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The Asymmetric Synthesis of Amines via Nickel-Catalyzed Enantioconvergent Substitution Reactions

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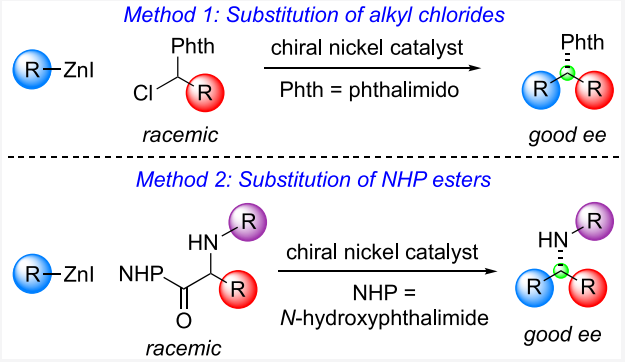
ABSTRACT: Chiral dialkyl carbinamines are important in fields such as organic chemistry, pharmaceutical chemistry, and biochemistry, serving for example as bioactive molecules, chiral ligands, and chiral catalysts. Unfortunately, most catalytic asymmetric methods for synthesizing dialkyl carbinamines do not provide general access to amines wherein the two alkyl groups are of similar size (e.g., CH_2R versus CH_2R^1). Herein, we report two mild methods for the catalytic enantioconvergent synthesis of protected dialkyl carbinamines, both of which use a chiral nickel catalyst to couple an alkylzinc reagent (1.1−1.2 equiv) with a racemic partner, specifically, an α-phthalimido alkyl chloride or an *N*-hydroxyphthalimide (NHP) ester of a protected α-amino acid. The methods are versatile, providing dialkyl carbinamine derivatives that bear an array of functional groups. For couplings of NHP esters, we further describe a one-pot variant wherein the NHP ester is generated in situ, allowing the generation of enantioenriched protected dialkyl carbinamines in one step from commercially available amino acid derivatives; we demonstrate the utility of this method by applying it to the efficient catalytic enantioselective synthesis of a range of interesting target molecules.



INTRODUCTION

Because a chiral dialkyl carbinamine subunit is found in a wide array of bioactive molecules (e.g., Figure 1A), the development of efficient methods for its synthesis, particularly catalytic and enantioselective processes, is an important objective in synthetic organic chemistry.[1] A variety of approaches have been described to date, each of which has limitations,[2] including the addition of alkyl nucleophiles to imines of aliphatic aldehydes (limited scope with respect to the nucleophile),[3] the reduction/hydrogenation of imines of unsymmetrical dialkylketones (modest enantioselectivity when the alkyl groups are similar) and enamines,[4−6] and the hydroamination of olefins (modest regioselectivity for many internal olefins).[7−9] After our study was completed, several groups independently demonstrated that nickel-catalyzed asymmetric reductive couplings of olefins and alkyl halides[10] can provide access to protected dialkyl carbinamines.[11−14]

With regard to retrosynthetic analysis, the nucleophilic substitution of an alkyl electrophile represents a straightforward approach to the synthesis of dialkyl carbinamines (top of Figure 1B). Although substitution by a nitrogen or by a carbon nucleophile could in principle afford the target molecules, in order to achieve high enantioselectivity, the use of a nitrogen nucleophile would require the effective differentiation between two alkyl groups, whereas the use of a carbon nucleophile would require the effective differentiation between an alkyl group and a nitrogen substituent. We viewed the latter approach to be more likely to provide a general solution to the asymmetric synthesis of dialkyl carbinamines, e.g., for those bearing similar alkyl groups (e.g., CH_2R versus CH_2R^1).

Recently, transition metals have been shown to catalyze an array of enantioconvergent couplings of racemic alkyl electrophiles with alkyl nucleophiles.[15−18] However, there have been no reports of such metal-catalyzed substitution reactions in the case of electrophiles that bear a nitrogen substituent geminal to the leaving group, as required for the strategy for the asymmetric synthesis of dialkyl carbinamines illustrated at the top of Figure 1B. Herein, we describe two complementary approaches to such enantioconvergent substitutions, specifically, nickel-catalyzed couplings of alkylzinc reagents with α-phthalimido alkyl chlorides (Method 1) and with *N*-hydroxyphthalimide (NHP) esters of α-amino acids (Method 2).

RESULTS AND DISCUSSION

Couplings of α-Phthalimido Alkyl Chlorides: Scope. The phthalimide functional group is a well-established protected

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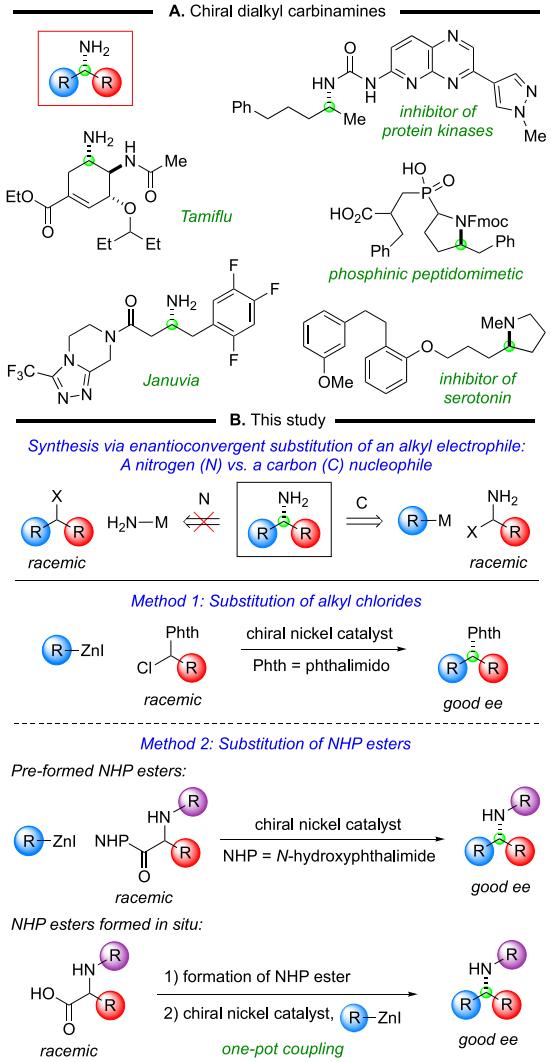

Figure 1. Dialkyl carbinamines. (A) Examples of compounds that include a chiral dialkyl carbinamine subunit. (B) This study: Nickel-catalyzed enantioconvergent substitution reactions of alkyl electrophiles to generate protected dialkyl carbinamines.

form of a primary amine.[19] We have determined that a chiral nickel/pybox catalyst can achieve the coupling of an alkylzinc reagent (1.1 equiv) with a racemic α-phthalimido alkyl chloride to afford a protected dialkyl carbinamine in good yield and enantioselectivity (Figure 2A, entry 1: 90% yield, 92% ee). Essentially no alkyl−alkyl bond formation is observed in the absence of $NiBr_2$·glyme or of the pybox ligand (entries 2 and 3), whereas a slightly diminished yield (but good ee) is obtained when half of the standard catalyst loading is used (entry 4). The presence of water or of air impedes carbon−carbon bond formation, while the enantioselectivity is not affected (entries 5 and 6[20]) (for the impact of other reaction parameters, see Section VI of the Supporting Information).

As illustrated in Figure 2B.1, the scope of this method for the catalytic enantioconvergent synthesis of protected dialkyl carbinamines is fairly broad with respect to the electrophile. For example, good yields and ee's are observed when alkyl substituent R (red) varies in size from methyl to isobutyl (products **1**−**4**), although a poor yield is observed if it is a bulky isopropyl group. A variety of functional groups are compatible with the method, including an aryl iodide, ester, carbonate, unactivated primary alkyl halide (fluoride, chloride, and bromide), indazole, and activated heteroaryl chloride (products **5**−**14**). In the case of an electrophile that bears a remote stereocenter, the stereochemistry of the catalyst, rather than that of the substrate, controls the stereochemistry of the product (products **15** and **16**). On a gram scale (1.40 g of product), the coupling to generate product **2** proceeds in similar yield and ee (93% yield, 92% ee) as for a reaction conducted on a 0.6 mmol scale (94% yield, 92% ee).

The scope of this enantioconvergent alkyl−alkyl coupling is also broad with respect to the nucleophile, leading to an array of protected dialkyl carbinamines with good yield and ee. For example, the R (blue) substituent can range in size from *n*-hexyl to isobutyl (Figure 2B.2, products **17**−**19**; however, the use of a secondary alkylzinc reagent results in a low yield of the coupling product), and a variety of functional groups can be present (entries **20**−**35**; for additional studies of the functional-group compatibility of the method, see the Supporting Information).

Couplings of α-Phthalimido Alkyl Chlorides: Mechanistic Observations. We have previously reported that two distinct nickel-catalyzed enantioconvergent couplings (Negishi reactions of propargylic halides and Kumada reactions of α-haloketones) appear to proceed through a common pathway (Figure 3A), wherein the predominant resting state of the catalyst is an organonickel(II) complex (**A**).[21,22] For the couplings of α-phthalimido alkyl chlorides with alkylzinc reagents described herein, our mechanistic observations are again consistent with this pathway.

For example, quantitative EPR analysis indicates that odd-electron nickel intermediates (e.g., Ni^{I} or Ni^{III}) do not accumulate to a significant extent during the reaction (<2% of the total nickel present). Furthermore, ESI−MS analysis of a coupling (Figure 2A) at partial conversion reveals masses consistent with $\mathbf{A}^{1}$ and $\mathbf{A}^{2}$ (Figure 3B). Finally, when the same coupling is conducted in the presence of TEMPO, a TEMPO adduct of the electrophile can be isolated (Figure 3C), consistent with the generation of an organic radical from the alkyl chloride.

Couplings of NHP Esters of α-Amino Acids: Scope. Redox-active esters (e.g., NHP esters) serve as useful partners in a variety of metal-catalyzed carbon−carbon bond-forming reactions.[23−27] The use of NHP esters derived from readily available α-amino acids[28−32] could provide a complementary strategy to the use of α-amino halides, many of which are relatively unstable, to generate an organic radical (Figure 3A) en route to enantioenriched dialkyl carbinamines.

After an extensive survey of reaction parameters, we determined that the desired decarboxylative coupling of a racemic NHP ester with an alkylzinc reagent can be achieved in the presence of a chiral nickel/diamine catalyst, providing the *N*-protected dialkyl carbinamine in good yield and ee (Figure 4A, entry 1; 79% yield, 91% ee). It is worth noting that only 1.2 equiv of the nucleophile is used, despite the presence of a potentially labile N−H proton; in contrast, most previous metal-catalyzed couplings of NHP esters have employed at least 2 equiv of the organometallic nucleophile, even in the absence of an acidic proton.[23,24]

Essentially no carbon−carbon bond formation is observed in the absence of $NiBr_2$·glyme (Figure 4A, entry 2), and the coupling proceeds in significantly lower yield and/or ee when chiral diamine **L2**, LiCl,[33,34] TMSCl,[35,36] or DMAP[37] is omitted (entries 3−6). The use of half of the standard catalyst loading results in a small loss in efficiency (entry 7; 65% yield, 88% ee).

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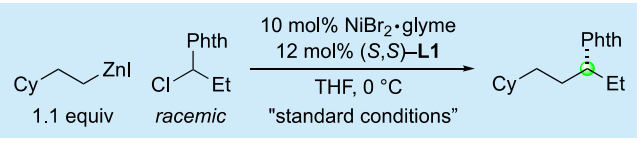
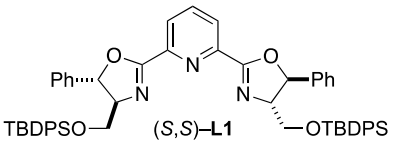
A. Effect of reaction parameters

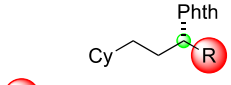




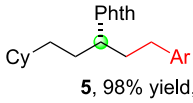
entry	variation from the standard conditions	yield (%)	ee (%)
1	none	90	92
2	no $NiBr_2$·glyme	<1	–
3	no **L1**	<1	–
4	5.0 mol% $NiBr_2$·glyme, 6.0 mol% (*S*,*S*)–**L1**	79	91
5	0.05 equiv H_2O added	31	92
6	1 mL air added	64	91

B. Scope

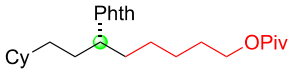
B.1. Variation of R



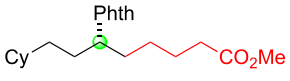
R = Me **1**, 95% yield, 88% ee
Et **2**, 94% yield, 92% ee
gram scale (1.40 g): 93% yield, 92% ee
n-Bu **3**, 95% yield, 91% ee
i-Bu **4**, 90% yield, 81% ee



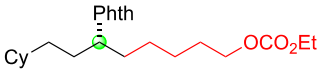
Ar = Ph **5**, 98% yield, 90% ee
p-$CF_3C_6H_4$ **6**, 96% yield, 88% ee
p-IC_6H_4 **7**, 84% yield, 89% ee



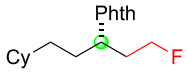
8, 92% yield, 90% ee



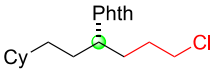
9, 91% yield, 91% ee



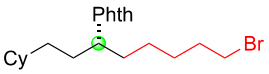
10, 86% yield, 90% ee



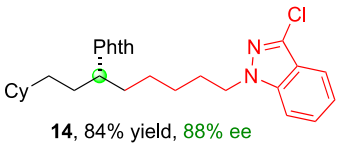
11, 75% yield, 88% ee



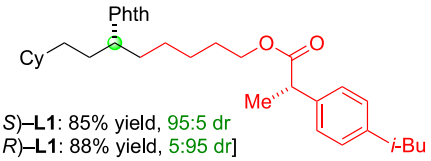
12, 96% yield, 90% ee



13, 87% yield, 91% ee



14, 84% yield, 88% ee



15, (*S*,*S*)–**L1**: 85% yield, 95:5 dr
[**16**, (*R*,*R*)–**L1**: 88% yield, 5:95 dr]

B.2. Variation of R

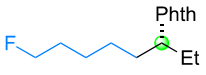
R = *n*-Hex **17**, 93% yield, 90% ee
CH_2Cy **18**, 97% yield, 95% ee[a]
i-Bu **19**, 91% yield, 94% ee[a]

20, 94% yield, 92% ee

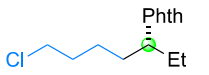
21, 99% yield, 90% ee

22, 99% yield, 89% ee

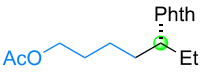
24, 96% yield, 90% ee



25, 94% yield, 90% ee



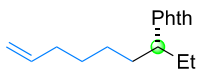
26, 89% yield, 91% ee



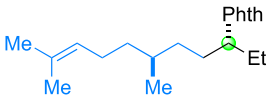
23, 79% yield, 90% ee

27, 93% yield, 90% ee

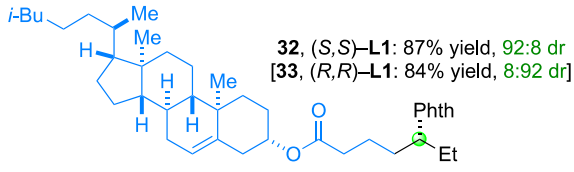
28, 78% yield, 91% ee



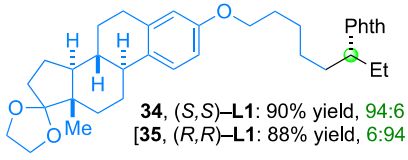
29, 61% yield, 89% ee



30, (*S*,*S*)–**L1**: 77% yield, 96:4 dr
[**31**, (*R*,*R*)–**L1**: 78% yield, 4:96 dr]



32, (*S*,*S*)–**L1**: 87% yield, 92:8 dr
[**33**, (*R*,*R*)–**L1**: 84% yield, 8:92 dr]



34, (*S*,*S*)–**L1**: 90% yield, 94:6 dr
[**35**, (*R*,*R*)–**L1**: 88% yield, 6:94 dr]

Figure 2. Enantioconvergent substitution reactions of alkyl chlorides to generate phthalimide-protected dialkyl carbinamines. (A) Effect of reaction parameters. (B) Scope. All data are the average of two experiments run on a 0.6 mmol scale (unless otherwise noted), and all yields are of purified products. [a]The reaction was conducted at r.t.

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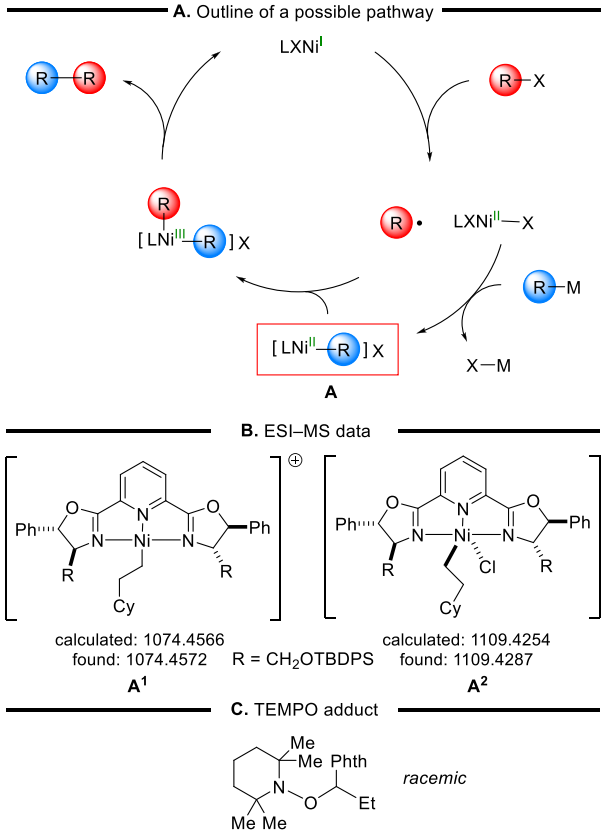

Figure 3. Nickel-catalyzed enantioconvergent substitution reactions: Mechanism. (A) Outline of a possible pathway. (B) ESI–MS data for the coupling illustrated in Figure 2A. (C) TEMPO adduct of the electrophile (Figure 2A). X = halide (an inner- or an outer-sphere ligand).

From a practical point of view, it is noteworthy that this enantioconvergent coupling is not highly water- or air-sensitive: the addition of 0.05 equiv of water or of 1 mL of air to the reaction vessel has only a minor deleterious effect (entries 8 and 9) (for the impact of other reaction parameters, see Section VI of the Supporting Information).

A variety of NHP esters serve as suitable coupling partners in these nickel-catalyzed enantioconvergent couplings to generate protected dialkyl carbinamines (Figure 4B.1 and B.2). The alkyl group R (red) can vary in steric demand from Me to *i*-Pr (products **36**–**40**), and it can bear a range of functional groups, including a thioether, an indole, and a thiophene (products **41**–**48**). The method can be applied to glutamic acid and proline derivatives, thereby affording enantioenriched protected γ-amino acids[38,39] and 2-alkylpyrrolidines[40,41] in good ee from readily available starting materials (products **47** and **48**). Not only Boc-protected, but also Fmoc- and Cbz-protected, amines are useful reaction partners (products **49** and **50**). The coupling products are generally crystalline, allowing ready enhancement of stereochemical purity (e.g., products **51** and **69**).

The scope of this method is also broad with respect to the nucleophile (Figure 4B.3). Unbranched and branched primary (but not secondary) alkylzinc reagents serve as suitable nucleophiles (products **51**–**54**), as do a variety of functionalized alkylzincs (products **55**–**72**;[42] see the Supporting Information for additional functional-group compatibility studies).

This approach to the catalytic asymmetric synthesis of protected dialkyl carbinamines can be achieved in a one-pot process without isolation of the NHP ester,[43] thereby providing the desired products in one step from commercially available protected α-amino acids (Figure 5A). The yields for the one-pot procedure are similar to or modestly lower than those for the corresponding couplings of purified NHP esters, and the enantioselectivities are essentially identical. The success of this process is a testament to the robustness of the method: impurities and side products from the DIC coupling, including *N*,*N*′-diisopropylurea, neither poison the catalyst nor consume the alkylzinc reagent via protonation, enabling the reaction to proceed with only 1.2 equiv of the nucleophile.[44]

Couplings of NHP Esters of α-Amino Acids: Applications. We have applied our catalytic asymmetric synthesis of protected dialkyl carbinamines to a variety of target molecules, starting from commercially available α-amino acid derivatives (Figure 5B). For example, urea **74**, an analogue of an inhibitor of protein kinases 1 and 2,[45] can be synthesized in two steps and 40% overall yield from *N*-Boc-alanine, via a one-pot coupling, followed by conversion of the carbamate to the urea. Furthermore, Fmoc-protected aminoalcohol **75**, an intermediate in the synthesis of a constrained peptidomimetic (prior route: eight steps),[46] can be produced in two steps from *N*-Fmoc-phenylalanine using our method; although the nickel-catalyzed coupling itself proceeds with moderate enantioselectivity (81% ee), Fmoc-protected aminoalcohol **75** can readily be recrystallized to >99% ee. Pyrrolidine **76**, which has previously been generated in four steps from *N*-Cbz-proline en route to a hydrazone-based chiral auxiliary,[47] can be synthesized in one pot and 72% yield from *N*-Boc-proline via our approach. Finally, pyrrolidine **78**, which has been employed as an intermediate in a study of serotonin inhibitors, can be formed in 50% overall yield in three, rather than eight, steps, via a nickel-catalyzed coupling.[48]

Couplings of NHP Esters of α-Amino Acids: Mechanistic Observations. Our working hypothesis is that these nickel-catalyzed enantioconvergent couplings of NHP esters may be following a pathway analogous to that outlined in Figure 3A for couplings of alkyl halides, wherein the same radical R· may be generated by the decarboxylative reduction of the NHP ester by LXNi^{I}.[23,49] As in the case of couplings of α-phthalimido alkyl chlorides (see above), the EPR spectrum of the nickel-catalyzed reaction of the NHP ester illustrated in Figure 4A indicates that odd-electron nickel intermediates do not accumulate to a significant extent during the coupling (<2% of the total nickel present). Furthermore, C–C bond formation is inhibited by the presence of TEMPO.[50]

We have examined whether the chiral nickel catalyst achieves any kinetic resolution in the enantioconvergent coupling of a racemic NHP ester. Although this issue has been explored in the case of alkyl halides,[51,52] we are not aware of corresponding investigations in the case of NHP esters. When the coupling of a racemic NHP ester is stopped at partial conversion, the unreacted NHP ester is still racemic (<1% ee; Figure 5C, experiment 1). Taken together with our observation that the enantioenriched NHP ester does not racemize under the reaction conditions (experiment 2), these data indicate that the chiral nickel catalyst is reacting at essentially identical rates with each enantiomer of the NHP ester (no kinetic resolution).

■ CONCLUSIONS

We have developed two versatile methods for the catalytic asymmetric synthesis of dialkyl carbinamines, an important family of molecules in chemistry and biology, through the use of

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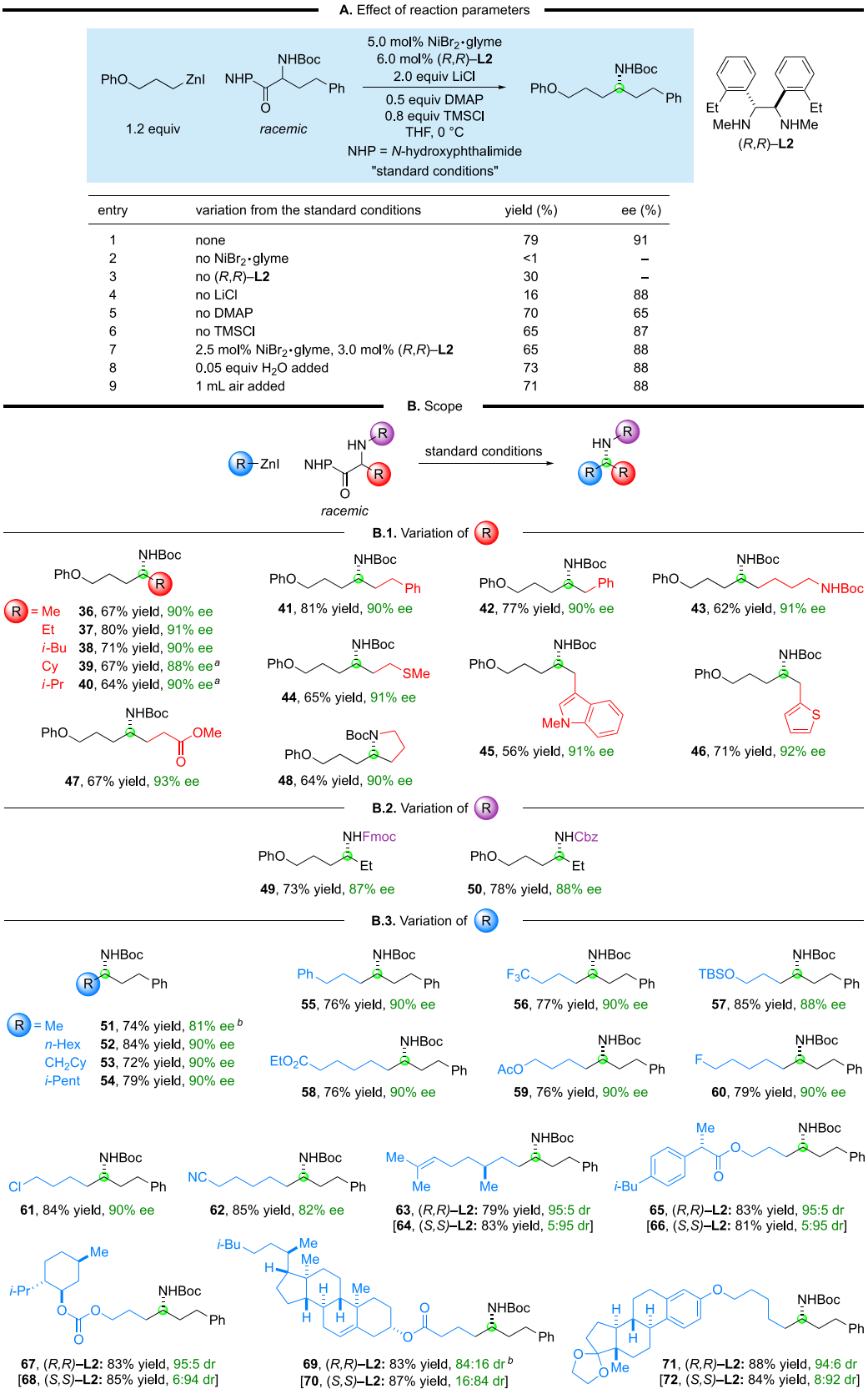

entry	variation from the standard conditions	yield (%)	ee (%)
1	none	79	91
2	no $NiBr_2$·glyme	<1	–
3	no (*R*,*R*)–**L2**	30	–
4	no LiCl	16	88
5	no DMAP	70	65
6	no TMSCl	65	87
7	2.5 mol% $NiBr_2$·glyme, 3.0 mol% (*R*,*R*)–**L2**	65	88
8	0.05 equiv H_2O added	73	88
9	1 mL air added	71	88

Figure 4. Enantioconvergent synthesis of protected dialkyl carbinamines from racemic NHP esters. (A) Effect of reaction parameters. (B) Scope. All data are the average of two experiments run on a 0.6 mmol scale, and all yields are of purified products. [a]10 mol % $NiBr_2$·glyme, 12 mol % **L2**, and 5.0 equiv of LiCl were used (no DMAP or TMSCl). [b]The product was recrystallized to >99% ee or >99.5:0.5 d.r.

chiral catalysts based on nickel, an earth-abundant metal. With an alkylzinc reagent (1.1−1.2 equiv) as the nucleophile, enantioconvergent couplings can be achieved under mild conditions with either an α-phthalimido alkyl chloride or an

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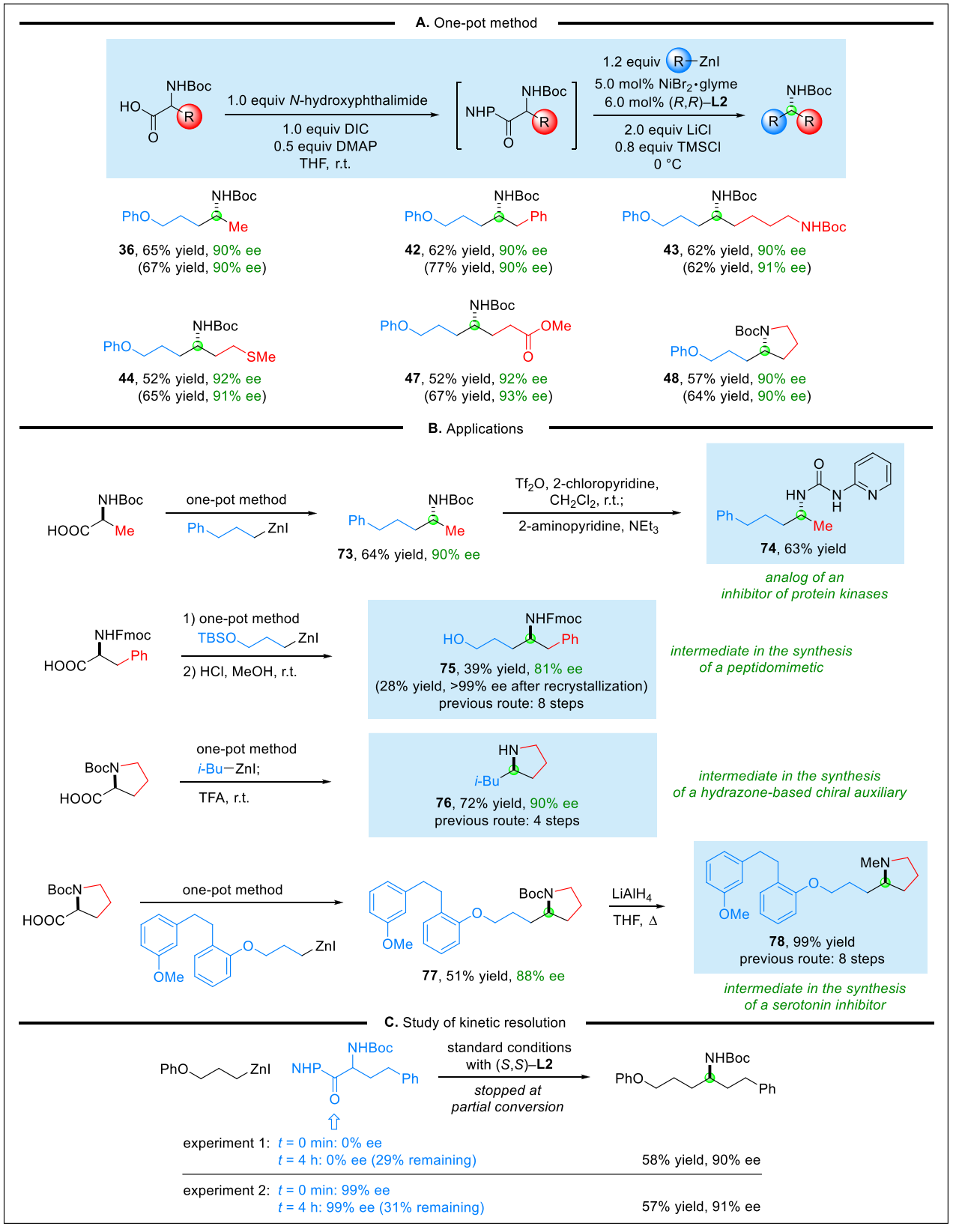

Figure 5. Asymmetric synthesis of protected dialkyl carbinamines via substitution reactions of NHP esters. (A) One-pot procedure. The values in parentheses are the data for the corresponding couplings of purified NHP esters (see Figure 4B). (B) Applications. (C) Study of kinetic resolution.

NHP ester of a protected α-amino acid; both methods display a broad scope and good functional-group tolerance. The NHP esters can be generated in situ from commercially available α-amino acid derivatives and coupled directly, resulting in a straightforward one-pot catalytic enantioselective synthesis of a variety of interesting target molecules.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13034.

Experimental details: general information, preparation of chiral ligands, preparation of electrophiles, preparation of nucleophiles, procedures for catalytic enantioconvergent cross-couplings, effect of reaction parameters, studies of functional-group compatibility, procedures for one-pot reactions, applications of the methods, mechanistic experiments, assignments of absolute configuration, NMR spectra, and data on determination of stereoselectivity (PDF)

Accession Codes

CCDC 2057330 and 2057338 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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