Chapter 4

ENANTIOCONVERGENT, NICKEL-CATALYZED CROSS-COUPLING FOR THE ASYMMETRIC SYNTHESIS OF PROTECTED THIOLS

4.1. Introduction

Enantioenriched alkyl-substituted organosulfur compounds are frequently encountered in organic synthesis, chemical biology, and agrochemistry.[1,2] Because sulfur is a frequent constituent of pharmaceuticals, its selective incorporation into complex molecular frameworks is an ongoing goal (and challenge) in medicinal chemistry (**Figure 4.1**).[3,4]

Common approaches to the synthesis of organosulfur compounds rely on the nucleophilicity of thiol derivatives. While thiols are versatile building blocks for a number of other sulfur-containing functionalities, there exist few examples of the reverse reaction (i.e., the conversion of organosulfur functional groups to thiols).[5–7] Thus, the development of efficient methods to synthesize enantioenriched thiols would grant access to a wide array of chiral organosulfur compounds (**Figure 4.2**).

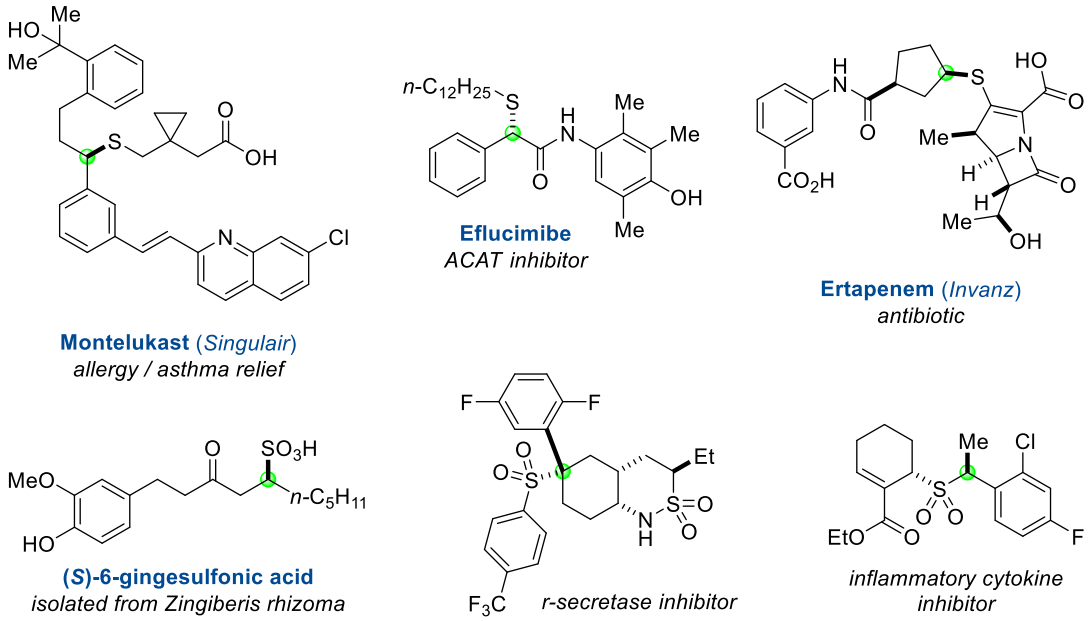


Figure 4.1. *Examples of chiral, alkyl-substituted organosulfur compounds.*

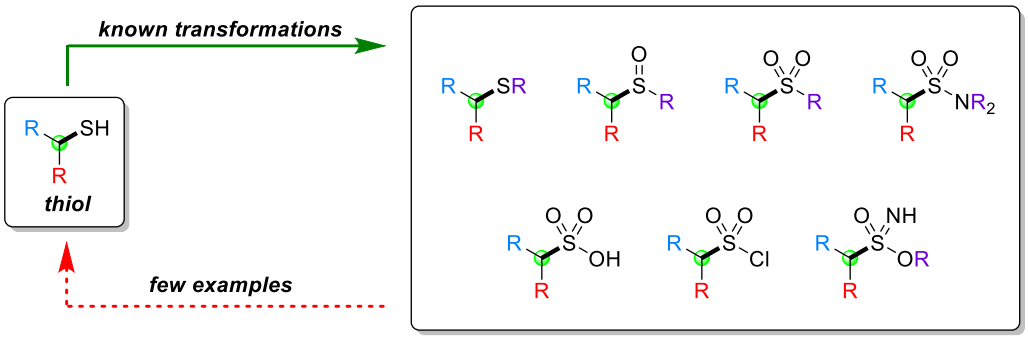
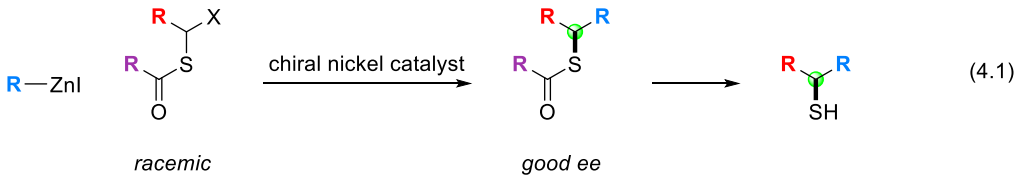


Figure 4.2. *Thiols as versatile building blocks for organosulfur compounds.*

Remarkably, despite the value of enantioenriched alkyl-substituted thiols as building blocks, there exist few methods for their synthesis. The S_N2 reaction and the Mitsunobu reaction have been applied, although these methods require the use of enantioenriched starting materials.[8–10] Other classical approaches require the use of a chiral auxiliary, such as intramolecular sulfur transfer reactions of oxazolidine-2-thiones[11,12] and nucleophilic attacks of α-thioenolates[13] and α-thioorganolithium reagents.[14] Catalytic asymmetric methods have provided efficient syntheses of enantioenriched thiols, although these approaches generally have limited scope. Sneddon reported the synthesis of allylic protected thiols through a palladium-catalyzed rearrangement of *O*-allyl carbamothioates (limited scope with respect to the alkyl groups).[15] Ellman described the enantioselective addition of thioacetic acid to nitroalkenes via *N*-sulfinyl urea organocatalysis,[16] and Connon disclosed the sulfonamide-catalyzed kinetic resolution of thiols (both methods are only applicable to the synthesis of benzylic thiols).[17] List reported a phosphoric acid-catalyzed nucleophilic ring opening of epoxides (limited to the formation of β-hydroxythiols).[18] To our knowledge, there exists no general catalytic method for the synthesis of enantioenriched aliphatic thiols, namely one that allows for facile modifications to both alkyl groups and exhibits broad functional group tolerance.



Our lab has applied nickel-catalyzed enantioconvergent substitution reactions to a range of readily-available racemic electrophiles, including those that contain a heteroatom that is geminal to the bond-forming center.[19–24] The incorporation of a sulfur functional group into a racemic electrophile would require the catalyst to differentiate between an alkyl group and a sulfur substituent, which we viewed as a promising strategy for the asymmetric synthesis of thiols (**eq 4.1**). In this chapter, we describe preliminary results that demonstrate the viability of this approach. Specifically, we disclose the synthesis of racemic NHP esters of α-thioester carboxylic acids and their application to cross-coupling with alkylzinc reagents.

4.2. Results and discussion

4.2.1. Synthesis of an α-thioester NHP ester

We initially targeted protected thiols in the form of thioesters, which are readily installed and can be easily cleaved under basic conditions (whereas the deprotection of other protecting groups, such as thioethers, require more forcing conditions).[25] In addition, the carbonyl substituent of the thioester may coordinate to the catalyst in the stereochemistry-determining step to improve the enantioselectivity of cross-coupling.

While our group's efforts in nickel catalysis have primarily focused on the use of alkyl halides as electrophiles, alkyl halides bearing a geminal thioester are unstable and difficult to synthesize.[26] In a recent study, we observed that redox-active esters of amino

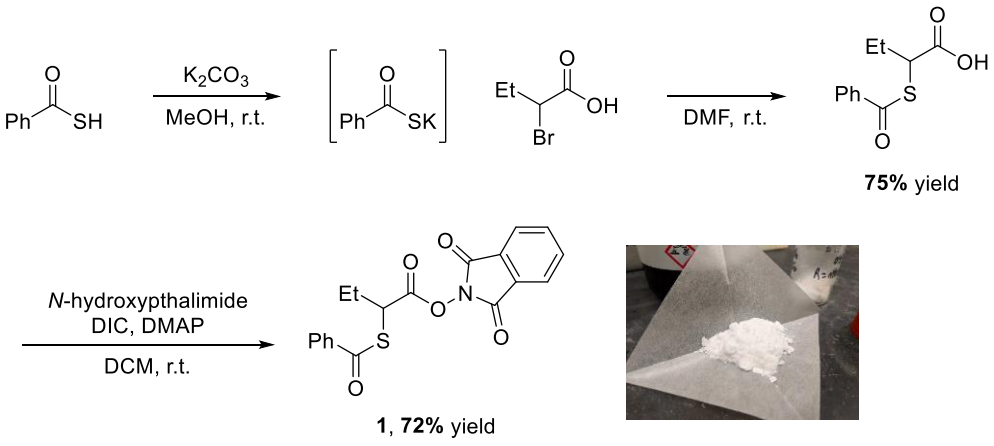


Figure 4.3. *Synthesis of* ***1****, an α-thioester NHP ester.*

acids are considerably more stable and easier to handle than their alkyl halide analogs (see *Chapter 2*),[23] motivating us to pursue a similar strategy in the synthesis of enantioenriched protected thiols. Carboxylic acids containing an α-thioester substituent are known compounds, often employed as synthetic building blocks due to the versatility of the thioester as a precursor to other functional groups.[27–29] However, these compounds have not been applied to decarboxylative couplings.

Using conditions developed for the synthesis of NHP esters of α-amino acids,[23] we generated NHP ester **1** in good yield (**Figure 4.3**). To our knowledge, this is the first synthesis of an NHP ester of a carboxylic acid containing an α-thioester substituent. **1** is a free-flowing white solid that can be stored under air and at room temperature for several months without detectable decomposition.

4.2.2. Nickel-catalyzed couplings of α-thioester NHP esters

Upon surveying a range of chiral ligands, we found that several nickel complexes can catalyze the coupling of an alkylzinc reagent and racemic NHP ester **1** in modest yield and enantioselectivity (**Figure 4.4**). Cyanobox ligands offer the most promising

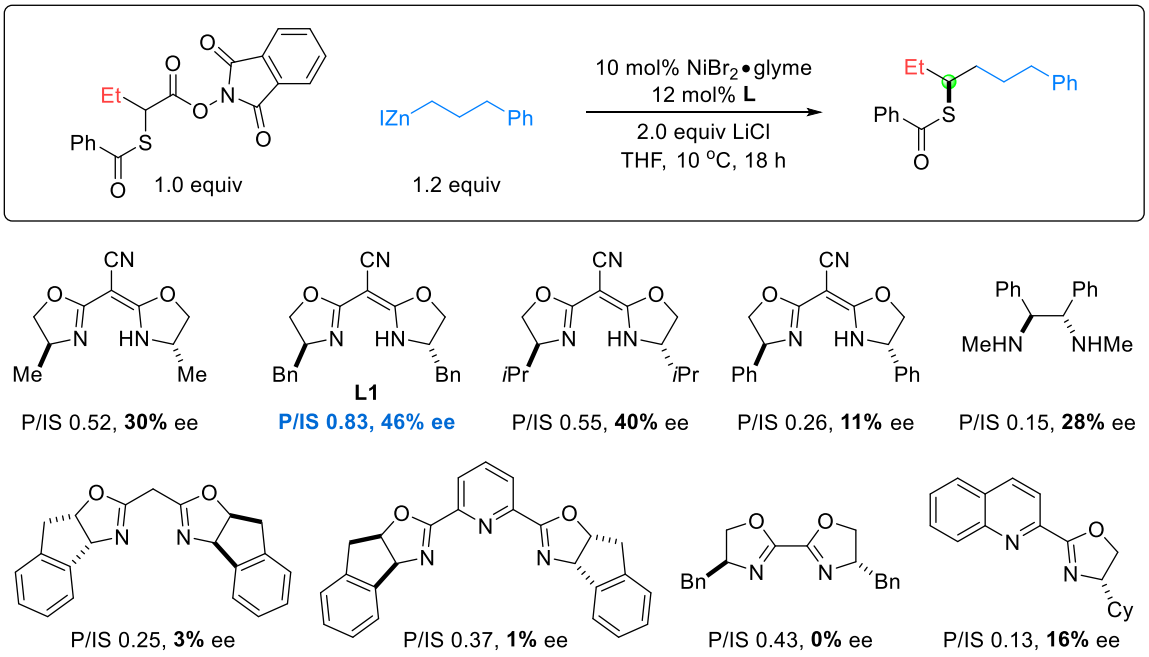
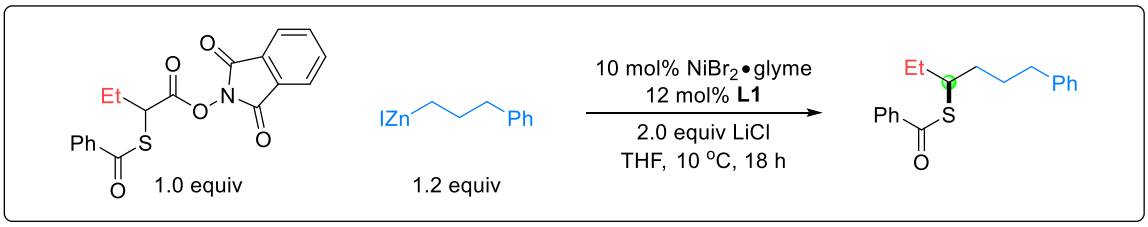


Figure 4.4. *Effect of ligand.*

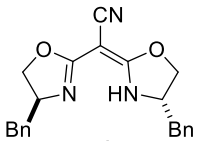
reactivity; benzyl-substituted cyanobox **L1** affords the product in 46% ee. At this stage of reaction development, the ratio of product to internal standard (P/IS) was determined by LC-MS analysis, and the P/IS of 0.83 obtained in the coupling with **L1** was estimated to correspond to a <20% yield. Under these conditions, a majority of the NHP ester remains unreacted and no major byproducts are observed.

Prior to continuing the optimization of this enantioconvergent coupling, we performed several control experiments to assess its reproducibility (**Table 4.1**). We determined that reactions run in parallel yield consistent results (**Table 4.1**, entries 1 and 2). Coupling does not proceed in the absence of nickel, the chiral ligand, or LiCl (entries 3–5). Increasing the loading of $NiBr_2$·glyme results in a slight improvement to the yield but a drop in ee, while increasing the amount of **L1** has the opposite effect (entries 6 and 7). Varying the stoichiometry of LiCl or the alkylzinc reagent, prolonging the reaction time, or removing stirring does not affect the outcome of the reaction (entries 8–12). While this transformation appears to be robust to minor changes in the conditions and setup procedure,

Table 4.1. *Control reactions and study of reproducibility.*



entry	variation from the standard conditions	P/IS	ee (%)
1	none	1.14	35
2	none	1.09	36
3	No $NiBr_2$•glyme	0	-
4	No **L1**	0	-
5	No LiCl	0	-
6	16 mol% $NiBr_2$•glyme, instead of 10 mol%	1.45	28
7	20 mol% **L1**, instead of 12 mol%	0.94	48
8	2.6 equiv LiCl, instead of 2.0 equiv	1.14	41
9	0.8 equiv Nu, instead of 1.2 equiv	1.05	39
10	1.5 equiv Nu, instead of 1.2 equiv	1.19	26
11	42 h, instead of 18 h	1.02	34
12	No stirring (no stir bar)	1.04	36
13	Ni and **L1** pre-stirred 5 for min, instead of 30 min	1.00	**47**
14	Ni and **L1** not pre-stirred at all	0.94	**53**

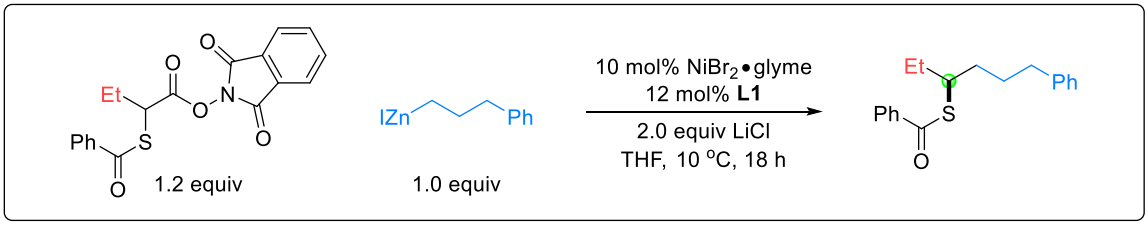


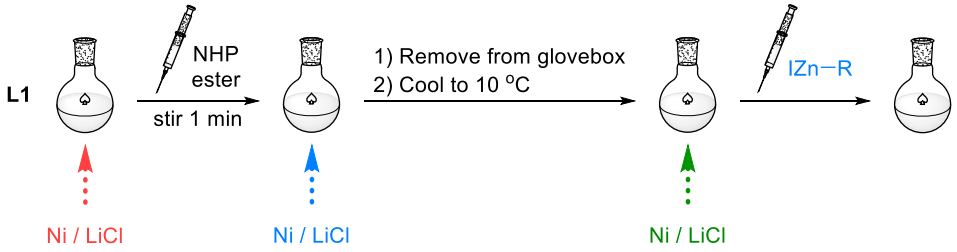
L1

we were surprised to find that decreasing the catalyst pre-stir time significantly improves the enantioselectivity (entries 13 and 14), prompting us to examine this phenomenon further.

Through systematic modifications to the reaction setup procedure, we studied the effect of catalyst pre-stirring (**Table 4.2**). These experiments indicated that the enantioselectivity of product formation increases as the catalyst pre-stir time decreases.[30] To our knowledge, this trend has not been reported in other asymmetric nucleophilic substitution reactions; in fact, our group generally observes the opposite effect, wherein a sufficiently long pre-stirring of the catalyst components is necessary to achieve good enantioselectivity (including other reactions catalyzed by a nickel-cyanobox complex).[31] Further optimization of the reaction was conducted using the conditions outlined in **Table 4.2**, entry 5, which affords the product in 81% ee.

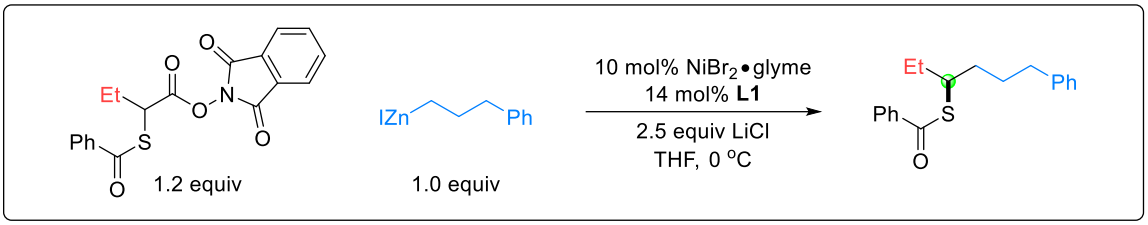
Table 4.2. *Effect of catalyst pre-stir time.*





entry	conditions	ee (%)
1	**Ni / LiCl** stirred with ligand for 1 h before adding NHP ester	29
2	**Ni / LiCl** stirred with ligand for 30 min before adding NHP ester	54
3	Stir **L1** and NHP ester, then add **Ni / LiCl** and immediately remove from glovebox	72
4	Once reaction is cooled, add **Ni / LiCl** and then add R–ZnI 5 min later	78
5	Once reaction is cooled, add **Ni / LiCl** and then add R–ZnI immediately	81

Table 4.3. *Time course study.*



entry	reaction time (h)	% NHP ester remaining	yield (%)	ee (%)
1	1	73	5	86
2	2	69	5	86
3	4	67	6	85
4	6	66	6	84
5	24	61	6	84
6	72	60	6	82

Under these new conditions, we examined the time course of the enantioconvergent coupling (**Table 4.3**). The product is formed in only 5% yield after 1 h (**Table 4.3**, entry 1), which does not increase upon prolonging the reaction to 72 h (entry 6). This poor yield is in part due to the low consumption of NHP ester, 60% of which remains unreacted after several days of stirring (entry 6). Variations of the temperature, solvent, nickel precatalyst, and catalyst loading did not lead to higher yields.

We reasoned that more aggressive modifications to the reaction system would be necessary to optimize this method, such as pursuing a different ligand class or introducing additives. However, replacing cyanobox **L1** with other classes of chiral ligands is deleterious to both the yield and enantioselectivity (**Figure 4.5**). In all cases, the conversion of NHP ester **1** is low. Although this transformation is not believed to proceed through the formation of a dative bond between sulfur and nickel, is possible that non-covalent coordination of sulfur poisons the catalyst, which may account for the unusually low reactivity of **1** compared to other NHP esters in nickel catalysis.

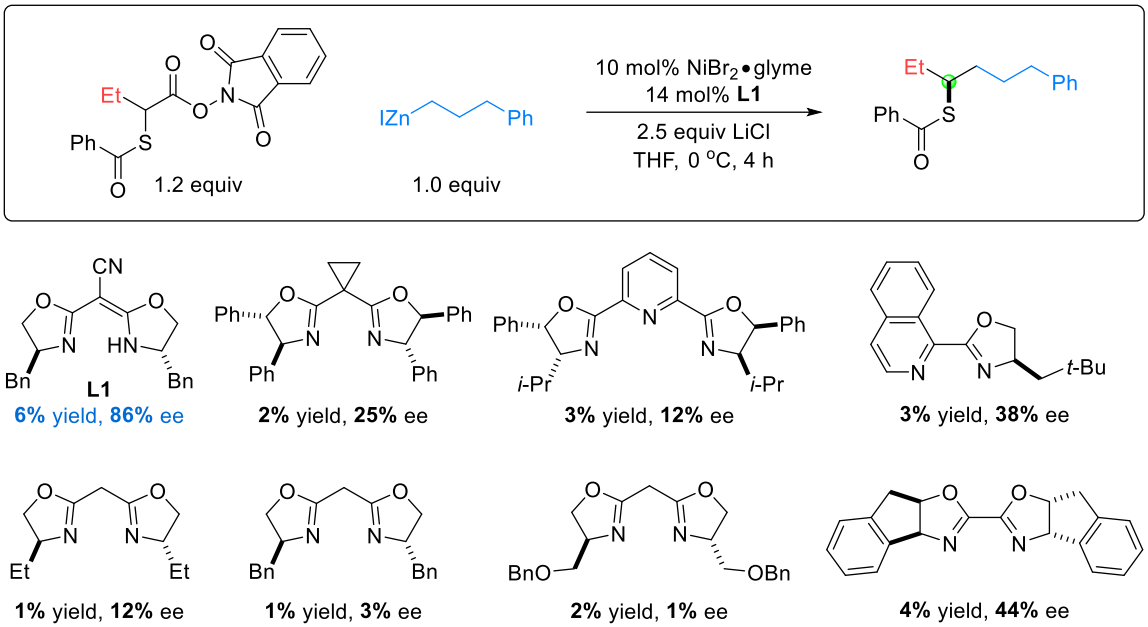


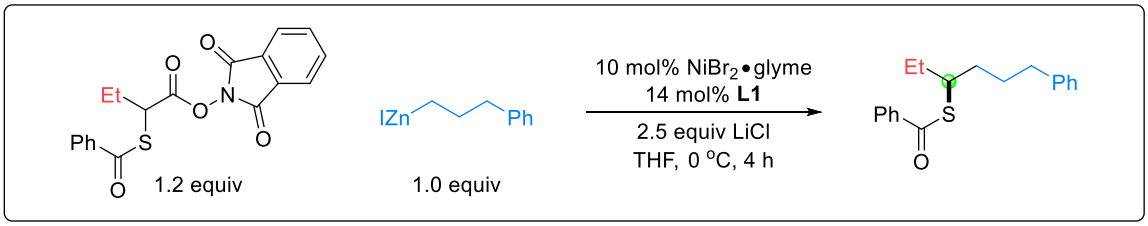
Figure 4.5. *Examining other families of chiral ligands.*

Previous work in our lab demonstrated that nickel-catalyzed alkylations of NHP esters with alkylzinc reagents can require a number of additives to proceed efficiently (see *Chapter 2*).[23] While LiCl indeed improves substrate conversion (**Table 4.1**, entries 1 and 5), the addition of other additives found to be beneficial for related couplings of NHP esters (such as TMSCl, DMAP, and DIC) are detrimental to this reaction (**Table 4.4**, entries 1–4). The addition of a zinc salt or an achiral phosphine, which has been shown to be necessary for product formation in other nickel-catalyzed Negishi couplings,[32] does not improve the yield (entries 5–7). Similarly, while the addition of a Lewis base leads to higher consumption of the NHP ester, the product yield remains low (entries 8–10).

4.2.3. Investigating other organosulfur electrophiles

Although the nickel-catalyzed enantioconvergent substitution of **1** proceeds with good enantioselectivity, its synthetic utility is hindered by low yields arising from poor conversion of starting materials. In related couplings of NHP esters, tuning the electronic properties of the phthalimide moiety is necessary to achieve appreciable reactivity.[33] Inspired by these findings, we synthesized NHP esters containing electron donating/withdrawing substituents on the phthalimide and applied them as substrates in

Table 4.4. *Effect of additives.*



entry	additive (1.0 equiv)	% NHP ester remaining	yield (%)	ee (%)
Additives shown to benefit couplings of NHP esters (see Chapter 2)				
1	None	49	7	85
2	TMSCl	71	7	70
3	DMAP	55	2	24
4	DIC	56	5	86
Zinc salts				
5	$ZnCl_2$	61	5	75
Achiral phosphines				
6	PPh_3 (40 mol%)	57	6	91
7	dppp (20 mol%)	57	0	-
Lewis bases				
8	TMEDA	43	0	-
9	TMP	0	3	55
10	DMPU	6	5	84

nickel-catalyzed enantioconvergent cross-couplings (**Figure 4.6**). These modifications led to improved yields, particularly when tetrachloro- and tetrabromo- phthalimides were used. Further optimizations of reactions employing these substrates may be a fruitful direction to pursue in the future.

Due to the propensity of thioesters to cleave under basic conditions, it is possible that, in the presence of an organozinc reagent, α-thioester NHP ester **1** is deprotected to form an anionic sulfide, which could inhibit cross-coupling (such as by poisoning the catalyst).[34] To examine this phenomenon, we synthesized NHP esters containing other carbonyl-based thiol protecting groups, namely those containing S–Fmoc and S–Cbz thiocarbonates. Although there exist no reported syntheses of NHP esters containing an α-thiocarbonate substituent, we found that they can be accessed from α-thio carboxylic acids using a modified procedure based on the preparation of carbamate-protected α-amino NHP esters (**eqs 4.2** and **4.3**).[23] Similarly to **1**, these α-thiocarbonate NHP esters are free-

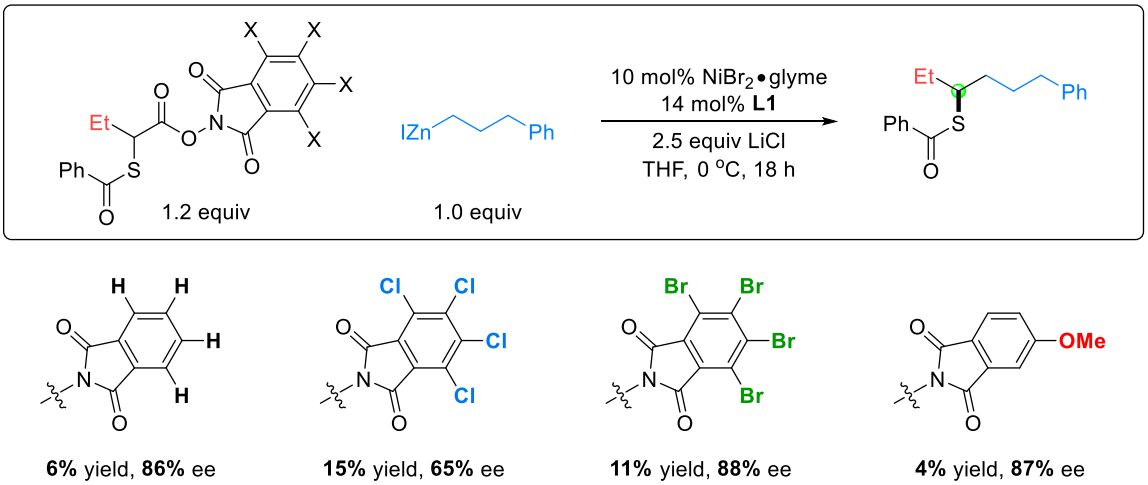
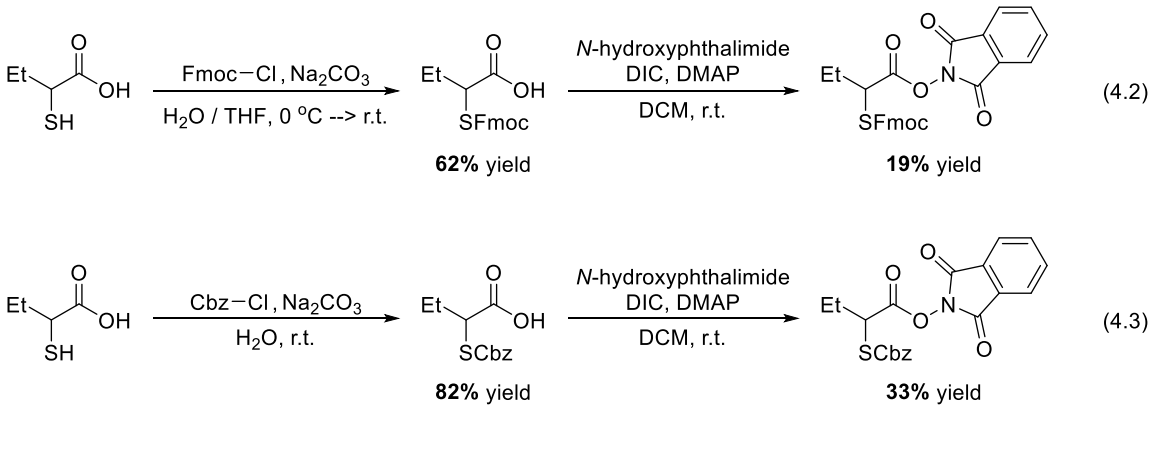
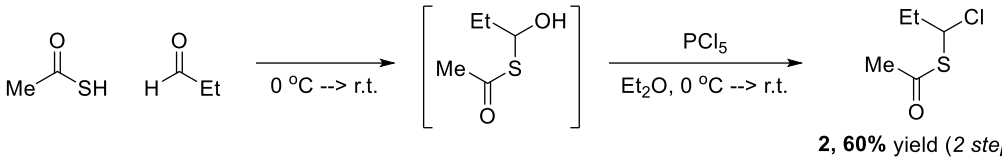


Figure 4.6. *Modification of the phthalimide substituent of* ***1****.*

flowing white solids that are stable under ambient conditions for several months. Upon applying these compounds to nickel-catalyzed couplings with alkylzinc reagents, however, we observed no reaction (**eq 4.4**).

Although NHP esters are stable and easy to handle, the poor reactivity of **1** might be enhanced by substituting the redox-active ester with a halide leaving group. We originally did not target alkyl halides containing an α-thioester substituent due to their instability; however, after modifications to a reported procedure,[26] we successfully



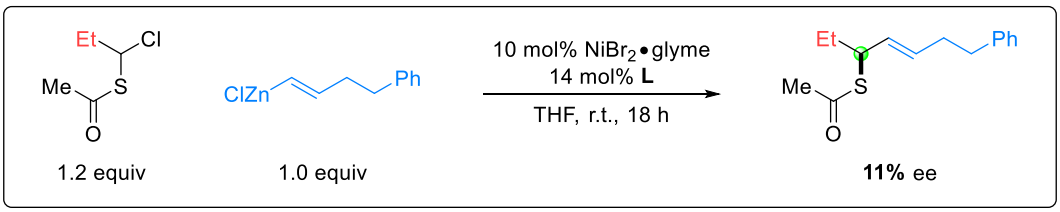


(4.5)

synthesized and isolated α-chloro thioester **2** in good yield through the *in situ* formation and chlorination of an α-hydroxy thioester (**eq 4.5**).

When **2** is allowed to stir with an alkylzinc reagent in the presence of a chiral nickel catalyst, no product is formed, even after changes to the ligand and other reaction conditions. Alkenylzirconium reagents, alkynylzinc reagents, and olefin / hydrosilane mixtures are unsuccessful nucleophiles in this transformation as well. However, **2** reacts with an alkenylzinc reagent to afford an allylic thioester in modest yield and 11% ee (**Figure 4.7**). The development of this reaction may be of interest due to the numerous applications of allylic organosulfur compounds in organic synthesis.[35,36]

Given the limitations in the reactivities of electrophiles containing carbonyl-based thiol protecting groups disclosed herein, we investigated electrophiles possessing a thioether substituent, specifically, an α-thiophenyl alkyl chloride and an NHP ester bearing an α-thiobenzyl substituent. When applied to enantioconvergent substitution reactions with an alkylzinc reagent in the presence of a chiral nickel catalyst, these electrophiles afford aliphatic thioethers in ~20% ee (**eqs 4.6** and **4.7**). These results suggest that the carbonyl



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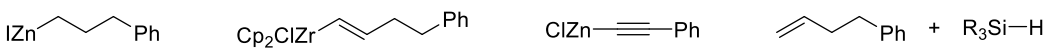
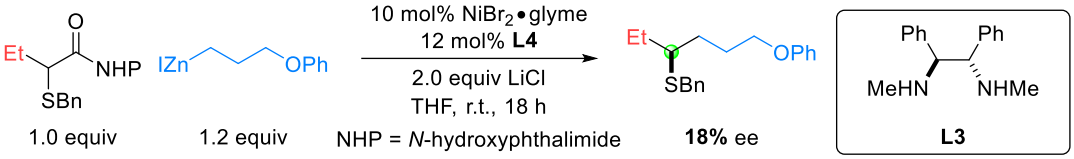


Figure 4.7. *Nickel-catalyzed enantioconvergent alkenylation of* ***2*** *using an alkenylzinc reagent, along with unsuccessful nucleophiles tested.*

(4.6)



(4.7)

substituent of thioester electrophiles such as **1** may play an important role in the stereochemistry-determining step of these transformations. However, further studies must be carried out on these thioethers in order to assess their potential as cross-coupling substrates more rigorously.

4.3. Conclusions

While enantioconvergent nucleophilic substitution reactions have been applied to the synthesis of numerous important families of compounds, this approach has not yet been applied to the asymmetric synthesis of alkyl-substituted thiols. We have developed a synthesis of an α-thioester NHP ester, a new type of substrate in cross-coupling, and found that this electrophile reacts with an alkylzinc reagent in the presence of a chiral nickel catalyst to afford aliphatic thioesters in high ee, albeit in modest yields. We have begun to explore variations in the reaction conditions, along with the effect of modifying the structure of the electrophile. During these efforts, we discovered that alkenylzinc reagents can be employed in couplings with α-chloro thioesters, which could serve as a straightforward route to synthetically-useful enantioenriched allylic thiols. We anticipate that this chemistry may draw attention to the potential of nickel-catalyzed nucleophilic substitution reactions as an appealing strategy to access enantioenriched organosulfur compounds.

4.4. Experimental section

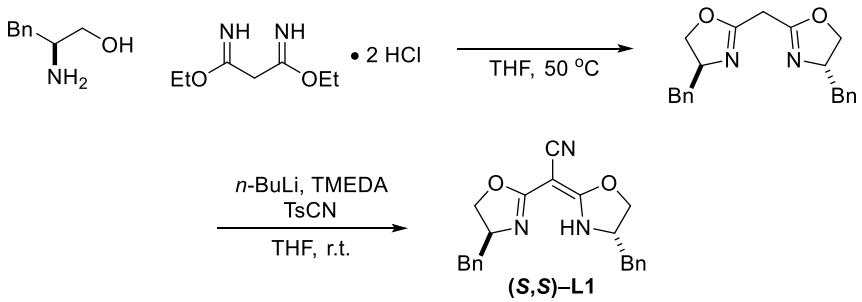
4.4.1. General information

Unless otherwise noted, reagents received from commercial suppliers were used as received. All reactions were performed under an atmosphere of dry nitrogen. Anhydrous THF was purchased from Sigma-Aldrich and stored under nitrogen; other solvents were purified by passage through activated aluminum oxide in a solvent-purification system.

NMR spectra were collected on a Bruker 400 MHz spectrometer at ambient temperature; chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, using the solvent resonance as the internal standard. SFC analyses were carried out on an Agilent 1260 Infinity II system with Daicel CHIRALPAK® columns (4.6 × 250 mm, particle size 5 μm). LC-MS were obtained on an Agilent 6140 UHPLC-MS system in electrospray ionization (ESI+) mode. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 μm, Silicycle).

4.4.2. Preparation of the chiral ligand

The yields have not been optimized.



(*E*)-2-((*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl)-2-((*S*)-4-benzyloxazolidin-2-ylidene) acetonitrile.[31] An oven-dried 100 mL round-bottom flask was equipped with a stir bar, (*S*)-phenylalaninol (4.00 g, 26.5 mmol, 2.0 equiv), and diethyl malonimidate dihydrochloride (3.06 g, 13.2 mmol, 1.0 equiv). The flask was sealed with a rubber septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (40 mL) via syringe. After the solution was stirred at 50 °C for 48 h, it was diluted with water (200 mL). The mixture was extracted with

dichloromethane (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (1:9 MeOH/DCM) to afford bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane as a white solid (2.50 g, 7.5 mmol, 56% yield).

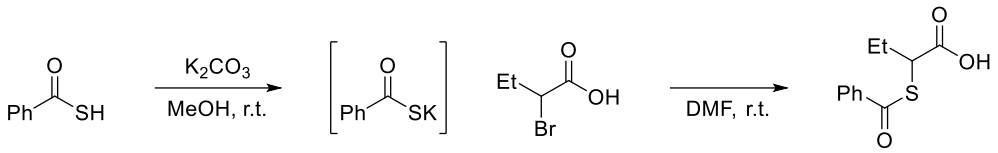
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.16 (m, 10H), 4.48 – 4.38 (m, 2H), 4.23 (dd, *J* = 9.4, 8.4 Hz, 2H), 4.02 (dd, *J* = 8.5, 7.2 Hz, 2H), 3.32 (s, 2H), 3.11 (dd, *J* = 13.8, 5.4 Hz, 2H), 2.68 (dd, *J* = 13.8, 8.5 Hz, 2H).

An oven-dried 250 mL round-bottom flask was equipped with a stir bar and bis((*S*)-4-benzyl-4,5-dihydrooxazol-2-yl)methane (2.50 g, 7.5 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of THF (100 mL). The solution was then cooled to –78 ºC. Next, *n*-BuLi (3.6 mL, 2.5 M in hexanes, 9.0 mmol, 1.2 equiv) was added dropwise over 5 min and TMEDA (1.3 mL, 9.0 mmol, 1.2 equiv) was added in a continuous flow via syringe. The solution was stirred at –78 ºC for 20 min, then at 0 ºC for 30 min, after which the flask was cooled back to –78 ºC. To an oven-dried 40 mL vial was added *p*-toluenesulfonyl cyanide (1.62 g, 9.0 mmol, 1.2 equiv), and the vial was placed under a nitrogen atmosphere by evacuating and back-filling (three cycles), followed by the addition of THF (10 mL). This solution was transferred via syringe to the 250 mL reaction flask in a continuous flow at –78 ºC. The resulting mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with a saturated NH_4Cl solution (100 mL) at room temperature and was diluted with H_2O (100 mL). The mixture was extracted with Et_2O (100 mL x 3), and the combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4, and concentrated. The crude product was recrystallized in hexanes / THF to afford the desired product (*S*,*S*)–**L1** as a white, crystalline solid (1.11 g, 3.1 mmol, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.15 (m, 6H), 7.11 – 7.06 (m, 4H), 4.38 (t, *J* = 8.4 Hz, 2H), 4.33 – 4.24 (m, 2H), 4.13 (dd, *J* = 8.3, 6.1 Hz, 2H), 2.88 (dd, *J* = 13.6, 6.4 Hz, 2H), 2.67 (dd, *J* = 13.6, 7.4 Hz, 2H).

4.4.3. Preparation of electrophiles

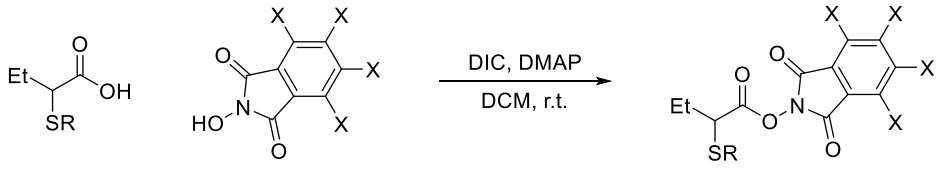
The yields have not been optimized.



2-(Benzoylthio)butanoic acid.[37] An oven-dried 100 mL two-neck flask was equipped with a stir bar and thiobenzoic acid (5.00 g, 36.2 mmol, 2.0 equiv). The flask was sealed with two rubber septa and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of MeOH (40 mL) via syringe. K_2CO_3 (2.50 g, 18.1 mmol, 1.0 equiv) was added to the flask under a positive pressure of nitrogen, at which point the evolution was gas was observed. After the mixture was allowed to stir for 5 min at room temperature, the solvent was evaporated under reduced pressure. The resulting residue was placed under a nitrogen atmosphere and re-dissolved in DMF (50 mL), and the solution was cooled to –40 °C. Next, 2-bromobutanoic acid (3.8 mL, 36.2 mmol, 2.0 equiv) was added dropwise via syringe, and the solution was warmed to room temperature and allowed to stir overnight. Water (100 mL) was added, and the mixture was extracted with Et_2O (50 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated, affording 2-(benzoylthio)butanoic acid as an orange oil (6.10 g, 27.2 mmol, 75% yield).

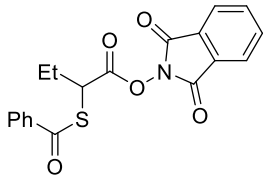
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 2H), 7.62 – 7.53 (m, 1H), 7.49 – 7.40 (m, 2H), 4.38 – 4.33 (m, 1H), 2.15 – 1.87 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H).

General Procedure 1 (GP-1).



Preparation of NHP esters: An oven-dried 250 mL round-bottom flask was charged with a stir bar, a derivative of *N*-hydroxyphthalimide (1.0 equiv), and DMAP (0.1 equiv),

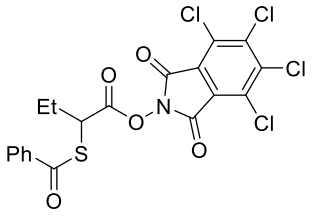
and then it was sealed with a rubber septum cap. The flask was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of anhydrous DCM (volume to generate a 0.2 M solution of the α-thio carboxylic acid) via syringe. The mixture was stirred for 5 min, after which the α-thio carboxylic acid (1.0 equiv) was added under a positive flow of nitrogen. After the mixture had stirred for an additional 5 min, DIC (1.0 equiv) was added dropwise via syringe over 5 min. The reaction was allowed to stir at room temperature overnight. The mixture was then filtered through a pad of celite and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the solution was then concentrated under reduced pressure. MeOH (~5.0 mL/mmol of the α-thio carboxylic acid) was added, and the mixture was stirred for 5 min. The mixture was cooled to –25 °C over 4 h, during which a white solid precipitated. The solid was filtered and washed with cold MeOH, affording the desired NHP ester. The NHP esters used in this study can be stored at room temperature for at least several months without decomposition.



1,3-Dioxoisoindolin-2-yl 2-(benzoylthio)butanoate (1). The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (5.10 g, 22.8 mmol) and *N*-hydroxyphthalimide (3.71 g, 22.8 mmol). 6.08 g, 16.4 mmol, 72% yield. White solid.

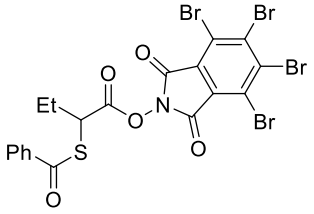
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.78 (dd, J = 5.5, 3.1 Hz, 2H), 7.66 – 7.57 (m, 1H), 7.48 (m, 2H), 4.72 (t, J = 7.1 Hz, 1H), 2.17 (ddq, J = 44.1, 14.3, 7.2 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H).

LC-MS (ESI-MS) m/z $[M+Na]^+$ calcd for $C_{19}H_{15}NNaO_5S$: 392.1, found: 392.1.



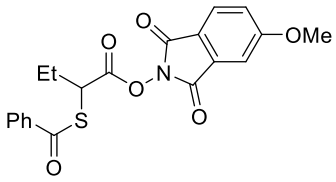
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (380 mg, 1.69 mmol) and tetrachloro-*N*-hydroxyphthalimide (509 mg, 1.69 mmol). 480 mg, 1.30 mmol, 77% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 7.66 – 7.59 (m, 1H), 7.52 – 7.45 (m, 2H), 4.69 (t, *J* = 7.1 Hz, 1H), 2.16 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).



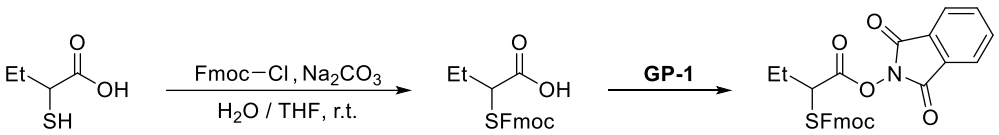
4,5,6,7-Tetrabromo-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (280 mg, 1.25 mmol) and tetrabromo-*N*-hydroxyphthalimide (597 mg, 1.25 mmol). 401 mg, 1.08 mmol, 87% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.66 – 7.58 (m, 1H), 7.53 – 7.45 (m, 2H), 4.70 (t, *J* = 7.2 Hz, 1H), 2.28 – 2.05 (m, 2H), 1.22 (t, *J* = 7.4 Hz, 3H).



5-Methoxy-1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate. The title compound was synthesized according to **GP-1** from 2-(benzoylthio)butanoic acid (670 mg, 2.98 mmol) and 4-methoxy-*N*-hydroxyphthalimide (577 mg, 2.98 mmol). 248 mg, 0.67 mmol, 22% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.54 – 7.43 (m, 2H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.71 (t, *J* = 7.1 Hz, 1H), 3.93 (s, 3H), 2.31 – 2.02 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

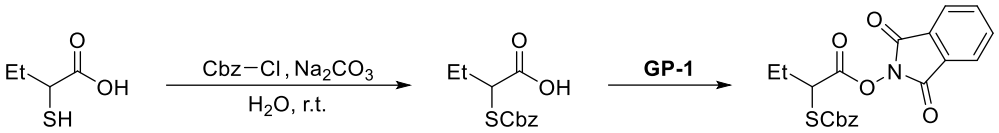


1,3-Dioxoisoindolin-2-yl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoate. A 100 mL round bottom flask was equipped with a stir bar, Na_2CO_3 (1.90 g, 17.9 mmol, 2.5 equiv), and 2-mercaptobutanoic acid (0.86 g, 7.2 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of water (3 mL) and 1,4-dioxane (30 mL) via syringe. The reaction mixture was cooled to 0 °C, after which a solution of Fmoc–Cl (1.85 g, 7.2 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) was added dropwise via syringe. The reaction was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stir overnight. Next, water (100 mL) was added, and the mixture was washed with EtOAc (50 mL x 3). The aqueous layer was cooled to 0 °C and slowly acidified by the dropwise addition of concentrated HCl. The resulting mixture was extracted with EtOAc (50 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated, affording 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoic acid as a white solid (1.52 g, 4.4 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.81 – 7.74 (m, 2H), 7.65 – 7.55 (m, 2H), 7.47 – 7.37 (m, 2H), 7.37 – 7.28 (m, 2H), 4.59 – 4.43 (m, 2H), 4.27 (t, *J* = 7.5 Hz, 1H), 4.09 – 4.02 (m, 1H), 2.01 – 1.78 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H).

The title compound was synthesized according to **GP-1** from 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)thio)butanoic acid (1.50 g, 4.39 mmol) and *N*-hydroxyphthalimide (716 mg, 4.39 mmol). 398 mg, 0.82 mmol, 19% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.82 – 7.74 (m, 4H), 7.65 – 7.58 (m, 2H), 7.45 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 4.62 – 4.45 (m, 2H), 4.38 (t, *J* = 7.1 Hz, 1H), 4.32 (t, *J* = 7.4 Hz, 1H), 2.24 – 1.89 (m, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

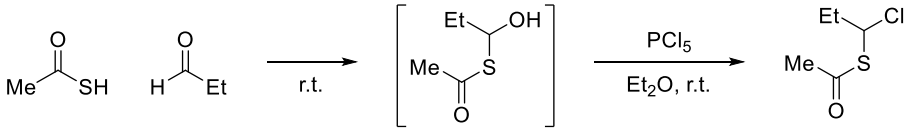


1,3-Dioxoisoindolin-2-yl 2-(((benzyloxy)carbonyl)thio)butanoate. A 40 mL vial was equipped with a stir bar, Na_2CO_3 (1.52 g, 14.3 mmol, 2.0 equiv), and 2-mercaptobutanoic acid (0.86 g, 7.2 mmol, 1.0 equiv). The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and backfilling the vial (three times), followed by the addition of water (10 mL) via syringe. Benzyl chloroformate (1.23 mL, 8.59 mmol, 1.2 equiv) was added dropwise via syringe, and the reaction was allowed to stir at room temperature overnight. After, water (20 mL) was added, and the mixture was washed with EtOAc (10 mL x 3). The aqueous layer was cooled to 0 ^oC and was slowly acidified by the dropwise addition of concentrated HCl. The resulting mixture was extracted with EtOAc (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated, affording 2-(((benzyloxy)carbonyl)thio)butanoic acid as a white solid (1.49 g, 5.9 mmol, 82% yield)

^1H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 7.41 – 7.33 (m, 5H), 5.32 – 5.20 (m, 2H), 4.05 (t, *J* = 7.1 Hz, 1H), 2.07 – 1.82 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

The title compound was synthesized according to **GP-1** from 2-(((benzyloxy)carbonyl)thio)butanoic acid (1.50 g, 5.88 mmol) and *N*-hydroxyphthalimide (960 mg, 5.88 mmol). 764 mg, 1.91 mmol, 33% yield. White solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 4.10 – 3.92 (m, 2H), 3.44 – 3.38 (m, 1H), 2.07 – 1.75 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).



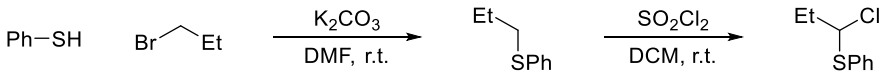
(1-Chloropropyl) ethanethioate (2).[26] An oven-dried 40 mL vial was equipped with a stir bar. The vial was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and backfilling the vial (three times), followed by the addition of freshly

distilled thioacetic acid (2.07 mL, 28.9 mmol, 1.0 equiv) via syringe. The reaction vial was cooled to 0 °C, after which freshly distilled propionaldehyde (2.09 mL, 28.9 mmol, 1.0 equiv) was added dropwise via syringe. The reaction was allowed to warm to room temperature and stir overnight. The conversion to (1-hydroxypropyl) ethanethioate (69%) was determined by ^{1}H NMR of an aliquot taken from the vial by syringe. Roughly 30% of the starting materials remained unreacted (no byproducts observed).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (t, *J* = 6.3 Hz, 1H), 2.32 (s, 3H), 1.89 – 1.66 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H).

An oven-dried 100 mL round bottom flask was equipped with a stir bar and PCl_5 (4.21 g, 20.2 mmol, 1.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition Et_2O (40 mL) via syringe. The mixture was then cooled to 0 °C, and (1-hydroxypropyl) ethanethioate was added dropwise as the crude mixture from the previous step (2.90 mL, 20.2 mmol, 1.0 equiv). The reaction was warmed to room temperature and allowed to stir overnight. Next, the solvent was evaporated under reduced pressure, and the residue was purified by vacuum distillation to afford the title compound as a colorless oil (1.84 g, 17.4 mmol, 60% yield over 2 steps).

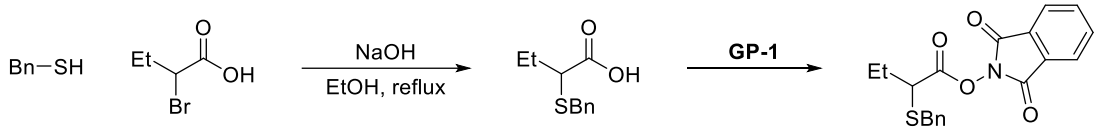
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, *J* = 6.4 Hz, 1H), 2.36 (s, 3H), 2.12 – 2.01 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H).



(1-Chloropropyl)(phenyl)sulfane.[38] Phenyl(propyl)sulfane was prepared according to a reported procedure.[39] An oven-dried 50 mL round bottom flask was equipped with a stir bar. The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of phenyl(propyl)sulfane (2.78 mL, 19.7 mmol, 1.0 equiv) and DCM (15 mL) via syringe. Next, sulfuryl chloride (1.92 mL, 23.6 mmol, 1.2 equiv) was added dropwise via syringe and the solution was allowed to stir at room temperature for 3 h. When the reaction was

complete, the solvent was removed under reduced pressure, and the resulting residue was purified by vacuum distillation, affording the title compound as a colorless oil (3.10 g, 16.6 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.40 – 7.33 (m, 3H), 5.26 – 5.20 (m, 1H), 2.20 – 2.05 (m, 2H), 1.16 (t, *J* = 7.3 Hz, 3H).



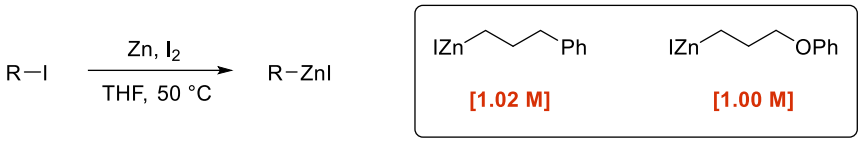
1,3-Dioxoisoindolin-2-yl 2-(benzylthio)butanoate. The synthesis of 2-(benzylthio) butanoic acid was based on a reported procedure.[40] An oven-dried 250 mL round bottom flask was equipped with a stir bar, a reflux condenser, and NaOH (2.58 g, 64.4 mmol, 2.0 equiv). The flask was sealed with a septum cap and was placed under a nitrogen atmosphere by evacuating and back-filling the flask (three cycles), followed by the addition of EtOH (100 mL), benzyl mercaptan (3.77 mL, 32.2 mmol, 1.0 equiv), and 2-bromobutanoic acid (3.43 mL, 32.2 mmol, 1.0 equiv) via syringe. The reaction was heated to reflux and allowed to stir overnight. Next, the solvent was removed under reduced pressure. The resulting residue was dissolved in water (50 mL) and acidified using 6 M HCl. The mixture was extracted with Et_2O (50 mL x 3). The combined organic layers were washed with $NaHCO_3$ (50 mL x 3), dried over Na_2SO_4, and concentrated to yield 2-(benzylthio)butanoic acid as a light beige oil (4.70 g, 22.4 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.41 – 7.22 (m, 5H), 3.96 – 3.80 (m, 2H), 3.07 (dd, *J* = 8.0, 6.9 Hz, 1H), 1.96 – 1.62 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

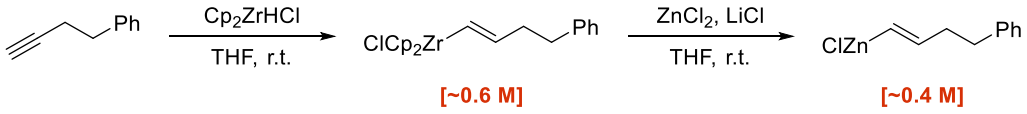
The title compound was synthesized according to **GP-1** from 2-(benzylthio)butanoic acid (2.19 g, 10.4 mmol) and *N*-hydroxyphthalimide (1.70 g, 10.4 mmol). The product was purified by column chromatography on silica gel (1:3 EtOAc/hexanes). 2.55 g, 7.18 mmol, 69% yield. White solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 4.08 – 3.93 (m, 2H), 3.40 (dd, *J* = 8.4, 6.7 Hz, 1H), 2.05 – 1.76 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

4.4.4. Preparation of nucleophiles

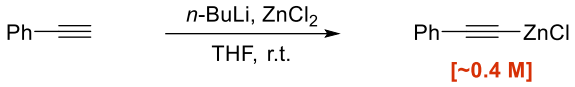


Preparation of alkylzinc reagents. In the air, an oven-dried 100 mL Schlenk tube was charged with a stir bar and zinc powder (1.5 equiv, ~100 mesh, Alfa, 99.9%), and then it was sealed with a rubber septum cap. The tube was placed under a nitrogen atmosphere by evacuating and back-filling the tube (three cycles). Then, the tube was heated with a heat gun (~250 °C) under vacuum (~1 torr) for 10 min. The Schlenk tube was allowed to cool to room temperature, and it was back-filled with nitrogen. THF (0.5 mL/mmol of the alkyl iodide) was added via syringe. The cap was removed, and iodine (0.050 equiv) was added in one portion under a positive flow of nitrogen (the cap was then replaced), leading initially to a red color that faded after ~5 sec of vigorous stirring (1000 rpm). A solution of the alkyl iodide (1.0 equiv) in THF (0.5 mL/mmol of the alkyl iodide), prepared in a 20 mL vial equipped with a nitrogen balloon, was added via syringe in one portion to the gray suspension of zinc powder. Then, the Schlenk tube was capped tightly under a nitrogen atmosphere and transferred to an oil bath. The reaction mixture was stirred vigorously at 50 °C for 12 h (the disappearance of the alkyl iodide and the formation of the alkylzinc reagent can readily be monitored via GC analysis of the quenched alkylzinc reagent). After the alkyl iodide had been consumed, the gray mixture was filtered through a syringe filter (PTFE, 0.45 μM) to afford a colorless solution. The alkylzinc solution was titrated by the method of Knochel, using iodine in THF.[41] The concentration of the alkylzinc reagents remained constant over one year when stored at room temperature in a glovebox.



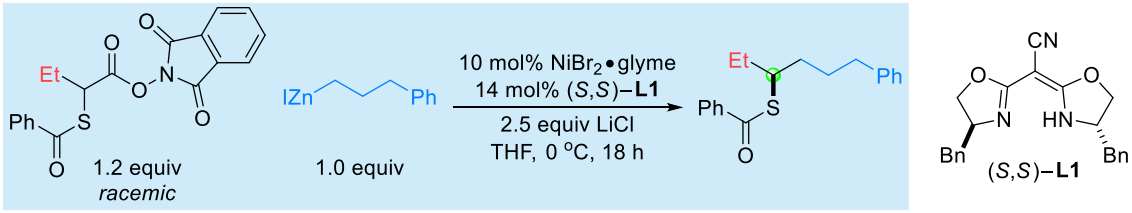
Preparation of alkenylzirconium and alkenylzinc reagents.[42,43] In the glovebox, an oven-dried 40 mL vial was equipped with a stir bar. Schwartz's reagent (1.0 equiv) and THF (1.7 mL / mmol of the alkyne) were added. Next, the alkyne (1.0 equiv) was added

dropwise via syringe, and the vial was sealed with a septum cap. The mixture was allowed to stir at room temperature for 1.5 h to yield the alkenylzirconium reagent as a ~0.6 M solution in THF. In a separate oven-dried vial, $ZnCl_2$ (1.0 equiv) and LiCl (1.3 equiv) were dissolved in THF (1.0 mL / mmol of $ZnCl_2$). This solution was added dropwise to the vial containing the alkenylzirconium reagent, and the mixture was allowed to stir at room temperature for 1 h to yield the alkenylzinc reagent as a ~0.4 M solution in THF.



Preparation of the alkynylzinc reagent.[44] An oven-dried 40 mL vial was equipped with a stir bar. The vial was sealed with a septum cap and placed under a nitrogen atmosphere by evacuating and back-filling the vial (three cycles). Next, phenylacetylene (1.0 equiv) and THF (3.3 mL / mmol of phenylacetylene) were added. The solution was cooled to 0 °C, after which *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added dropwise via syringe. The reaction was warmed to room temperature and allowed to stir for 1 h, after which the mixture was cooled back to 0 °C. In a separate oven-dried 40 mL vial, a solution of $ZnCl_2$ (1.2 equiv) in THF (1.0 mL / mmol of $ZnCl_2$) was prepared under a nitrogen atmosphere. This solution was transferred to the reaction vial dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 h to yield the alkynylzinc reagent as a ~0.4 M solution in THF.

4.4.5. Catalytic enantioconvergent cross-couplings



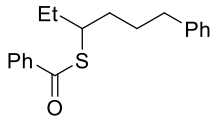
General Procedure 2 (GP-2).

Reaction setup: In a nitrogen-filled glovebox, an oven-dried 4 mL vial was equipped with a stir bar and charged with (*S*,*S*)–**L1** (5.0 mg, 0.014 mmol, 14 mol%) and the NHP ester (0.12 mmol, 1.2 equiv). Next, THF (0.6 mL) was added, and the vial was sealed with

a septum cap and wrapped with electrical tape. The vial was then removed from the glovebox and cooled to 0 °C using an *i*-PrOH cooling bath. After the reaction was cooled, a stock solution of $NiBr_2$·glyme (3.1 mg, 0.010 mmol, 10 mol%) and LiCl (10.6 mg, 0.25 mmol, 2.5 equiv) in THF (0.5 mL) was added in one portion, followed immediately by dropwise addition of the alkylzinc solution (0.10 mmol, 1.0 equiv) via microsyringe. The punctures on the septum cap were sealed with grease, and the mixture was stirred at 0 °C for 18 h.

Work-up: The reaction was quenched at 0 °C by the addition of EtOH (0.1 mL). The resulting mixture was allowed to warm to room temperature, and then 1-indanone (2.6 mg, 0.020 mmol) was added as an internal standard. The mixture was filtered through a small plug of silica gel, which was flushed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography.

The yields were determined via LC-MS analysis of an aliquot of the crude product mixture, with 1-indanone as the internal standard. The ee values were determined via SFC analysis after purification by preparative thin-layer chromatography.

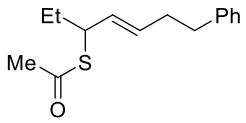


***S*-(6-Phenylhexan-3-yl) benzothioate**. The title compound was synthesized according to **GP-2** from 1,3-dioxoisoindolin-2-yl 2-(benzoylthio)butanoate and (3-phenylpropyl) zinc(II) iodide. The product was purified by preparative thin-layer chromatography (1:9 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IC column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times for compound obtained using (*S*,*S*)**–L1**: 7.7 min (major), 8.6 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.23 (m, 2H), 7.20 – 7.14 (m, 3H), 3.84 – 3.67 (m, 1H), 2.64 (m, 2H), 1.89 – 1.63 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 3H).

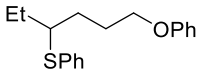
LC-MS (ESI-MS) *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{22}NaOS$: 321.1, found: 321.1.



(*E*)-*S*-(7-Phenylhept-4-en-3-yl) ethanethioate. The title compound was synthesized using a procedure adapted from **GP-2** (no LiCl; $NiBr_2$·glyme and the chiral ligand were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from *S*-(1-chloropropyl) ethanethioate and (*E*)-(4-phenylbut-1-en-1-yl)zinc(II) chloride. The product was purified by preparative thin-layer chromatography (1:9 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK IG-3 column (3% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 3.3 min, 4.2 min.

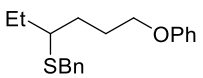
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 5H), 5.70 – 5.57 (m, 1H), 5.35 – 5.22 (m, 1H), 3.94 – 3.81 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 2.32 – 2.24 (m, 2H), 2.23 (s, 3H), 1.60 – 1.53 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).



(6-Phenoxyhexan-3-yl)(phenyl)sulfane. The title compound was synthesized using a procedure adapted from **GP-2** (no LiCl; **L2** used instead of **L1**; $NiBr_2$·glyme and **L2** were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from (1-chloropropyl)(phenyl)sulfane and (3-phenoxypropyl)zinc(II) iodide. The product was purified by preparative thin layer chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (5% *i*-PrOH in supercritical CO_2, 2.5 mL/min); retention times: 6.0 min, 6.5 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.31 – 7.21 (m, 5H), 6.97 – 6.86 (m, 3H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.15 – 3.04 (m, 1H), 2.09 – 1.87 (m, 2H), 1.85 – 1.57 (m, 4H), 1.04 (t, *J* = 7.3 Hz, 3H).



Benzyl(6-phenoxyhexan-3-yl)sulfane. The title compound was synthesized using a procedure adapted from **GP-2** (**L3** used instead of **L1**; $NiBr_2$·glyme and **L3** were pre-stirred for 30 min prior to addition of the electrophile; reaction run at room temperature) from (1,3-dioxoisoindolin-2-yl 2-(benzylthio)butanoate and (3-phenoxypropyl)zinc(II)

iodide. The product was purified by preparative thin layer chromatography on silica gel (1:4 EtOAc/hexanes). Colorless oil.

SFC analysis: The ee was determined via SFC on a CHIRALPAK AD-3 column (5% MeOH in supercritical CO_2, 2.5 mL/min); retention times: 6.5 min, 7.1 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 6H), 7.00 – 6.81 (m, 4H), 3.88 (t, *J* = 6.3 Hz, 2H), 3.71 (s, 2H), 2.59 – 2.45 (m, 1H), 1.98 – 1.53 (m, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

4.5. Notes and references

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