Ni-Catalyzed Enantioselective Decarboxylative Acylation: Rapid, Modular Access to α-Amino Ketones

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ABSTRACT: A new approach to the enantiocontrolled synthesis of α-amino ketone derivatives is disclosed by employing a decarboxylative acylation strategy. Thus, when an acyl chloride and an α-amido-containing redox-active ester are exposed to Ni-catalysis, a chiral ligand, and metal reductant, α-amido ketones are produced in good yield and high ee. The reaction exhibits broad substrate scope, can be easily scaled up, and is applied to dramatically simplify the synthesis of several known structures.

Chiral α-amino ketones represent valuable building blocks serving as key intermediates for the synthesis of a vast array of natural products and medicines.[1] Thus far, the most common retrosynthetic disconnections involve classic 2e-based disconnections relying on either α-amination strategies[2] or the homologation of chiral pool-derived α-amino acids.[3] For instance, building block **1** (Figure 1A), an intermediate used for the synthesis of ACE inhibitors has been constructed via the latter strategy from L-phenylalanine in 6-8 steps[4] wherein most of the reaction steps do not forge strategic bonds resulting in low ideality. In principle, a far more direct means of accessing **1** would employ a radical retrosynthetic strategy[5] wherein the redox active ester (RAE) of phenylalanine (**2**, racemic or enantiopure) could be combined with the simple succinate derivative **3** through an enantioselective decarboxylative acylation. Forging C-acyl bonds through radical cross coupling is not new.[6] As shown in Figure 1B, three basic strategies have been reported for the construction of α-chiral ketones through Ni-catalysis.[7] In the first of these (Strategy A), an alkyl halide[8] or dihydropyridine[9] motif serves as a radical precursor for reductive (chemical or photochemical) activation before entering the Ni-catalytic cycle and reacting with an activated acyl group. In the second strategy (B), photoinduced HAT of labile C–H bonds (benzylic or adjacent to a benzamide) leads to the requisite radical donor.[10] The final strategy (C) uses a terminal olefin input in a three component coupling with a chloroformate and suitable radical donor.[11] Building on these pathpointing disclosures, the targeted transformation to access **4** was explored as shown in Figure 1C using **2** and **3**. Unfortunately, as the aforementioned methods (Strategy A) were largely developed using alkyl halides, applying these conditions to substrates **2** and **3** all gave unfruitful results with only trace quantities of **4** observed (Figure 1C). It is worthing noting that RAE **2** was fully consumed under the conditions of Reisman and co-workers[8a] while it largely remained intact using the protocols of Wang[8b] and Chen.[8c] Herein a highly enantioselective and general Ni-catalyzed decarboxylative acylation is described that can deliver 68% yield (92% ee) of **4** through a simple protocol that can be used repeatedly to simplify the synthesis of such structures.

Optimization studies began with the reductive decarboxylative acylation of RAE **2** and acid chloride **3** (Table 1). Extensive investigation revealed that the final optimal conditions utilized $NiCl_2$•glyme (10 mol%), a commercially available chiral ligand **L9** (15 mol%) and Mn powder (3.0 equiv) in CH_3CN/DME (1:1, 0.1 M) at room temperature for 5 h, affording ketoester **4** in 68% isolated yield and 92% ee. An in situ activation protocol offered comparable reaction efficiency (entry 1). Numerous reaction paramters were examined, some of which are summarized in Table 1. Using $Ni(acac)_2$ as the nickel source significantly diminished the reaction efficiency (entry 2). Surprisingly, replacing Mn with Zn as reductant completely failed to provide any product (entry 3). An unusual solvent choice proved to be extremely critical to both reactivity and asymmetric induction, with a 1:1 mixture of CH_3CN and DME proving superior to a single solvent (entries 4–5). A wide variety of chiral ligands were also tested (entries 6–12), and chiral bis(oxazoline) ligands (**L1**, **L2**, **L8**, **L9**) generally gave higher yield and ee than other types of chiral ligands (**L4**–**L7**), which was consistent with previous reports.[8-11] A fine-tuning of the steric properties of BOX ligands showed that **L9** was optimal. Control experiments indicated that essentially no detectable product formed when reactions were conducted without nickel catalyst or chiral ligand (entries 13–14). The reaction was not very sensitive to oxygen because only a slight loss of yield was observed when the reaction was conducted under air in a capped vial, although the deliberate addition of water (1.0 equiv) significantly reduced the reaction efficiency (entries 15–16). Other acyl surrogates, including in situ activation protocols (entries 17–18) and an isolated thioester precursor (entry 19), did not produce any product. In all cases, both starting materials **2** and **3** were mostly recovered.

With a concrete set of conditions in hand, the generality of the substrate scope was evaluated, as depicted in Table 2. A broad array of acid chlorides derived from primary carboxylic acids were tested, delivering the desired chiral α-amino

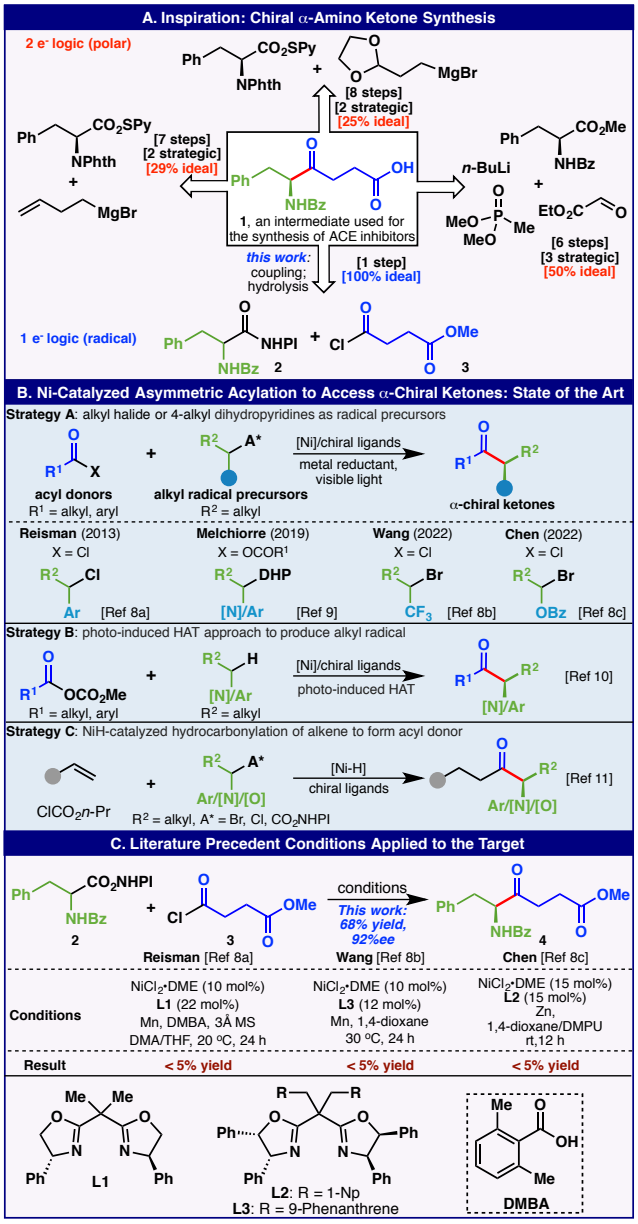
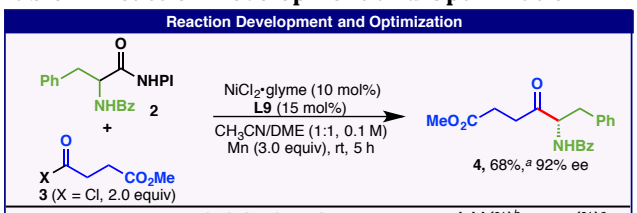


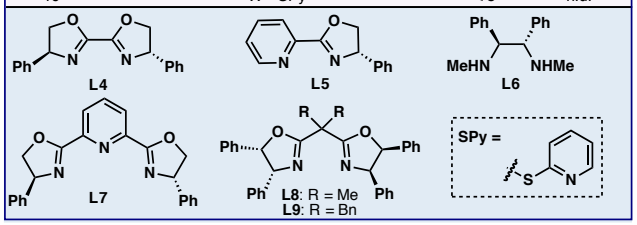
Figure 1. Historical Context and Precedent Related to Enantioselective Decarboxylative Acylation.

ketones in moderate to good yields and with excellent enantioselectivity. Aside from simple alkyl chains (**5**, **6**, **9**, **13**, **16**, **18** and **19**), a wide range of functional groups could be tolerated, such as alkyl halides (**7**, **8**), esters (**10**), terminal alkenes (**11**), ethers (**12**, **14**), internal alkenes (**21**, **22**), ketones (**23**, **24**), electron-rich aromatic rings (**15**, **20**), and aryl bromides (**25**). Acid chlorides derived from secondary carboxylic acids and aromatic acids were also suitable coupling partners (**16**, **17**, **19**, **25** and **26**), providing desired products in moderate yields and excellent enantioselectivity. Various redox-active esters derived from easily accessible α-amino acids (racemic or enantiopure) were also applied in this enantioconvergent coupling reaction (products **5–14**, **16**, **17**, **21**, **27**, **30**, **34**, **35** and **38–42** were derived from racemic RAEs while **15**, **18-20**, **22–26**, **28**, **29**, **31**, **32**, **33**, **36** and **37** were synthesized from L-α-amino acids-derived RAEs). Besides RAEs bearing simple alkyl chains (**27**,

Table 1. Reaction Development and Optimization[a,b,c,d,e]



entry	deviation from above	yield (%)[b]	ee (%)[c]
1	*in situ* activation[d]	60[a]	92
2	$Ni(acac)_2$ instead of $NiCl_2$•glyme	27	85
3	Zn instead of Mn	< 5	n.d.
4	CH_3CN only	24	74
5	DME only	20	88
6	**L1** instead of **L9**	61	36
7	**L2** instead of **L9**	52	91
8	**L4** instead of **L9**	30	34
9	**L5** instead of **L9**	23	6
10	**L6** instead of **L9**	17	0
11	**L7** instead of **L9**	21	4
12	**L8** instead of **L9**	59	68
13	no $NiCl_2$•glyme	< 5	n.d.
14	no **L9**	< 5	n.d.
15	under air in a capped vial	61	92
16	entry 15 plus 1.0 equiv H_2O[d]	43	90
17[e]	X = OH, w/ Boc_2O, $MgCl_2$	< 5	n.d.
18[e]	X = OH, w/ $(PhCO)_2O$, $MgCl_2$	< 5	n.d.
19[e]	X = SPy	< 5	n.d.



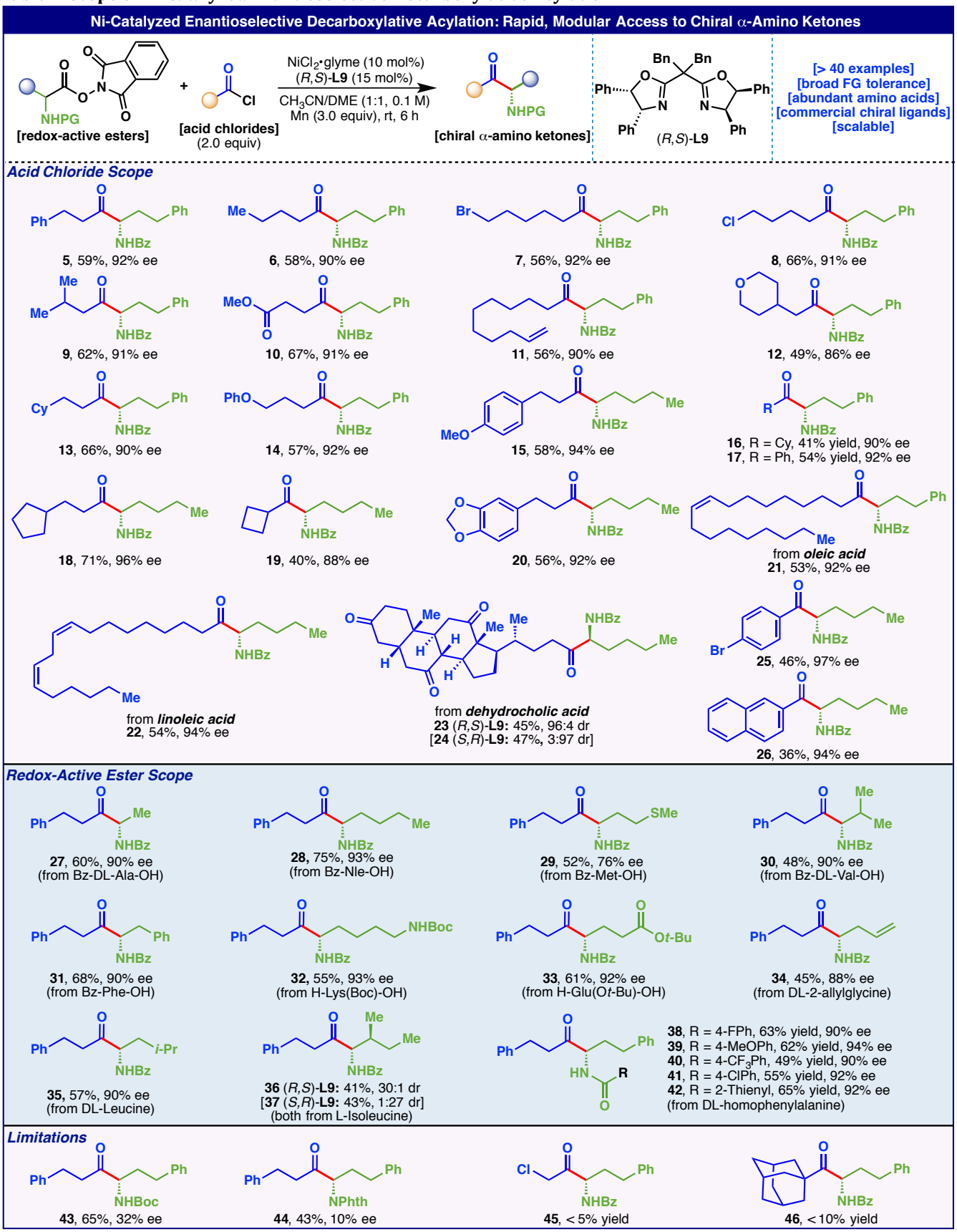
[a]Isolated yield. [b]Yields determined by crude ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]ee values determined by chiral HPLC analysis. [d]0.5 mmol scale. [e]Both starting materials **2** and **3** were mostly recovered. n.d. = not determined.

28, **30**, **31**, **35**, **36** and **37**), those with functional groups such as thioethers (**29**), carbamates (**32**), esters (**33**), terminal alkenes (**34**), aryl halides (**38**, **41**), trifluoromethyl groups (**40**) and heterocycles (**42**), could be smoothly coupled with acid chlorides. The benzoyl substituents on the amino position also could be varied (**38–42**).

Diastereoselectivity can be highly controlled by chiral ligands rather than the pre-existing stereocenters such as in the cases of substrates **23**, **24**, **36** and **37**. With the exception of compounds **17**, **23**, **24**, **26** and **28**, none of these structures have been prepared before either in racemic or enantioenriched form. With regard to limitations, switching the protecting groups from Bz to Boc or phthalimide led to considerable loss of ee (**43**, **44**). α-Chloro acid chlorides and tertiary acid chlorides were not competent coupling partners under current optimal conditions (**45**, **46**).

The developed chemistry outlined herein can have a tangible simplifying impact on the synthesis of seemingly simple structures as shown in Figure 2. For instance, compound **1** (Figure 2A) was previously accessed in 6-8 steps using polar bond analysis requiring numerous protecting groups, functional group interconversions, redox manipulations, and pyrophoric reagents. In contrast, this method enables single step access through enantioselective decarboxylative acylation of **2** with **3** followed by hydrolytic workup. The enantiopure allylated α-amido-ketone **56** (Figure 2B) was

Table 2. Scope of Ni-Catalyzed Enantioselective Decarboxylative Acylation[a]



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

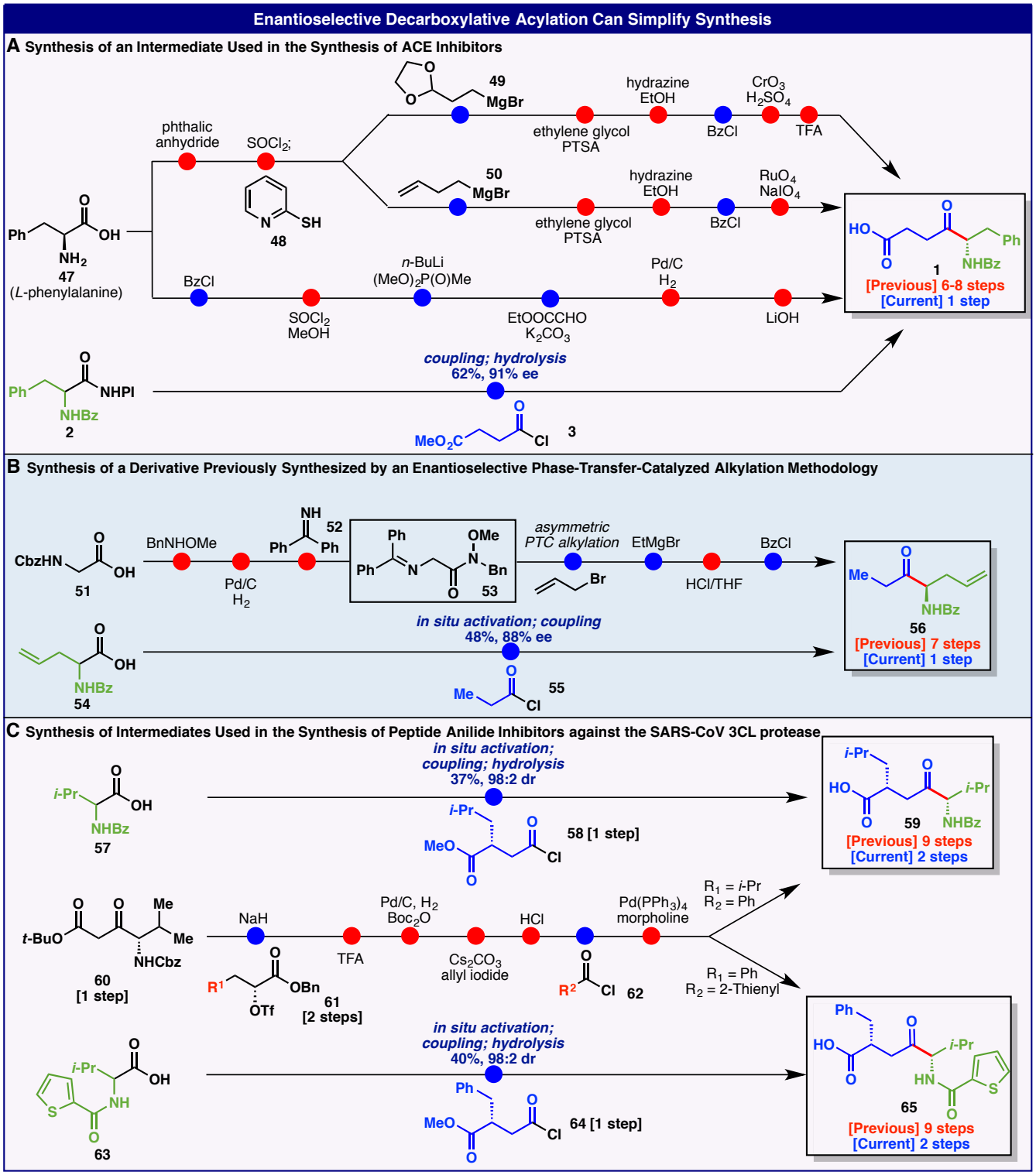


Figure 2. Enantioselective Decarboxylative Acylation Can Simplify Synthesis.

previously accessed using classic asymmetric phase-transfer alkylation chemistry[12] again requiring a number of concession steps (7 steps total). The current method simplifies this route considerably accessing the same structure in only one step. Similarly, structures **59** and **65** (Figure 2C), intermediates in a medicinal chemistry program for the discovery of anilide inhibitors against the SARS-CoV 3CL protease, were accessed in nine step routes wherein the majority of operations do not form strategic bonds.[13] In contrast, enantioselective decarboxylative acylation furnishes the same structures in a fraction of the steps previously required. From the standpoint of logic employed in a medicinal chemistry setting this method offers increased convergency and modularity that is, in principle, amenable to parallel library synthesis.

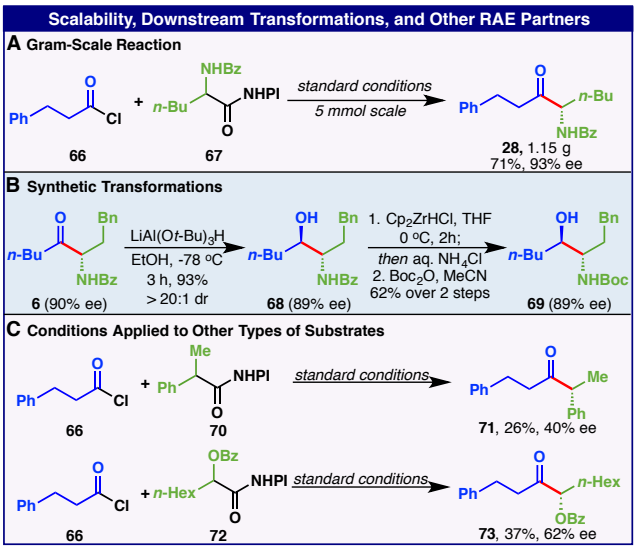


Figure 3. Scalability, Downstream Transformations, and Other RAE Partners.

In terms of scalability, the reaction is easily conducted on a gram-scale as exemplified with the preparation of compound **28** without significant loss of reaction efficiency (Figure 3A). To further demonstrate the synthetic utility of this method, chiral α-amino ketone **6** was smoothly reduced to *anti*-1,2-amino alcohol **68** in a highly stereoselective fashion.[14] The benzoyl group of **68** could be readily removed under mild conditions and swapped to Boc group with no erosion of enantiopurity (Figure 3B). In addition, the optimal conditions outlined herein provide promising preliminary results for the coupling of acid chloride **66** and other types of substrates **70** and **72** (Figure 3C). It is anticipated that further optimization of these substrate classes through ligand screening would lead to general methods. In terms of the mechanism of this transformation, it is likely following a similar pathway to other Ni-catalyzed reductive cross coupling reactions studied previously.[8]

To conclude, this study delineates a useful and practical approach to the synthesis of enantioenriched α-amino/amido ketones using Ni-catalysis. Predicated on a radical retrosynthetic strategy, it dramatically simplifies the routes to such structures allowing for convergent assembly of two carboxylates, one of which is a simple acyl chloride and one of which is an α-amido-containing RAE. The chemoselectivity of the reaction is high and as such the substrate scope is broad. The documented ability of this method to render access to known structures using only a fraction of the effort previously required bodes well for its widespread adoption.

ASSOCIATED CONTENT

Supporting Information

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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