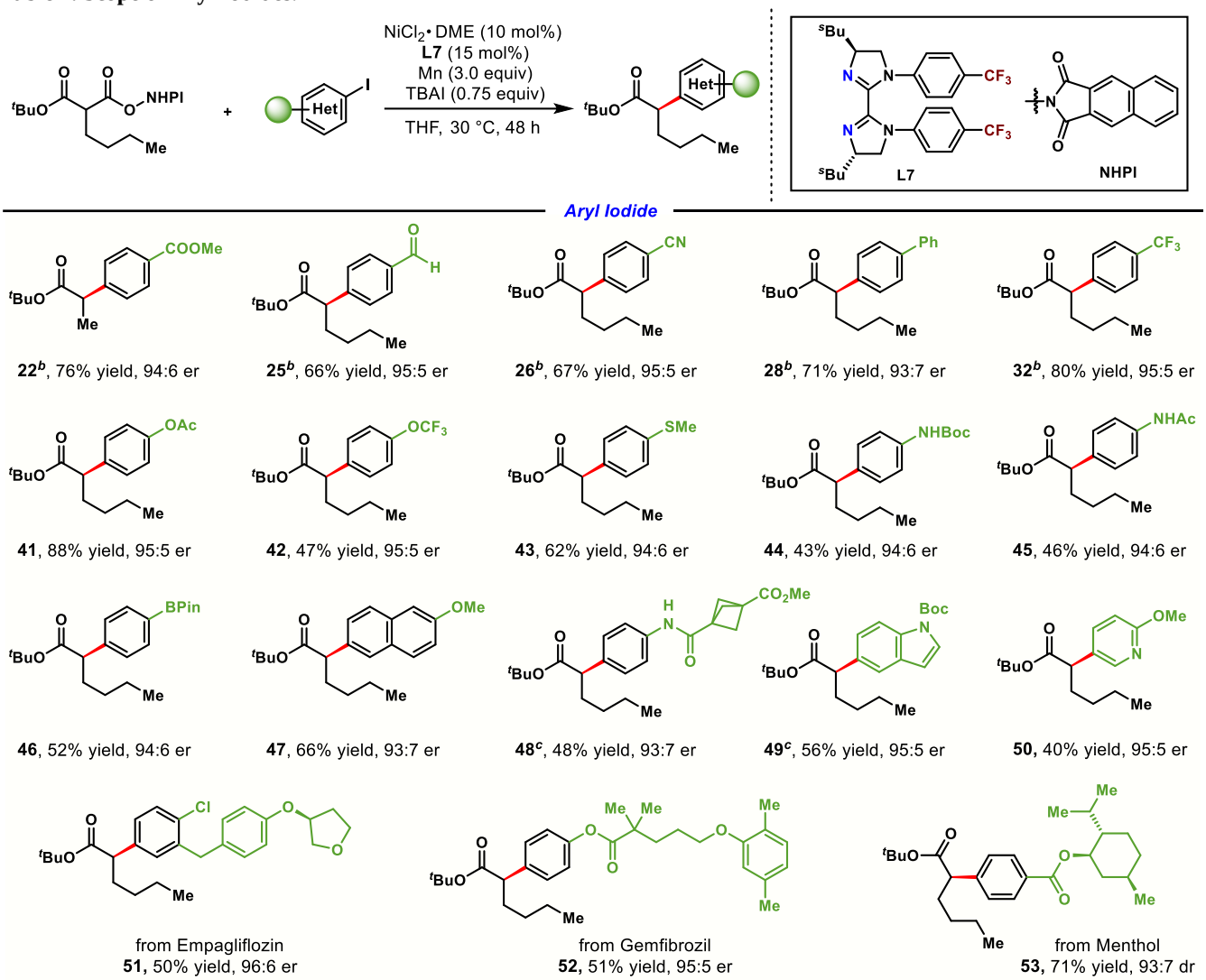
As shown in Figure 3a, our reaction could be scaled up without an erosion in enantioselectivity. Considering both aryl bromides and aryl iodides could be coupled in this reaction, we were wondering if $C(sp^2)$-I and $C(sp^2)$-Br could be distinguished if they are present on the same aromatic ring. If successful, such a scenario would offer an opportunity to rapidly increase the molecular complexity via iterative and programable asymmetric cross-coupling strategy. Gratifyingly, treating 1-bromo-4-iodobenzene (**2c**) and **1b** with the standard conditions but using Zn powder as reductant, the enantioselective rDCC reaction proceeded to give **56** with good $C(sp^2)$−I selectivity (10:1) and high enantioselectivity (94:6 er). Notably, **56** could be readily converted to nonsteroidal anti-inflammatory drug (NSAID) Ibuprofen (Figure 3b).[11] Derivatization of the chiral α–aryl ester products were also examined using **16** to further demonstrate the synthetic potential of this reaction (Figure 3c). For example, the ester functional group could be hydrolyzed into carboxylic acid and further coupled with an dipeptite, furnishing **59** in high yield and high level of stereoselectivity. Treating **16** with mCPBA afforded the epoxidation product **60** in 82% yield, 2:1 dr. In addition, the successful preparation of diol compound **61** from **16** was achieved by reduction of ester and ketone group simultaneously with $LiAlH_4$ (Figure 3c).

Table 3. Scope of Aryl Bromides.[a]



Yields of isolated products are indicated in each case; reaction conditions: [a] redox active esters (0.25 mmol, 2.5 equiv), aryl bromide (0.1 mmol, 1.0 equiv), $NiBr_2$·diglyme (10 mol%), **L7** (15 mol%), Mn (0.3 mmol, 3.0 equiv), KI (0.075 mmol, 0.75 equiv), THF (0.33 M), 30 °C, 48 h.

Table 4. Scope of Aryl Iodides.[a]



Yields of isolated products are indicated in each case; reaction conditions: [a] redox active esters (0.25 mmol, 2.5 equiv), aryl iodide (0.1 mmol, 1.0 equiv), $NiCl_2$·DME (10 mol%), **L7** (15 mol%), Mn (0.3 mmol, 3.0 equiv), TBAI (0.075 mmol, 0.75 equiv), THF (0.33 M), 30 °C, 48 h. [b] **L8** (15 mol%) and TBAI (2.0 equiv) were used. [c] $NiCl_2$·DME (20 mol%), **L7** (30 mol%).

In summary, we describe herein an enantioselective protocol for the decarboxylative cross-coupling of malonic acid derived RAEs with both (hetero)aryl/ alkenyl bromides and (hetero)aryl iodides. This reaction is enabled by a newly modified chiral bis-imidazoline ligand and features simple experimental operations, mild conditions as well as broad scope and generality across a wide range of functional groups, providing chiral α–arylated esters products in good yields and high enantioselectivities. Moreover, mechanistic studies revealed that a radical intermediate was involved in this reaction, making it distinct from previously reported 2-e decarboxylative approach of malonic acid derivatives.

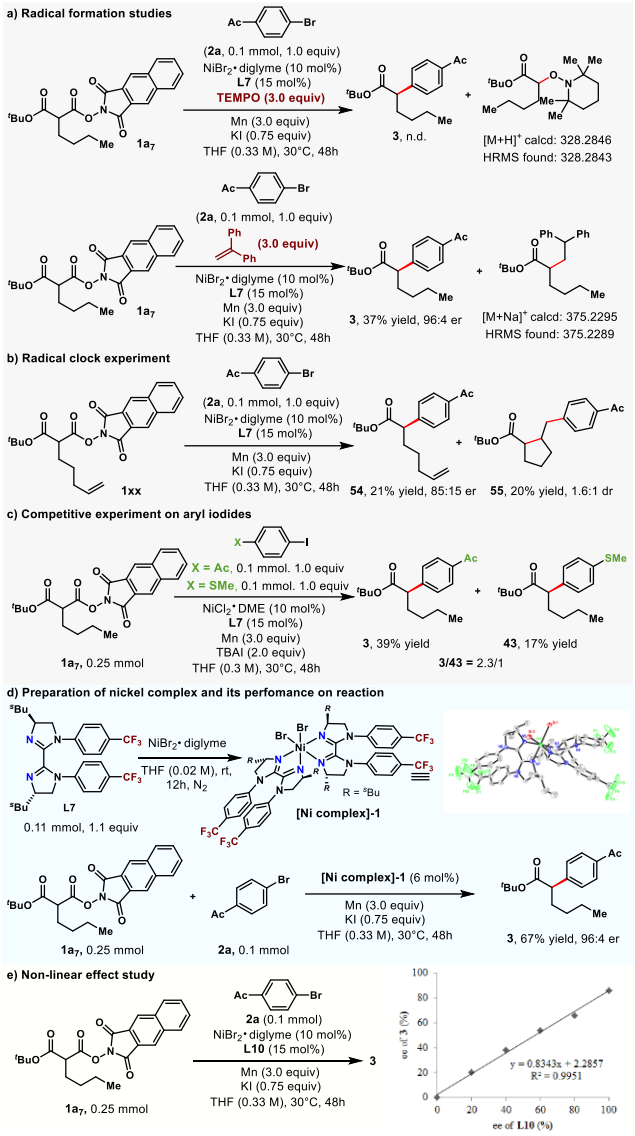


Figure 2. Mechanistic studies.

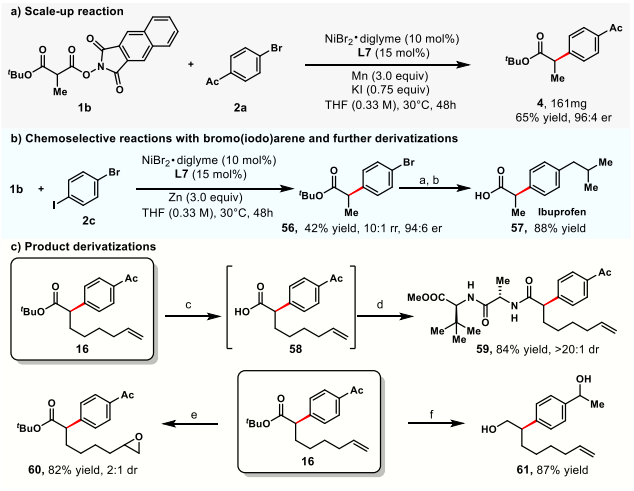


Figure 3. Synthetic Applications.

Reaction conditions for product derivatizations: [a]*i*-BuZnBr, 2 mol% $Pd(dba)_2$, 2 mol% Qphos, THF, 55°C, 1h. [b]TFA, DCM, 23°C, 45h. [c]TFA (10.0 equiv), DCM (0.1 M), rt. [d]HATU (1.2 equiv), DIPEA (3.0 equiv), dipeptide hydrochloride (1.2 equiv), DCM (0.1 M), 0 C to rt. [e]mCPBA (2.0 equiv), $NaHCO_3$ (3.0 equiv), DCM (0.1 M), rt. [f] LiAlH4 (6.0 equiv), THF (0.1 M), 0 °C to rt.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The Supporting Information contains all experimental procedures, analysis, and compound characterization data.

Author Contributions

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Notes

The authors declare no competing financial interest.

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