Ni-Electrocatalytic Enantioselective Doubly Decarboxylative C(sp^3)-C(sp^3) Cross Coupling

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ABSTRACT: The first examples of enantioselective doubly decarboxylative cross coupling are disclosed. Malonate half amides are smoothly coupled to a variety of primary carboxylic acids after formation of the corresponding redox-active esters under Ni-electrocatalytic conditions using a new chiral ligand based on PyBox resulting in amides with α-alkylated stereocenters. The scope of the reaction is broad tolerating numerous functional groups and uniformly proceeds with high ee. Finally, the potential utility of this enantioselective radical-radical reductive cross coupling to simplify synthesis is demonstrated with numerous case studies.

The enantioselective α-alkylation of carbonyl compounds is a staple transformation in organic synthesis that has been widely studied.[1] With regards to ester and amide alkylation, the use of chiral auxiliaries is still commonplace due to the predictable outcomes and practical ease with which diastereomers can be separated.[2] Such an approach is also intuitive as it takes advantage of polar-bond analysis resulting in an enolate nucleophile reacting with an alkyl halide electrophile. In 1983, Frejd reported a different approach wherein an electrophilic α-halocarbonyl compound could be cross coupled with an aryl zinc nucleophile via Ni catalysis.[3] In 2005, the Fu group reported an enantioselective variant of such a reaction setting the stage for a number of advances in catalytic enantioselective access to α-alkylated ester and amide derivatives (Figure 1A).[4] Indeed, numerous studies built off of those seminal findings to combine electrophilic ester and amide derivatives with olefins under Ni-catalysis (Figure 1A).[5-7] In 2022, the Fu group further demonstrated that in situ generated Reformansky-type reagents could be coupled to alkyl halides in enantioselective fashion (Figure 1B).[8] Recent findings from the Xu group have subsequently demonstrated that two electrophiles such as α-halo boronic esters and alkyl halides could also be coupled with high enantiocontrol under photoreductive conditions (Figure 1C).[9] Meanwhile, doubly decarboxylative cross coupling (dDCC) has emerged as a powerful method to construct Csp^3-Csp^3 bonds under electrochemical conditions (with and without Ni, Figure 1D).[10-12] In this Communication, the first examples of enantio- and diasteroselective dDCC between redox-active esters (RAEs) derived from readily available alkyl carboxylic acids and malonate derivatives are disclosed.[13] This Ni-electrocatalytic reaction is simple to conduct, uses inexpensive components, and demonstrates a wide substrate scope. Its tactical application results in a significant reduction in step count in a variety of different contexts.[14]

The development of enantioselective dDCC required extensive screening of conditions and ligands, some of which is

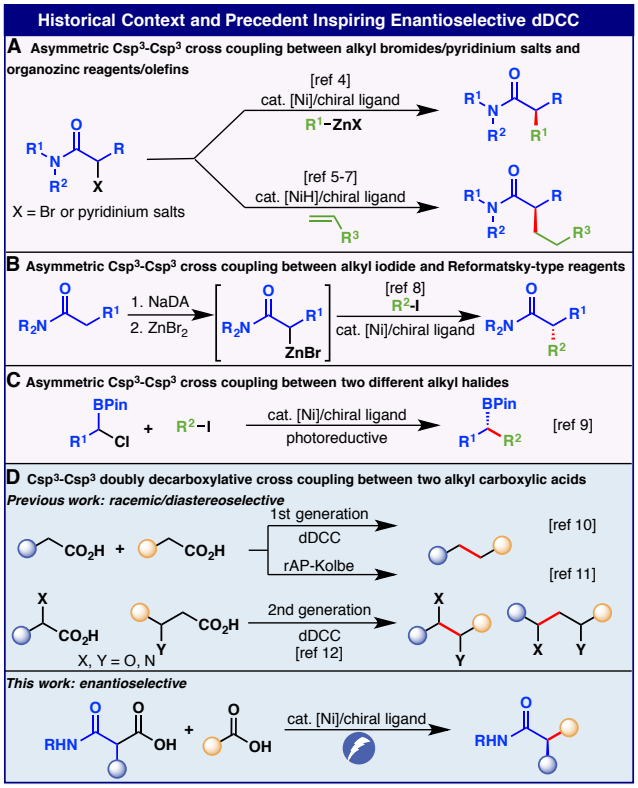
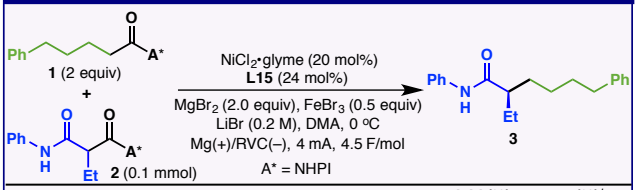


Figure 1. Historical Context and Precedent Inspiring Enantioselective dDCC

summarized in Table 1 using RAEs **1** and **2**. The final optimized conditions utilized $NiCl_2$•glyme (20 mol%), chiral ligand **L15** (24 mol%), $MgBr_2$ (2.0 equiv.), $FeBr_3$ (0.5 equiv.), and LiBr (0.2 M) as the electrolyte in DMA (0.04 M) at 0 °C, affording **3** in 54% isolated yield and 90% ee after 3 hours of electrolysis (0.1 mmol scale, Mg anode and RVC cathode). In contrast, either 1st [10] or 2nd [12] generation dDCC condition proved to be much less effective (Table 1, entries 2 and 3). In terms of additives, $MgBr_2$ appeared to be crucial for this reaction whereas $MgCl_2$ gave similar yield and much lower **Table 1. Reaction Development**

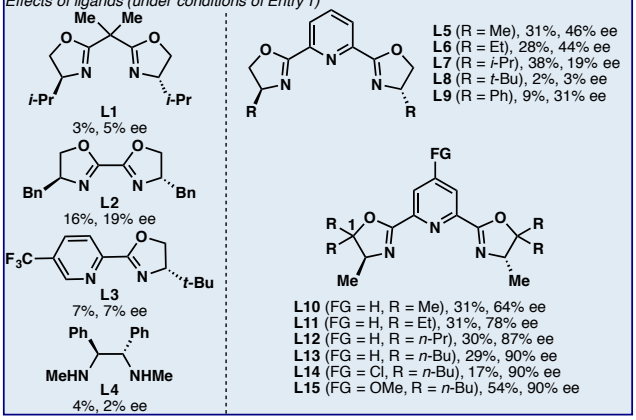
and **Optimization**[a,b,c,d]

Reaction Development and Optimization



entry	deviation from above	yield (%)[a]	ee (%)[b]
1	none	54[c]	90
2	1st generation (ref 10), using L15 as ligand	3	16
3	2nd generation (ref 12), using L15 as ligand	15	77
4	$MgCl_2$ instead of $MgBr_2$	52	64
5	$MgBr_2$•Et_2O instead of $MgBr_2$	31	86
6	$FeBr_2$ instead of $FeBr_3$	28	87
7	NMP instead of DMA	32	82
8	$TBAPF_6$ instead of LiBr	20	88
9	rt instead of 0 °C	47	87
10	A* = TCNHPI	< 5	n.d.[d]
11	no $NiCl_2$•glyme	< 5	n.d.
12	no L15	< 5	n.d.
13	no $FeBr_3$	46	82
14	no $MgBr_2$	24	90
15	no electricity	< 5	n.d.
16	Zn, Mn instead of electricity	< 5	n.d.

Effects of ligands (under conditions of Entry 1)



[a]Yields determined by GC-MS analysis. [b]ee values determined by chiral SFC analysis. [c]Isolated yield. [d]Not determined.

ee, and $MgBr_2$•Et_2O only provided 31% **3** (Table 1, entries 4 and 5). Replacing $FeBr_3$ with $FeBr_2$ also led to inferior results (Table 1, entry 6). Changing other parameters such as solvent, electrolyte and temperature resulted in unsatisfactory outcomes (Table 1, entries 7–9). In addition, TCNHPI-based RAEs proved to be too reactive under these conditions, undergoing unmediated cathodic reduction without affording desired cross-coupled product (Table 1, entry 10). A series of control experiments indicated that nickel catalyst, ligand and electricity were crucial to promote this reaction, while $MgBr_2$ and $FeBr_3$ were indispensable components to ensure its efficiency (Table 1, entries 11–16).

The ligands had a substantial effect on the outcome of this reaction. As observed in our previous report,[10] tridentate ligands proved to be superior to bidentate analogues in the Ni-catalyzed Csp^3–Csp^3 dDCC reaction. For example, bidentate ligands with different backbones (**L1**–**L4**) all gave very poor yield and ee. To our delight, preliminary screening of PyBox ligands provided promising results, and the use of **L5** gave **3** in 31% yield and 46% ee. Further modification of **L5** revealed that alkyl chain substituents at the C-1 position dramatically improved enantioselectivity (**L10**–**L13**). Final adjustment of the C-4 substituent of the pyridine ring increased the yield without loss of enantiopurity.

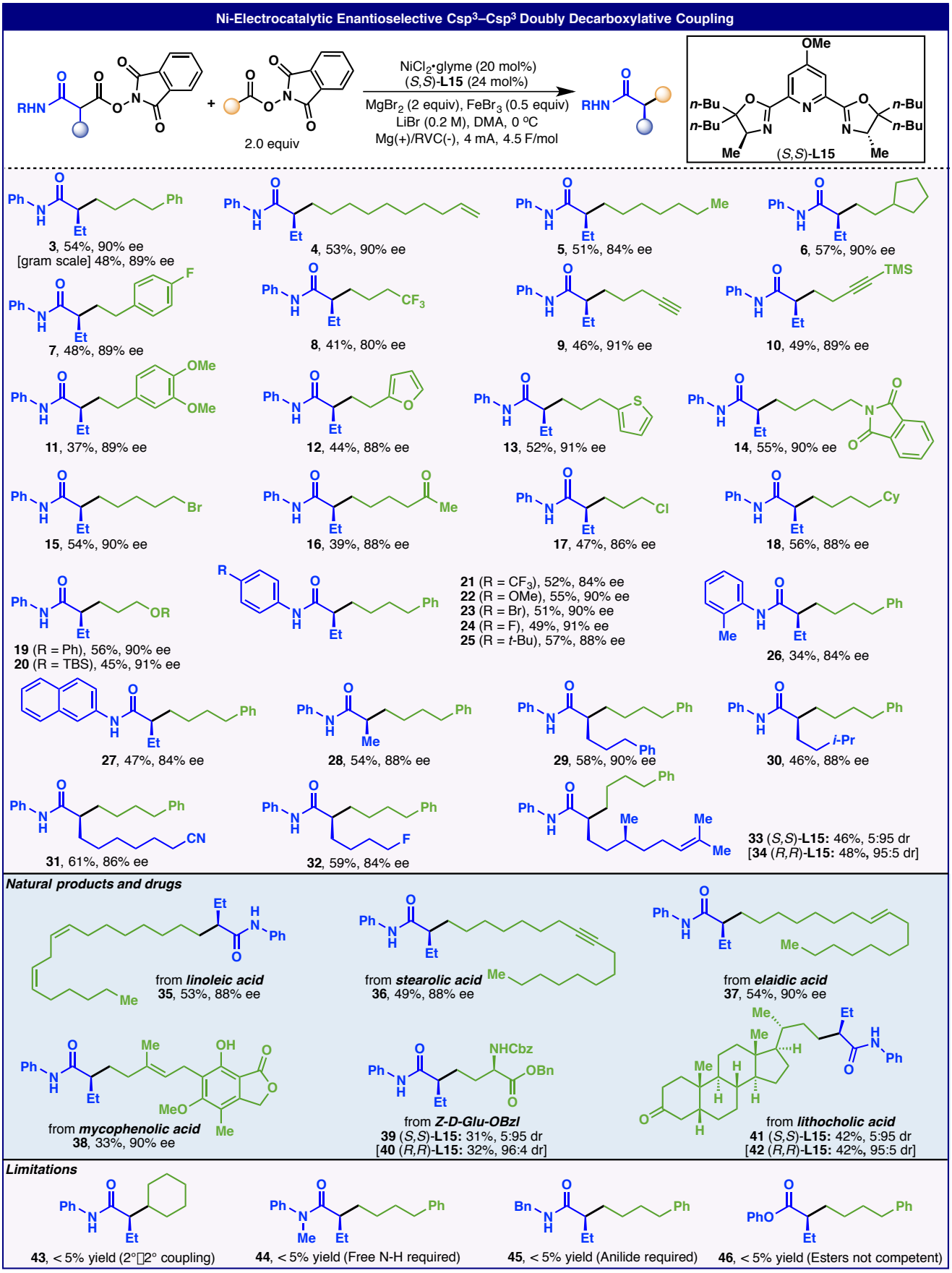
With the optimal conditions in hand, the scope of enantioselective doubly decarboxylative Csp^3-Csp^3 cross coupling was investigated, as shown in Table 2. A vast array of RAEs derived from readily available alkyl carboxylic acids were tested. Aside from simple alkyl chains (**3**, **5**, **6**, **18**), a broad range of functional groups could be tolerated, such as terminal alkenes (**4**), internal alkenes (**35**, **37, 38**), trifluoromethyl group (**8**), terminal alkynes (**9**), internal alkynes (**10**, **36**), alkyl halides (**15**, **17**), aryl halides (**7**), ketones (**16, 41, 42**), silyl ethers (**20**), ethers (**11**, **19**), imides (**14**), heterocycles (**12**, **13**), lactones (**38**), carbamates (**39**, **40**), and esters (**39**, **40**). Several RAEs derived from malonate derivatives were also explored ranging from various substitutions on the phenyl ring (**21**-**27**) to substrates containing alkyl fluorides (**32**), nitriles (**31**) and internal alkenes (**33**, **34**). Even with pre-existing stereocenters, the reaction can be programmed to access diastereomers with high control (**33**, **34**, **39**, **40**, **41** and **42**). With the exception of compounds **27** and **28**, none of these structures have been prepared before. However, several related derivatives of some of these molecules (**3**, **6**, **7**, **14**, **16**, **17**, **19** and **20**) have been synthesized in racemic form, often through laborious routes (see SI for graphical comparison).

It is worth noting that compound **3** has been prepared on a gram scale with no significant reduction in both yield and enantiopurity. With regard to limitations, coupling of **2** and secondary alkyl carboxylic acids was unsuccessful (**43**). As for the malonate-derived RAEs, the secondary aryl amide group proved to be critical as evidenced by the fact that the corresponding analogs containg tertiary amides (**44**), secondary aliphatic amides (**45**) and esters (**46**) all gave unproductive results.

The enantioselective dDCC outlined herein can be applied to simplify the synthesis of both medicinally important structures and intermediates employed in natural product total synthesis (Figure 2). For instance, the bile-acid derivative **49** (Figure 2A) was previously prepared from commercial hyodeoxycholic acid **47** as an inseparable mixture of diasteromers at C-24 in 15 steps with only one of those steps making a key C–C bond.[15] In contrast, the same starting material could be enlisted to afford the desired product in only four steps as the major isomer (96:4 dr). The key dDCC proceeded in 34% yield with high diastereoselectivity (96:4 dr) thereby enabling this rapid route. Similarly, indole building block **54** (Figure 2B) required a 10-step sequence featuring an Evans alkylation.[16] In contrast, the dDCC approach was far more direct requiring only 3 steps from commercial **53** (42% yield and 88% ee for the coupling step). In the next case study, the total synthesis of penicitide A employed a simple chiral alcohol **57** that was prepared from D-aspartic acid **55** in 12 steps.[17] In contrast, the same structure could be accessed in only five steps from carboxylic acid **56** followed by a diasteroselective dDCC (51% yield, 96:4 dr) and am-

ide reduction. Finally, carboxylic acid **61** was recently employed to complete the total synthesis of fluvirucinin B_1.[18] Its preparation involved a circuitous 12-step route that

Table 2. Scope of Ni-Electrocatalytic Enantioselective Csp^3–Csp^3 Doubly Decarboxylative Coupling (dDCC)[a]



[a]Yields of isolated products are indicated in each case unless otherwise specified.

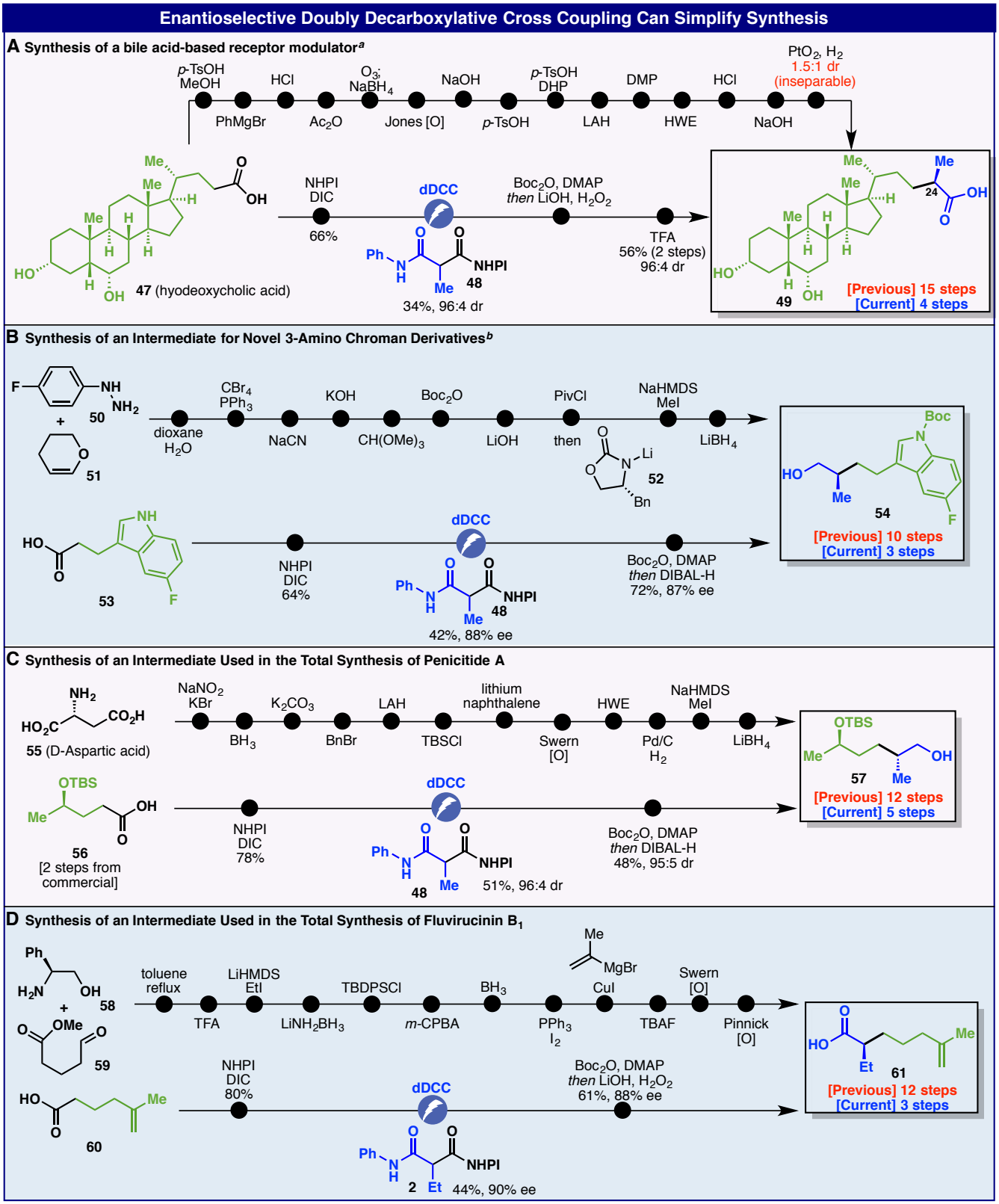


Figure 2. Enantioselective Doubly Decarboxylative Cross Coupling Can Simplify Synthesis. [a]**47** (0.1 mmol), **48** (0.3 mmol) and 6.0 F/mol were used. [b]Reaction was conducted at -5°C.

could be completely circumvented by employing an enantioselective dDCC on carboxylic acid **60** (44% yield, 90% ee) followed by mild amide hydrolysis to enable 3-step access. In all four of these cases, the use of pyrophoric and/or toxic reagents and expensive transition metals was eliminated as well as numerous functional group interconversions, protecting group manipulations, and redox fluctuations. This is yet another example of how radical retrosynthetic logic[14] can often lead to more direct and ideal synthetic routes.[19]

A mechanistic analysis of this reaction system will be the subject of a future study. Currently, the elementary steps are understood by analogy to prior art (See SI for proposed mechanism). The precise role of the enabling Mg- and Fe-based additives is unclear at the present moment. To elucidate the active catalytic species a non-linear effect study was performed (see SI) suggesting that a monomeric Ni-complex bearing a single chiral ligand is operative.[20] A CV study (see SI) was also performed suggesting that the most reducible species in solution is the Ni-ligand complex. Two reduction peaks are observed, which may be attributed to the reduction potential of Ni(II)/Ni(I) and Ni(I)/Ni(0), respectively.[21] The moderate yields observed in several cases might originate from the different rates of generating the alkyl radicals from the electronically differing RAEs. Based on this assumption, a fine-tuning the electronic properties of the NHPI moiety of the two different RAEs (e.g. install different substitution groups on the benzene ring) might be a potential strategy to enhance the yields.

This work discloses a unique example of forging C–C bonds adjacent to a carbonyl group using dDCC with high stereocontrol. As an addition to the growing body of literature wherein the stereochemical course of radical cross couplings can be controlled with judicious ligand choice it expands the scope of this newly emerging reaction class.[22] It also represents a useful precedent for the development of electrocatalytic asymmetric transformations.[23] The simple reaction setup, readily available reagents, and high enantiocontrol combined with illustrative examples that simplify synthesis through radical retrosynthetic logic are suggestive of broad applicability.

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.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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