Chapter 2

Pd-Catalyzed Fukuyama Cross-Coupling of Secondary Organozinc Reagents for the Direct Synthesis of Unsymmetrical Ketones[†]

2.1 INTRODUCTION

Transition metal-catalyzed cross-coupling reactions have emerged as a transformative methodology in the field of organic synthesis, enabling the rapid generation of complex molecules under mild, selective, and catalytic conditions. While initial reports focused on $C(sp^2)$–$C(sp^2)$ couplings, the burgeoning field of $C(sp^3)$ bond-forming processes has rapidly expanded in the past decade.[1] In a seminal report, Hayashi and coworkers found that Pd complexes supported by bulky, bidentate phosphines with large bite angles (e.g., 1,1'-bis(diphenylphosphino)ferrocene) (dppf) can catalyze the cross-coupling between aryl or vinyl halides and primary or secondary organomagnesium and organozinc reagents.[2] In 2003, Fu and coworkers demonstrated that similar bulky,

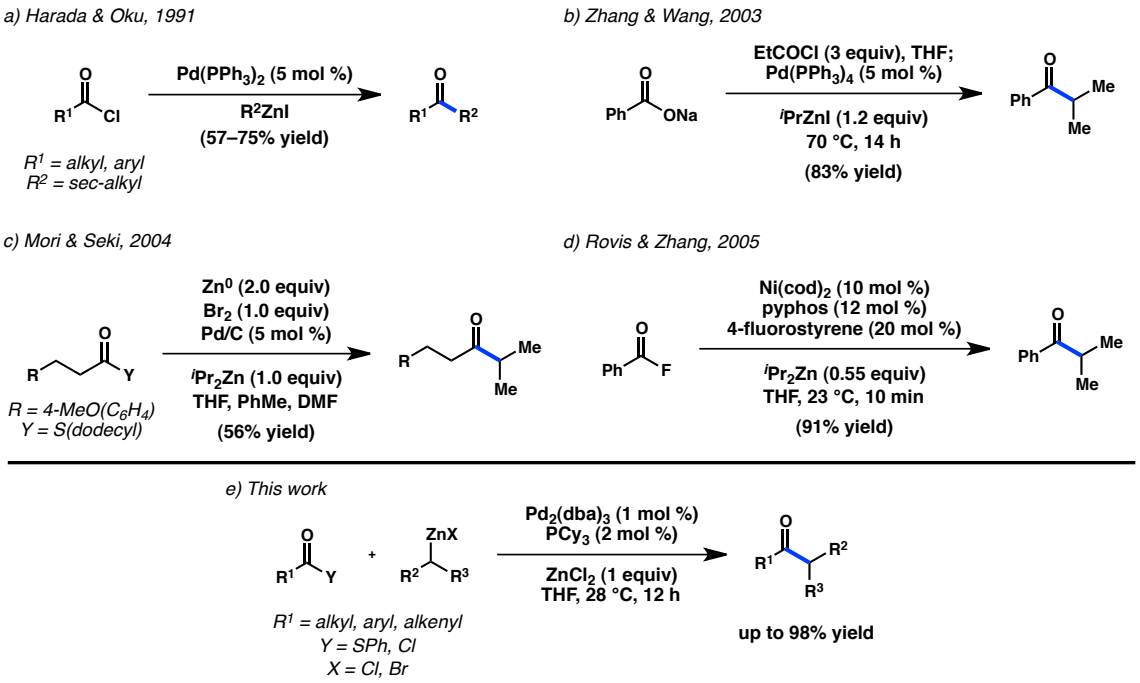
[†] Portions of this chapter have been reproduced from published studies (see reference 19) and the supporting information found therein.

electron-rich phosphines enable a general Pd-catalyzed Negishi coupling of C(sp^3)-hybridized electrophiles with alkyl, alkenyl, and aryl nucleophiles.[3] In the decade that has followed, steady advances have been made in Pd- and Ni-catalyzed cross-coupling reactions of both *secondary* C(sp^3) organometallic reagents and *secondary* C(sp^3) electrophiles, giving rise to a wide variety of products now accessible via simple alkyl building blocks.[4,5,6]

One transformation that remains underdeveloped is the transition metal-catalyzed cross-coupling reaction between carboxylic acid derivatives and C(sp^3) organometallic reagents to prepare ketones, despite the fact that the Pd-catalyzed reaction between acid chlorides and alkyl tin reagents was first reported over thirty years ago.[7] In 1998, Fukuyama and coworkers disclosed the Pd-catalyzed coupling of thioesters and primary alkyl organozinc or hydride reagents, generating ketone or aldehyde products, respectively.[8] A number of functional groups are tolerated due to the relative stability of both coupling components. Seki and coworkers have since developed both heterogeneous and phosphine-free Pd-catalyzed Fukuyama couplings, as well as a Ni-catalyzed Fukuyama coupling.[9] Despite these advances, the use of *secondary* C(sp^3) organometallic reagents still proves challenging. While α,α-disubstituted ketones can be prepared by direct attack of a variety of strongly nucleophilic organometal species onto acyl electrophiles, such protocols are frequently accompanied by over-addition products due to the electrophilicity of the newly formed ketone.[10] Specialized acyl derivatives such as Weinreb amides can minimize over-addition, but require the use of organolithium or Grignard reagents, which suffer from poor functional group tolerance.[11] Recent strategies

to eliminate the need for alkyl organometallic reagents in ketone synthesis include reverse-polarity cross-couplings[12] and reductive cross-couplings (see Chapter 3).[13]

Figure 2.1. *Acyl cross-coupling reactions of secondary organozinc reagents.*



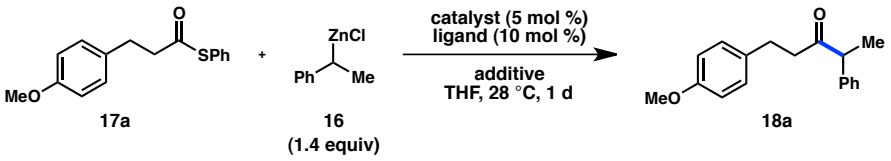
Although substantial progress has been made on the transition metal-catalyzed cross-coupling between acyl electrophiles and primary alkyl organometallic reagents, there are far fewer reports describing the coupling of secondary alkyl organometallics. In an early study, Harada and Oku disclosed the coupling of secondary organozinc reagents with acid chlorides and obtained moderate to good yields of the ketone product, although the functional group tolerance of the reaction was not further explored (Figure 2.1).[14] Zhang and Wang reported a high-yielding reaction between ^{i}PrZnI and the mixed anhydride generated from sodium benzoate; however, additional substrate scope was not disclosed.[15] Subsequently, Mori and Seki reported a Pd-catalyzed coupling between a thioester and $^{i}Pr_2Zn$ that proceeds in moderate yield.[16] Rovis and Zhang have also

reported a single case of a high-yielding coupling reaction between an acid fluoride and $^{i}Pr_2Zn$.[17] Organoboron reagents are another class of nucleophiles utilized in the related Liebskind–Srogl cross-coupling of thioesters. However, these reactions only proceed with primary organoboron reagents despite efforts to extend the reaction to secondary reagents.[18] With the objective of expanding the synthetic utility of metal-catalyzed acyl cross-coupling reactions, herein we report a general method for the cross-coupling of *secondary* organozinc reagents and thioesters.[19]

2.2 DEVELOPMENT OF A RACEMIC FUKUYAMA CROSS-COUPLING OF SECONDARY ORGANOZINC REAGENTS

The scarcity of *sec*-alkylmetal couplings with acyl derivatives is indicative of the inherent difficulties of transition metal-catalyzed reactions involving C(sp^3)-hybridized coupling partners.[1d] In general, alkyl organometallic reagents are prone to β-hydride elimination as well as proto-demetalation under typical cross-coupling reaction conditions. Additionally, many alkyl organometallics suffer from slow transmetalation to the transition metal catalyst. Furthermore, reductive elimination from a transition metal is also slow due to σ-donation of the alkyl group to the metal. The sluggishness of reductive elimination enhances side reactions such as β-hydride elimination and isomerization. Acceleration of the reductive elimination pathway, either through catalyst and ligand tuning or through the use of additives, can prevent this undesired isomerization. Significantly, alkylzinc reagents display relatively broad use in C(sp^3) cross-couplings because of their ability to undergo a facile transmetalation with Pd as compared to other organometallic partners used in cross-coupling chemistry.

Table 2.1. *Optimization of reaction conditions.*



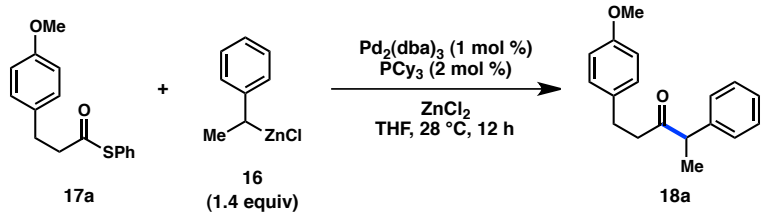
Entry	Catalyst	Ligand[a]	Additive	Conversion (%)[b]	Yield (%)[b]
1	$Ni(acac)_2$[c]	-	-	75	10
2	$NiCl_2(dme)$[c]	-	-	83	14
3	$Pd_2(dba)_3$	-	-	94	13
4	$Pd(OAc)_2$[c]	-	-	75	15
5	$PdCl_2(dppf)$[c]	-	-	88	20
6	$Pd_2(dba)_3$	PPh_3	-	92	16
7	$Pd_2(dba)_3$	PCy_3	-	89	34
8	$Pd_2(dba)_3$	SPhos	-	93	16
9	$Pd_2(dba)_3$	XPhos	-	82	14
10	$Pd_2(dba)_3$	PCy_3	DMF[e]	78	52
11	$Pd_2(dba)_3$	PMe_3	DMF[e]	100	23
12	$Pd_2(dba)_3$	PEt_3	DMF[e]	80	35
13	$Pd_2(dba)_3$	P^nBu_3	DMF[e]	90	32
14	$Pd_2(dba)_3$	P^tBu_3	DMF[e]	88	22
15	$Pd_2(dba)_3$[d]	PCy_3	DMF[e]/$ZnCl_2$[f]	100	83
16	$Pd_2(dba)_3$[d]	PCy_3	$ZnCl_2$[f]	93	89
17	$Pd_2(dba)_3$[d]	dCyb	$ZnCl_2$[f]	49	44

[a] 1:1 Pd:phosphine was used. [b] Conversion of **17a** and yield of **18a** were calculated by ^1H NMR analysis with internal standard. [c] 10 mol % was used. [d] 1 mol % was used. [e] 10 vol % was added. [f] 1 equiv was added.

We therefore began our studies by evaluating the cross-coupling between thioester **17a** and organozinc **16**. An analysis of metal catalysts revealed that Ni sources performed poorly (Table 2.1, entries 1–2), whereas $PdCl_2$(dppf) was more promising (Table 2.1, entry 5). A screen of several phosphine ligands revealed that the bulky, monodentate, electron-rich ligand PCy_3 furnished ketone **18a** in 34% yield (entries 6–9). Despite their success in a number of Negishi couplings, the Buchwald ligands SPhos and XPhos showed low reactivity.[20] On the other hand, use of 10 vol % DMF as a polar cosolvent further increased the yield to 52% (entry 10), although additional DMF had no

effect on the reaction. Other trialkylphosphines resulted in lower yields of **18a** (entries 11–14). Interestingly, these conditions of $Pd_2(dba)_3/PCy_3$/DMF closely resemble Fu's general conditions ($Pd_2(dba)_3/PCyp_3$/NMI) for Negishi cross-couplings of alkyl electrophiles.[3] Notably, *no isomerized linear product was observed*.

Table 2.2. *Effect of zinc chloride on the Fukuyama cross-coupling.*

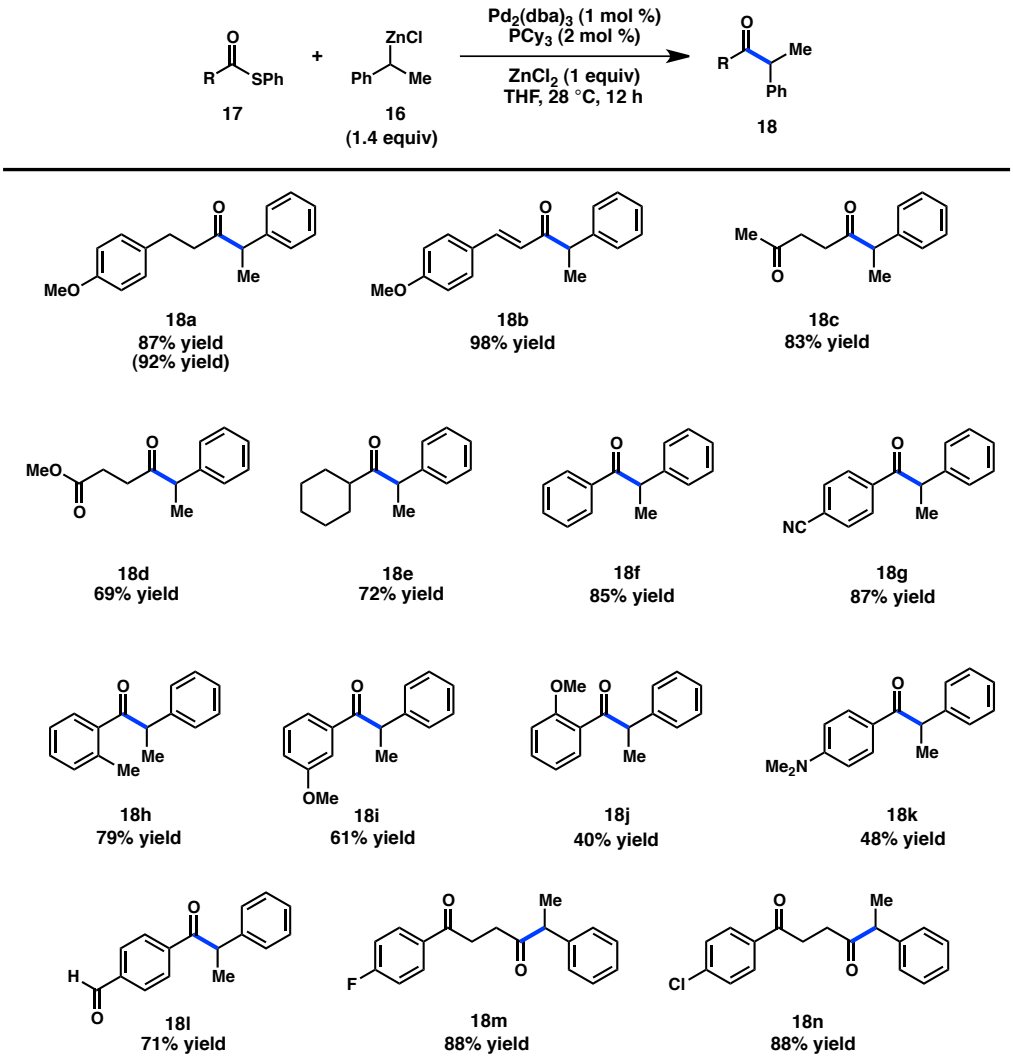


Entry	Equiv $ZnCl_2$	Yield (%)
1	0	57
2	0.1	68
3	0.5	72
4	0.75	68
5	1.0	77
6	2.0	88

Previous studies of the Fukuyama coupling have noted that addition of inorganic zinc salts may shift the Schlenk equilibrium of the organozinc reagent toward a more reactive organozinc halide and may also activate Pd toward oxidative addition.[9] Gratifyingly, addition of $ZnCl_2$ increased both the conversion and yield of the reaction, while allowing the catalyst loading to be reduced to 1 mol % $Pd_2(dba)_3$ without an appreciable decrease in yield (entry 15). Use of $ZnCl_2$ as the sole additive also obviated the need for DMF, delivering **18a** in 89% yield (entry 16). Replacement of PCy_3 for a bidentate phosphine analog, 1,4-bis(dicyclohexylphosphino)butane (dCyb), resulted in a lower conversion of **17a** and a lower yield of **18a**. To understand the effect of $ZnCl_2$, an analysis of additive loading revealed that as increasing amounts of $ZnCl_2$ are used, the

yield of ketone **18a** rises (Table 2.2). This behavior is consistent with $ZnCl_2$ modulating a Schlenk equilibrium, although further studies to establish its exact role are desirable.

Figure 2.2. *Thioester substrate scope.*

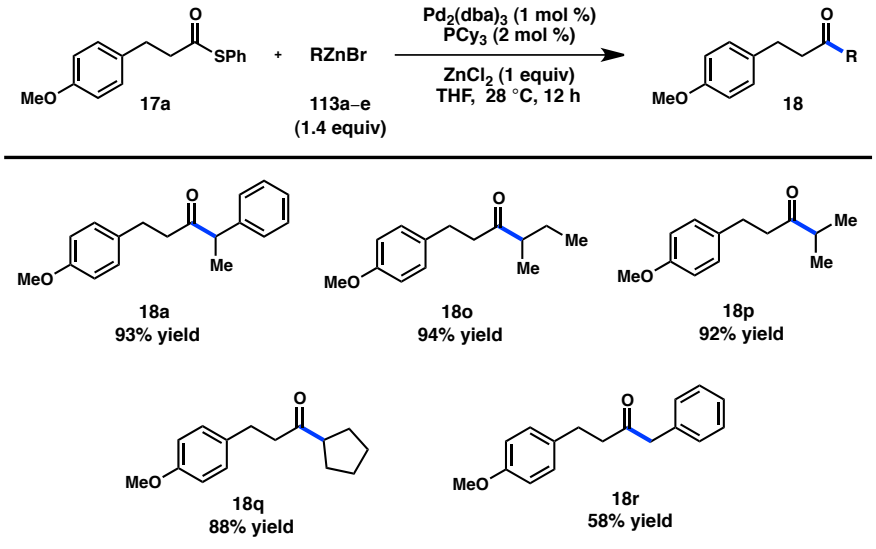


Isolated yields; reactions conducted on a 0.2 mmol scale under an N_2 atmosphere in a glovebox. Number in parentheses indicates reaction conducted on a 1.0 mmol scale under an N_2 atmosphere on the benchtop using standard Schlenk techniques.

Having developed optimized coupling conditions for secondary organozinc halides, we applied our $Pd_2(dba)_3/PCy_3/ZnCl_2$ system to a series of thioesters to determine the scope of the reaction (Figure 2.2). The cross-coupling reaction proceeds in excellent

yields for alkyl (**17a**), aryl (**17f–l**), and α,β-unsaturated thioesters (**17b**). A variety of thioesters with electrophilic functional groups such as a ketone (**17c, 17m**, **17n**), aldehyde (**17l**), ester (**17d**), or nitrile (**17g**), all of which would be incompatible with standard Weinreb ketone synthesis conditions, generate the desired coupling products in high yields. Aryl fluorides (**17m**) and chlorides (**17n**) both react with the thioester chemoselectively. The reaction can also tolerate a more sterically encumbered thioester to form **18h** in 79% yield. In contrast, a decreased yield was observed when **17j**, containing an *o*-methoxy group, was employed. α,α-Disubstituted thioester **17e** furnishes the desired product in 72% yield despite the increased steric hindrance. To illustrate the robustness of the methodology, the cross-coupling reaction was performed on a 1.0 mmol scale on the benchtop using standard Schlenk techniques, under which conditions **18a** was obtained in 92% yield.

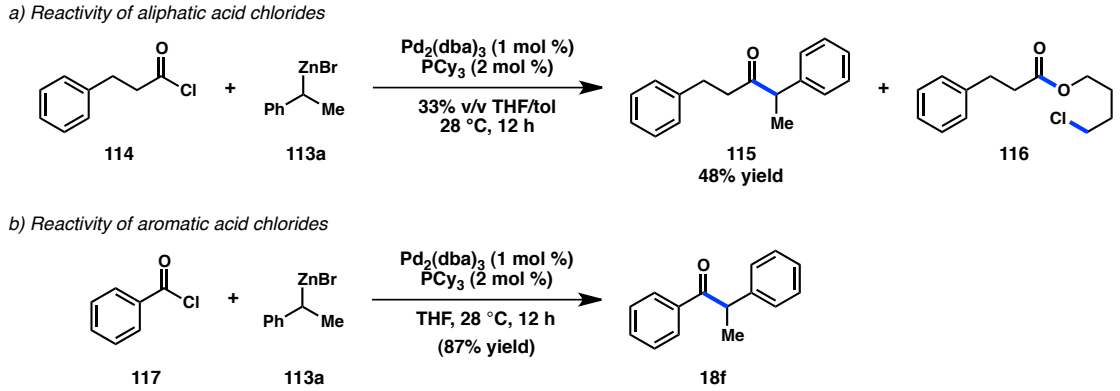
Figure 2.3. *Organozinc substrate scope.*



Isolated yields; reactions conducted on a 0.2 mmol scale under an N_2 atmosphere in a glovebox.

Given that organozinc **16** was prepared via direct insertion of Zn^0 into (1-chloroethyl)benzene (see Experimental Section), we sought to test whether commercial Rieke organozinc reagents,[21] possessing a different mixture of solubilized salts, would be equally active under our cross-coupling conditions. We were pleased to observe that ketone **18a** could be prepared in 93% yield when using Rieke organozinc reagent **113a** (Figure 2.3). Non-activated cyclic and acyclic Rieke organozinc bromides furnished the desired products in excellent yields. In the case of **18o** and **18p**, no isomerized linear product was observed.

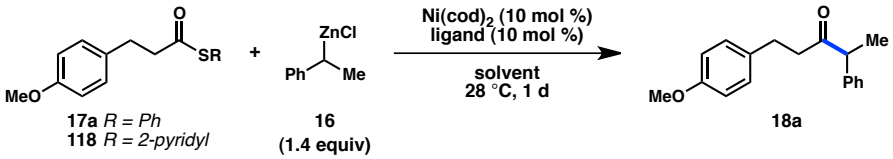
Scheme 2.1. *Extension to acid chlorides.*



While thioesters are air- and moisture-stable building blocks, acid chlorides represent one of the most commonly used types of acyl electrophile. As such, our optimized conditions were tested against several acid chloride coupling partners. Under conditions developed for the coupling of thioesters, aliphatic acid chlorides reacted slowly and primarily underwent a competitive Lewis acid-mediated reaction with THF to form ester **116** (Scheme 2.1, a).[22] However, treatment of acid chloride **114** with organozinc **113a** in a mixed solvent system, and in the absence of excess $ZnCl_2$, delivered ketone **115** in 48% yield. Aromatic acid chlorides proved to be more reactive toward

cross-coupling than their aliphatic counterparts: in the absence of excess $ZnCl_2$, benzoyl chloride (**117**) could be coupled to generate **18f** in 87% yield (Scheme 2.1, b).

Table 2.3. *Optimization of a Ni-catalyzed Fukuyama cross-coupling.*



17a *R = Ph*
118 *R = 2-pyridyl*

16
(1.4 equiv)

18a

Entry	Thioester	Ligand	Solvent	Conversion (%)[a]	Yield (%)[a]
1[b]	17a	PCy_3	THF		0
2[b]	17a	phen	THF	32	0
3	17a	phen	THF	54	11
4	17a	phen	4:1 THF/DMF	56	23
5	17a	bipy	4:1 THF/DMF	37	12
6	17a	terpy	4:1 THF/DMF	49	7
7	17a	bathophen	4:1 THF/DMF	54	21
8	118	phen	4:1 THF/DMF	100	71
9	118	phen	THF	100	70

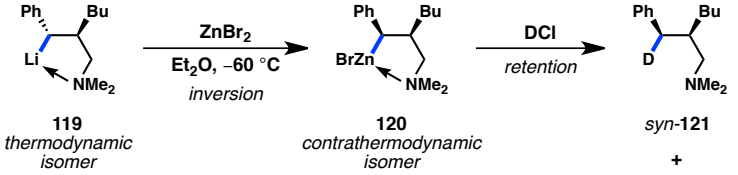
[a] Conversion of **17a** and **118** and yield of **18a** were calculated by ^1H NMR analysis with internal standard. [b] 1 equiv $ZnCl_2$ was added.

Having successfully identified conditions for a Pd-catalyzed Fukuyama cross-coupling between thioesters and secondary organozinc reagents, the potential for Ni catalysis was reinvestigated. The presence of excess $ZnCl_2$ prevented product formation when either phosphorus or nitrogen ligands were employed (Table 2.3, entries 1–3). A screen of cosolvents revealed that the addition of DMF, with phenanthroline serving as a bidentate ligand, produced ketone **18a** in 23% yield (entry 4). A further evaluation of nitrogen-based ligands failed to increase the conversion of thioester **17a** or the yield of ketone **18a** (entries 5–7). In contrast, utilization of 2-pyridyl thioester **118** provided full conversion of the starting material and furnished **18a** in 70% yield when THF was employed as the sole solvent (entries 8 and 9).[23]

2.3 EFFORTS TOWARD AN ENANTIOSELECTIVE FUKUYAMA CROSS-COUPLING

Having identified conditions for the coupling of thioesters and secondary organozinc reagents, we initiated an investigation of whether the coupling between organozinc **16** and thioester **17a** would be amenable to asymmetric catalysis. We realized that benzylzinc halides might possess a suitable configurational lability about the C–Zn bond, permitting a fast equilibration between the two enantiomers of organometallic **16**. If this equilibration is rapid in relation to transmetalation, then an appropriate chiral catalyst could selectively react with a single enantiomer of the nucleophile and cause a dynamic kinetic resolution (DKR). Indeed, Marek and coworkers have demonstrated that benzylzinc halides epimerize rapidly at elevated temperatures and at a moderate rate at 0 °C (Figure 2.4).[24] Only when cooled to –30° C is epimerization of **120** minimized, providing *syn*-**121** after quenching with DCl.

Figure 2.4. *Configurational lability of benzylzinc halides.*



Interval before quench:

Temperature (°C)	Time (h)	*syn-121/anti-121*
–30	4	98:2
0	1	50:50
50	2	2:98

A series of chiral ligand scaffolds were evaluated under our previously optimized conditions in order to assess the validity of the proposed DKR. Several common chiral

bidentate phosphine ligands failed to deliver ketone **18a** in appreciable yields (Figure 2.5). Notably, ferrocenylphosphine **L17**, which has previously been demonstrated to promote asymmetric Kumada–Corriu cross-couplings through a DKR mechanism, was ineffective in this system.[25] On the other hand, we were pleased to realize that monodentate phosphines, including NMDPP (**L64**) and Monophos (**L65**), delivered moderate yields of the desired product, albeit with little enantioinduction. Nitrogen-based ligands from the PHOX, Box, and PyBox families provided poor yields and ee's of the desired ketone.

Figure 2.5. *Preliminary study of chiral ligand scaffolds.*

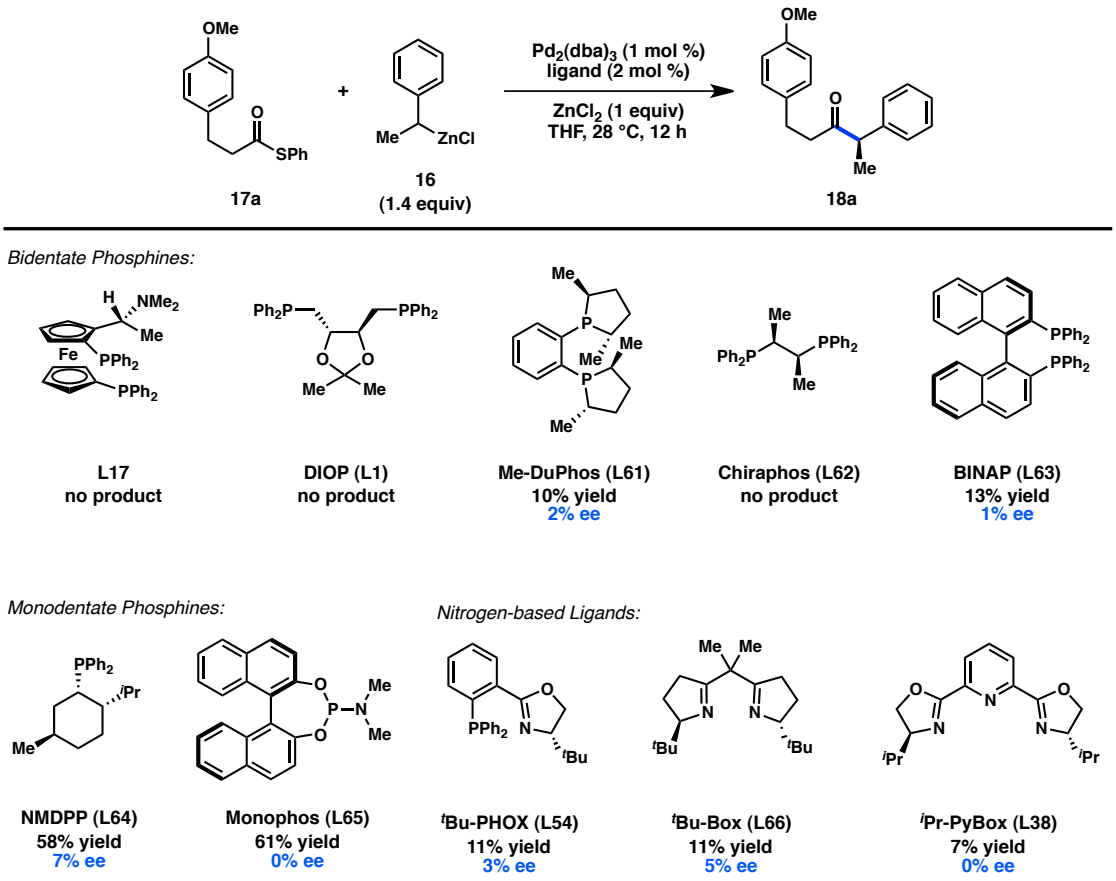
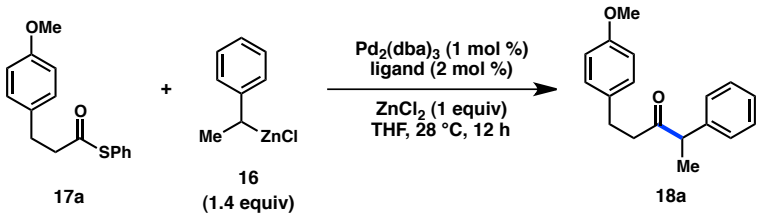
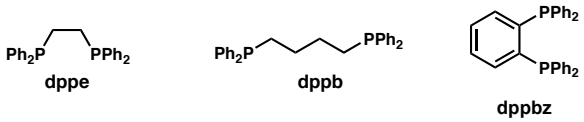


Table 2.4. *Activity of monodentate and bidentate phosphine ligands.*



Entry	Ligand	Pd:Ligand	Conversion (%)	Yield (%)
1	PPh_3	2:1	95	55
2	PPh_3	1:1	100	90
3	PPh_3	1:2	100	82
4	PPh_3	1:4	81	74
5	dppe	1:1	12	9
6	dppb	1:1	31	13
7	dppbz	1:1	11	10



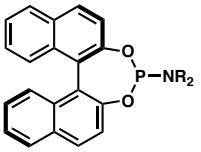
In order to better understand the divergent activity of monodentate and bidentate phosphines, additional mechanistic studies were conducted prior to further ligand development. Variation of the metal/ligand ratio revealed that complete conversion and excellent yields are realized when a 1:1 ratio is employed (Table 2.4, entries 1–4). When an excess of ligand is utilized, a systematic decrease in product yield is observed. These results corroborate the superiority of a 1:1 stoichiometry between metal and ligand, but they also suggest that excess phosphine may exhibit an inhibitory effect on Pd, as evidenced by the incomplete conversion witnessed when four equivalents of phosphine are used relative to Pd (entry 4). In contrast to PPh_3, bidentate ligands strongly disfavor formation of monoligated Pd species; indeed, switching to such ligands delivers poor yields of ketone **18a** and additionally inhibits conversion of thioester **17a**. These results

indicate that additional investigation of chiral ligand scaffolds should focus on chiral monodentate ligands as opposed to their bidentate counterparts.

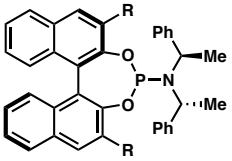
While good yields were expected with NMDPP (**L64**) because of its steric and electronic similarity to PCy_3, we were pleased that Monophos (**L65**) also displayed similar reactivity (see Figure 2.5). In contrast to NMDPP, phosphoramidites have seen widespread use in asymmetric catalysis, including in monophosphine-metal-catalyzed reactions.[26] Despite finding diverse applications in conjugate addition and allylic substitution chemistry, few examples exist of phosphoramidites being used in Pd-catalyzed non-Heck cross-couplings.[27] Inspired by these other successes using phosphoramidites, we sought to evaluate more members of the ligand family under our previously optimized reaction conditions. In a first generation approach, incorporation of simple amine groups into the phosphoramidite framework provided measurable asymmetric induction (Figure 2.6, **L67–L69**). In a second generation of ligand synthesis, we reasoned that phosphoramidites bearing chiral amines might better impart high levels of enantioinduction. Gratifyingly, phosphoramidite **L70** delivered ketone **18a** in 72% yield and 32% ee, while the ligand diastereomer **L71** only provided the product in 25% ee. A structure-activity study revealed the important nature of both the phenyl rings and the chiral centers on the amine (**L72–L76**). Replacement of the phenyl groups with other aromatic moieties did not succeed in increasing the enantioselectivity of the Fukuyama coupling (**L77–L79**). Lastly, chiral diaryl pyrrolidines, acting as tethered analogues of **L70**, resulted in reduced ee's of ketone **18a** (**L80** and **L81**). Having identified an optimal amine substituent, third generation ligands were prepared with substitution at the 3,3' position on the BINOL backbone. In all cases, substitution delivered ketone **18a** in lower

Figure 2.6. *Phosphoramidite ligands in the Fukuyama cross-coupling.*

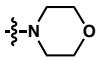
Backbone for First and Second Generation Ligands



Backbone for Third Generation Ligands



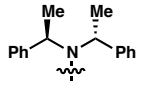
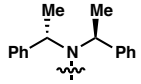
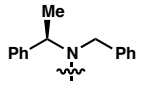
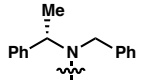
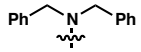
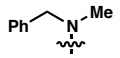
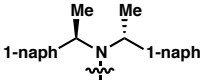
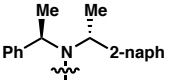
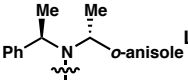
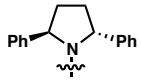
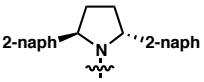
First Generation Ligands - Simple Amines

Entry	NR_2	Ligand	Yield (%)	ee (%)
1		L65	61	0
2		L67	35	12
3		L68	35	8
4		L69	53	2

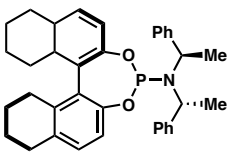
Third Generation Ligands - BINOL Substitution

Entry	R	Ligand	Yield (%)	ee (%)
1	Me	L82	19	1
2	Ph	L83	15	9
3	F	L84	20	10

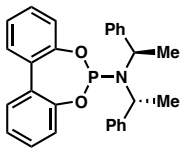
Second Generation Ligands - Chiral Amines

Entry	NR_2	Ligand	Yield (%)	ee (%)
1		L70	72	32
2		L71	58	25
3		L72	61	28
4		L73	66	32
5		L74	55	20
6		L75	39	19
7		L76	51	12
8		L77	41	17
9		L78	56	27
10		L79	68	23
11		L80	63	20
12		L81	52	19

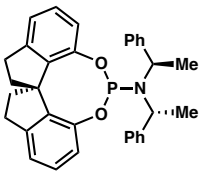
Fourth Generation Ligands - Other Backbones



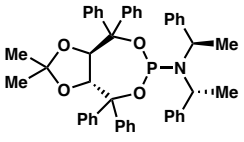
L85
82% yield
27% ee



L86
76% yield
12% ee



L87
21% yield
23% ee



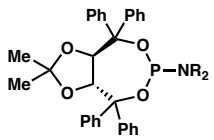
L88
16% yield
7% ee

yield and ee than when **L70** was utilized (**L82–L84**). Fourth generation ligands focused on novel backbone structures: the octahydro-BINOL backbone provided similar results to **L70**, while a biphenyl backbone provided ketone **18a** in lower ee, illustrating the importance of an interplay between both the central and axial chirality of **L70**. Spirocyclic and TADDOL backbones also did not form product in greater ee than **L70**.

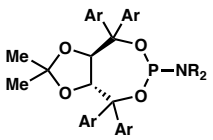
Table 2.5. *TADDOL-Based phosphoramidites in the Fukuyama cross-coupling.*

Entry	NR_2	Ligand	Yield (%)	ee (%)
1		L55	83	24
2		L89	72	28
3		L90	16	6
4		L91	16	–11
5		L92	39	21
6		L93	66	19
7		L94	55	19
8		L95	83	24
9		L96	43	9
10		L97	51	7

For entries 1–8:



For entries 9 and 10:



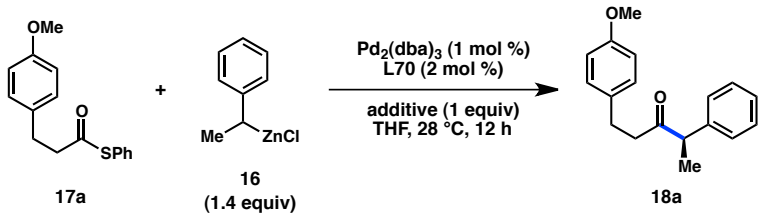
Ar = 2-naphthyl

While only low enantioinduction could be achieved with BINOL-based phosphoramidites, commercially-available TADDOL-based ligand **L55** delivered a promising 83% yield and 24% ee of ketone **18a** (Table 2.5, entry 1). Unfortunately, evaluation of a series of TADDOL-based phosphoramidites bearing simple amines did not significantly raise the level of asymmetric induction (**L89–L95**). Utilization of a bulkier TADDOL backbone, as in the case of **L96** and **L97**, led to a reduction in

enantioselectivity. In contrast to the BINOL-based ligands, use of chiral amine groups did not lead to an increase in the ee of ketone **18a** (see Figure 2.6, **L88**).

As phosphoramidite **L70** furnished ketone **18a** in the greatest ee, we began to explore **L70** with other parameters to enhance the asymmetric induction. Altering the catalyst loading, Pd:L ratio, Pd source, and solvent gave little improvement in ee. Use of either an analogous *S*-ethyl thioester or an acid chloride generated ketone products in similar ee's, suggesting that these leaving groups have little effect on the stereochemistry-determining step.

Table 2.6. *Effect of zinc halides on enantioinduction.*

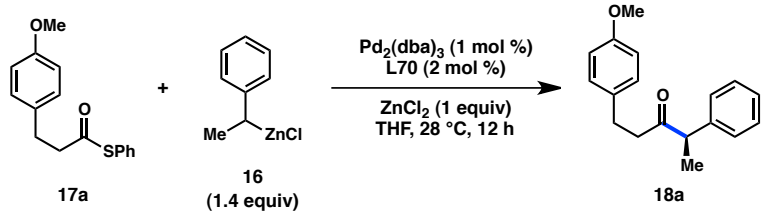


Entry	Additive	Yield (%)	ee (%)
1	none	51	22
2	ZnF_2	59	28
3	$ZnCl_2$	68	31
4	$ZnBr_2$	77	27
5	ZnI_2	79	12

A series of salts were assessed to evaluate the role of inorganic additives on enantioinduction. $ZnCl_2$ was observed to have a positive effect on the ee of ketone **18a** when compared with no additive (Table 2.6, entries 1 and 3). While $ZnBr_2$ and ZnI_2 gave slightly improved yields of the ketone product, the ee decreased to 27% and 12%, respectively (entries 4 and 5). This observed counterion effect may result from an exchange of the halide moiety of organozinc **16**: less electronegative counterions on **16** would increase the covalency of the C–Zn bond, hindering its propensity to invert and

establish a DKR. Polar additives have also been shown to increase enantioselectivity in organozinc additions to aldehydes by sequestering diorganozinc species that contribute to background reactivity. Unfortunately, NMP nearly shut down the reaction, DMF decreased the ee, and TMEDA had little effect on the reaction outcome. To date $ZnCl_2$ remains the most potent additive for increasing the enantioselectivity of the reaction.

Table 2.7. *Understanding the origin of enantioinduction.*



Effect of conversion on ee:

Entry	Time (h)	Conversion (%)	ee (%)
1	0.25	20	30
2	3	73	30
3	23	100	28

Effect of equivalents of organozinc reagent on ee:

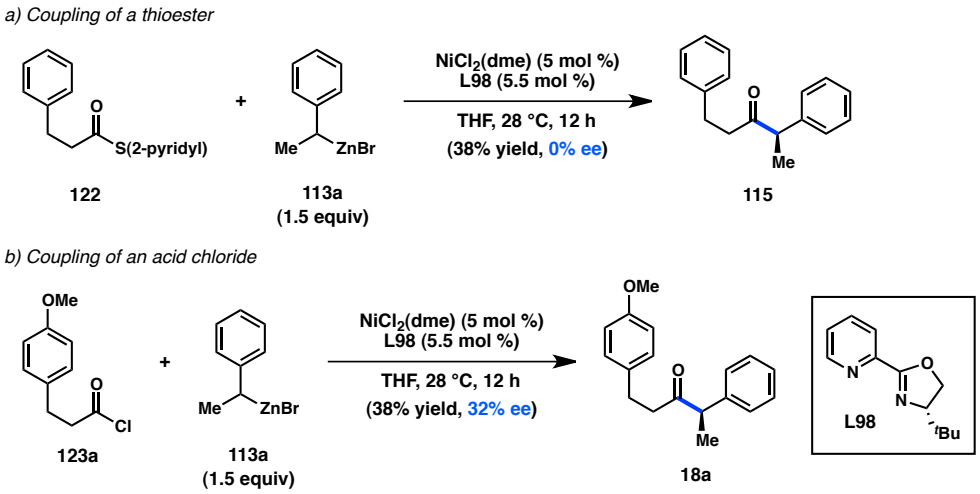
Entry	Equivalents	Yield (%)	ee (%)
1	1.2	68	26
2	2.4	87	28
3	3.6	90	29

Several experiments have been conducted to better understand the origin of enantioinduction in this system. Measuring the enantioselectivity as a function of conversion reveals that asymmetric induction is independent of reaction progress (Table 2.7). This result supports enantioinduction arising from a DYKAT instead of a simple kinetic resolution, as simple kinetic resolutions often lead to erosion of ee as all the starting material is consumed. It has also been determined that the ee of ketone **18a** is independent of the organozinc loading. If interconversion of the enantiomers of **16** was slow and a simple kinetic resolution was taking place, then addition of excess reagent would be expected to increase the enantioselectivity of the transformation significantly. Taken together, these results suggest that the asymmetric transformation proceeds

according to a DYKAT instead of a simple kinetic resolution. To date, there is not enough data to determine whether a fast racemization of organozinc **16** relative to transmetalation (as in a DKR) or a subsequent epimerization of diastereomeric Pd complexes is the cause of the enantioinduction. Likewise, further studies are necessary to determine whether the stereochemistry-determining step is transmetalation or reductive elimination.

A preliminary study of an asymmetric Ni-catalyzed acyl cross-coupling was conducted with an array of chiral bidentate nitrogen ligands. In the presence of 2-pyridyl thioester **122**, moderate yields but no enantioinduction was observed for all ligands that were tested (Scheme 2.2). Surprisingly, treatment of acid chloride **123a** with ^{t}Bu-PyOx (**L98**) delivered ketone **18a** in 38% yield and 32% ee. Other chiral ligands, including additional members of the PyOx ligand family, failed to impart any asymmetric induction. These results illustrate the non-innocent nature of the 2-pyridyl leaving group in this asymmetric cross-coupling.

Scheme 2.2. *Asymmetric Ni-catalyzed acyl cross-coupling.*



2.4 CONCLUDING REMARKS

In conclusion, a practical method for the Pd-catalyzed Fukuyama cross-coupling of thioesters and *secondary* organozinc reagents has been developed. The $Pd_2(dba)_3/PCy_3/ZnCl_2$ system furnishes high yields of complex ketone products in a convergent fashion. These conditions also allow for the Negishi coupling of aryl acid chlorides to proceed in high yield. An analysis of chiral ligands revealed that modestly enantioenriched ketone products could be achieved in the presence of a chiral phosphoramidite ligand. Mechanistic studies currently favor a DYKAT instead of a simple kinetic resolution to explain the origin of enantioinduction. Efforts to increase the synthetic utility of the Fukuyama coupling and further extension to asymmetric catalysis are ongoing in our laboratory.

2.5 EXPERIMENTAL SECTION

2.5.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were dried by passing through activated alumina columns. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. $Pd_2(dba)_3$ and PCy_3 were purchased from Aldrich and used as received. Phosphoramidite ligands were either purchased from Aldrich or synthesized according to literature procedures. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV,

p-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed as described by Still et al.[28] using silica gel (particle size 0.032-0.063) purchased from Silicycle. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), and are reported relative to internal chloroform (^1H, δ = 7.26, ^{13}C, δ = 77.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

2.5.2 Substrate Synthesis

General Procedure 1 for Synthesis of Thioesters

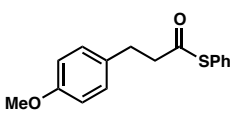
According to the protocol of Tanabe and coworkers,[29] a flask was charged with 3-(4-methoxyphenyl)propionic acid (58.2 mmol, 1 equiv) followed by MeCN (60 mL) and *N*-methyl imidazole (174.6 mmol, 3 equiv). The solution was cooled to 0 °C and tosyl chloride (1.5 M solution in MeCN, 87.3 mmol, 1.5 equiv) was added. The reaction was stirred at 0 °C under N_2 for 0.5 h, after which time thiophenol (1.0 M solution in MeCN,

58.2 mmol, 1 equiv) was added. The reaction was stirred at 0 °C under N_2 for 2 h and then allowed to warm to room temperature. The resulting solution was diluted with ether and water. The aqueous layer was extracted with ether and the combined organic layers were washed with water, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

General Procedure 2 for Synthesis of Thioesters

A flame-dried flask was charged with 4-cyanobenzoic acid (5.8 mmol, 1 equiv) and CH_2Cl_2 (12 mL). The reaction was cooled to 0 °C and isobutyl chloroformate (6.38 mmol, 1.1 equiv) and Et_3N (5.8 mmol, 1 equiv) were added dropwise. The resulting mixture was stirred vigorously for 10 min under N_2, after which time Et_3N (5.8 mmol, 1 equiv) and thiophenol (12.76 mmol, 2.2 equiv) were added dropwise. The reaction was stirred at 0 °C under N_2 for 1 h. The reaction was warmed to room temperature and washed with 1 M HCl, water, 1 M NaOH, water, and brine. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography.

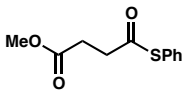
***S*-Phenyl 3-(4-methoxyphenyl)propanethioate (17a)**



Prepared from 3-(4-methoxyphenyl)propionic acid (10.5 g, 58.2 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (2:98 to 10:90 EtOAc:hexanes) to yield 13.19 g (83% yield) of **17a** as a white solid, mp 31 – 32 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.36 (m, 5H), 7.18 – 7.09 (m, 2H), 6.89 – 6.81 (m, 2H), 3.80 (s, 3H), 3.03 – 2.89 (m, 4H);

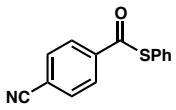
^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 158.1, 134.5, 131.9, 129.3, 129.2, 129.1, 127.6, 113.9, 55.2, 45.4, 30.5; IR (NaCl/thin film): 2932, 2834, 1706, 1611, 1512, 1477, 1440, 1247 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 271.0798, found 271.0799.

Methyl 4-oxo-4-(phenylthio)butanoate (17d)



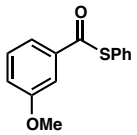
Prepared from monomethyl succinate (2.56 g, 19.4 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 2.21 g (51% yield) of **17d** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 5H), 3.69 (s, 3H), 3.00 (t, J = 6.9 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.14, 172.2, 134.5, 129.5, 129.2, 127.2, 51.9, 38.0, 28.9; IR (NaCl/thin film): 3061, 2997, 2952, 1739, 1707, 1478, 1440 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 223.0434, found 223.0285.

***S*-Phenyl 4-cyanobenzothioate (17g)**



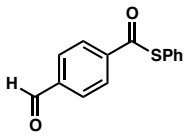
Prepared from 4-cyanobenzoic acid (859 mg, 5.8 mmol) following General Procedure 2. The crude residue was recrystallized from ether to yield 991 mg (71% yield) of **17g** as a slightly yellow solid, mp 127 – 129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 8.17 – 8.06 (m, 2H), 7.84 – 7.76 (m, 2H), 7.57 – 7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.1, 139.8, 134.9, 132.6, 130.0, 129.5, 127.9, 126.2, 117.8, 116.9; IR (NaCl/thin film): 3089, 2231, 1683, 1668, 1479, 1404, 1207, 1172 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 238.0332, found 238.0327.

_S_-Phenyl 3-methoxybenzothioate (17i)



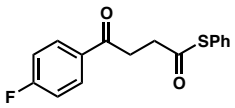
Prepared from 3-methoxybenzoic acid (2.95 g, 19.4 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 2.41 g (51% yield) of **17i** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 1H), 7.57 – 7.35 (m, 7H), 7.16 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 159.8, 137.9, 135.0, 129.7, 129.5, 129.3, 129.2, 127.3, 120.0, 111.7, 55.5; IR (NaCl/thin film): 3060, 3004, 2938, 2835, 1679, 1597, 1583, 1484, 1440, 1288, 1260 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 242.0485, found 242.0462.

_S_-Phenyl 4-formylbenzothioate (17l)



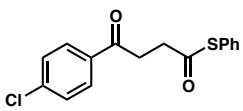
Prepared from 4-formylbenzoic acid (870 mg, 5.8 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (2:98 EtOAc:hexanes) to yield 88 mg (6% yield) of **17l** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.22 – 8.12 (m, 2H), 8.06 – 7.95 (m, 2H), 7.58 – 7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 189.6, 141.0, 139.4, 134.9, 129.9 (2C), 129.4, 128.0, 126.6; IR (NaCl/thin film): 3064, 2844, 2744, 1700, 1676, 1575, 1438, 1383, 1198 cm^{-1}; HRMS (MM) calc'd for $[M–CHO]^-$ 213.0374, found 213.0373.

_S_-Phenyl 4-(4-fluorophenyl)-4-oxobutanethioate (17m)



Prepared from 3-(4-fluorobenzoyl)propionic acid (1.14 g, 5.8 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 1.44 g (86% yield) of **17m** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.94 (m, 2H), 7.49 – 7.35 (m, 5H), 7.19 – 7.07 (m, 2H), 3.34 (t, *J* = 6.6 Hz, 2H), 3.14 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.8, 195.9, 165.8 (d, *J*C-F = 254.8 Hz), 134.5, 132.8, 130.7 (d, *J*C-F = 9.0 Hz), 129.4, 129.2, 127.5, 115.7 (d, *J*C-F = 21.8 Hz), 37.3, 33.3; IR (NaCl/thin film): 3075, 2915, 1705, 1687, 1597, 1506, 1478, 1441, 1409, 1234 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 287.0548, found 287.0542.

_S_-Phenyl 4-(4-chlorophenyl)-4-oxobutanethioate (17n)



Prepared from 3-(4-chlorobenzoyl)propionic acid (1.23 g, 5.8 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 1.08 g (61% yield) of **17n** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.85 (m, 2H), 7.48 – 7.35 (m, 7H), 3.33 (t, *J* = 6.6 Hz, 2H), 3.14 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 196.3, 139.7, 134.6, 134.5, 129.4, 129.3, 129.2, 128.9, 127.4, 37.2, 33.4; IR (NaCl/thin film): 3060, 2914, 1706, 1685, 1590, 1478, 1441, 1400 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 305.0398, found 305.0406.

Preparation of Organozinc 16

According to the protocol of Orito and coworkers,[30] a flame-dried Schlenk flask was charged with zinc dust (2.80 g, 42.6 mmol, 1.5 equiv), TMSCl (0.14 mL, 1.12 mmol, 0.04 equiv), and THF (14 mL). The reaction was stirred at room temperature under N_2 for 15 min. To the reaction was added (1-chloroethyl)benzene (4.00 g, 28.4 mmol, 1 equiv) dropwise. The reaction was stirred at 40 °C under N_2 for 4 h. The mixture was cooled to room temperature and the excess zinc dust was allowed to settle. The solution was titrated with I_2 according to Knochel and coworkers.[31] The yellow organozinc solution was transferred to a flame-dried flask and stored under N_2 at –20 °C. Concentrations of 1.0 M were obtained.

General Procedure for Synthesis of Phosphoramidite Ligands

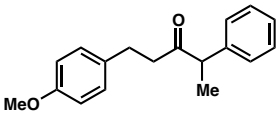
A flame-dried flask was charged with PCl_3 (1 mmol, 1 equiv) and CH_2Cl_2 (5 mL). The reaction was cooled to 0 °C and Et_3N (5 mmol, 5 equiv) was added dropwise, followed by addition of amine (1 mmol, 1 equiv). The reaction was stirred at 23 °C under N_2 for 5 h. Diol (1 mmol, 1 equiv) was added and the reaction was stirred at 23 °C under N_2 for 11 h. The reaction was filtered and concentrated. The crude residue was purified by column chromatography (100% CH_2Cl_2) to obtain a white foamy solid.

2.5.3 General Procedure for Fukuyama Cross-Coupling Reaction

In a glovebox, a vial was charged with $Pd_2(dba)_3$ (0.002 mmol, 0.01 equiv), PCy_3 (0.004 mmol, 0.02 equiv), and THF (1 mL). The deep purple solution was stirred at 28 °C for 10

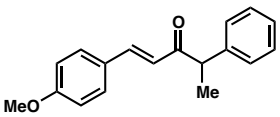
min. The thioester substrate **17** (0.2 mmol, 1 equiv), the (1-phenylethyl)zinc(II) chloride (**16**, 1.0 M THF, 0.28 mmol, 1.4 equiv), and $ZnCl_2$ (1.0 M THF, 0.2 mmol, 1 equiv) were added to the reaction. The reaction was stirred at 28 °C for 12 h, after which time it was removed from the glovebox, quenched with 0.1 mL sat. aq. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

1-(4-methoxyphenyl)-4-Phenylpentan-3-one (18a)



Prepared from *S*-phenyl 3-(4-methoxyphenyl)propanethioate (**17a**, 54.1 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 46.8 mg (87% yield) of **18a** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 3H), 7.22 – 7.14 (m, 2H), 7.05 – 6.96 (m, 2H), 6.84 – 6.75 (m, 2H), 3.79 (s, 3H), 3.72 (q, J = 7.0 Hz, 1H), 2.88 – 2.57 (m, 4H), 1.39 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 157.8, 140.4, 133.0, 129.2, 128.9, 127.8, 127.1, 113.7, 55.2, 53.2, 42.8, 29.1, 17.3; IR (NaCl/thin film): 3060, 3027, 2973, 2931, 2834, 1713, 1611, 1513, 1493, 1452, 1300, 1247 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 267.1391, found 267.1391.

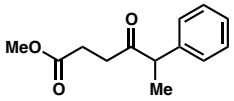
(*E*)-1-(4-methoxyphenyl)-4-Phenylpent-1-en-3-one (18b)



Prepared from (*E*)-*S*-phenyl 3-(4-methoxyphenyl)prop-2-enethioate (**17b**, 54.1 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 52.0 mg (98% yield) of **18b** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 15.9 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.19 (m, 5H), 6.91 – 6.80 (m, 2H), 6.60 (d, J =

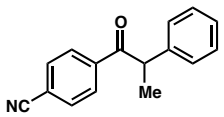
15.9 Hz, 1H), 4.01 (q, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 1.49 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 161.4, 142.4, 140.9, 130.0, 128.9, 128.0, 127.2, 127.0, 122.4, 114.2, 55.3, 51.7, 17.9; IR (NaCl/thin film): 2971, 2930, 2837, 1684, 1654, 1598, 1572, 1511, 1254 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 265.1234, found 265.1239.

Methyl 4-oxo-5-phenylhexanoate (18d)



Prepared from methyl 4-oxo-4-(phenylthio)butanoate (**17d**, 44.9 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 30.3 mg (69% yield) of **18d** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.16 (m, 5H), 3.79 (q, *J* = 7.0 Hz, 1H), 3.63 (s, 3H), 2.77 – 2.38 (m, 4H), 1.41 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 173.2, 140.4, 128.9, 127.9, 127.2, 52.9, 51.7, 35.6, 27.9, 17.3; IR (NaCl/thin film): 3062, 3027, 2977, 2952, 2932, 1739, 1716, 1494, 1453, 1437, 1372, 1356, 1211 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 221.1172, found 221.1173.

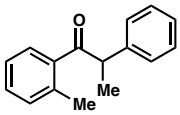
4-(2-phenylpropanoyl)Benzonitrile (18g)



Prepared from *S*-phenyl 4-cyanobenzothioate (**17g**, 47.9 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 40.8 mg (87% yield) of **18g** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.71 – 7.61 (m, 2H), 7.39 – 7.17 (m, 5H), 4.61 (q, *J* = 6.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 140.4, 139.5, 132.3, 129.3, 129.1, 127.6, 127.3, 117.9, 115.9, 48.6, 19.3; IR

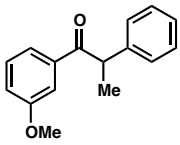
(NaCl/thin film): 3061, 2976, 2930, 2230, 1685, 1600, 1452, 1404, 1218, 1199 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 234.0924, found 234.0932.

2-Phenyl-1-(*o*-tolyl)propan-1-one (18h)



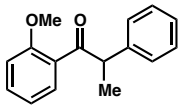
Prepared from *S*-phenyl 2-methylbenzothioate (**17h**, 45.7 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 EtOAc:hexanes) to yield 35.6 mg (79% yield) of **18h** as a slightly yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.06 (m, 8H), 4.53 (q, *J* = 6.9 Hz, 1H), 2.34 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.6, 140.4, 138.5, 137.8, 131.5, 130.7, 128.8, 127.9, 127.8, 126.9, 125.3, 50.7, 20.8, 18.5; IR (NaCl/thin film): 3061, 3026, 2971, 2929, 2870, 1685, 1600, 1492, 1452, 1220 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 238.1128, found 238.1128.

1-(3-methoxyphenyl)-2-Phenylpropan-1-one (18i)



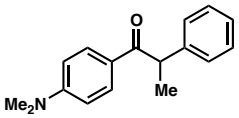
Prepared from *S*-phenyl 3-methoxybenzothioate (**17i**, 48.9 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 EtOAc:hexanes) to yield 29.2 mg (61% yield) of **18i** as a slightly yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 2H), 7.34 – 7.25 (m, 5H), 7.24 – 7.15 (m, 1H), 7.02 (ddd, *J* = 8.2, 2.7, 0.9 Hz, 1H), 4.67 (q, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 1.53 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 159.7, 141.5, 137.8, 129.4, 129.0, 127.7, 126.9, 121.4, 119.3, 113.1, 55.3, 48.0, 19.5; IR (NaCl/thin film): 3062, 3025, 2973, 2930, 2835, 1681, 1596, 1581, 1488, 1451, 1426, 1263 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 239.1078, found 239.1088.

1-(2-methoxyphenyl)-2-Phenylpropan-1-one (18j)



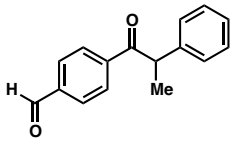
Prepared from *S*-phenyl 2-methoxybenzothioate (**17j**, 48.9 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 EtOAc:hexanes) to yield 19.2 mg (40% yield) of **18j** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.39 (ddd, *J* = 8.3, 7.3, 1.8 Hz, 1H), 7.34 – 7.13 (m, 5H), 6.95 – 6.89 (m, 2H), 4.75 (q, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 157.5, 141.3, 135.1, 132.7, 130.4, 128.4, 128.1, 126.6, 120.5, 111.3, 55.3, 51.8, 18.7; IR (NaCl/thin film): 2929, 1736, 1666, 1597, 1485, 1466, 1284, 1245, 1198 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 241.1223, found 241.1223.

1-(4-(dimethylamino)phenyl)-2-Phenylpropan-1-one (18k)



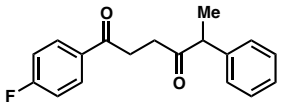
Prepared from *S*-phenyl 4-(dimethylamino)benzothioate (**17k**, 51.5 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 24.4 mg (48% yield) of **18k** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 2H), 7.36 – 7.23 (m, 4H), 7.23 – 7.13 (m, 1H), 6.62 – 6.55 (m, 2H), 4.64 (q, *J* = 6.9 Hz, 1H), 3.00 (s, 6H), 1.51 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 153.1, 142.6, 131.0, 130.9, 128.7, 126.5, 124.3, 110.6, 46.9, 39.9, 19.6; IR (NaCl/thin film): 3027, 2974, 2928, 2820, 1651, 1615, 1492, 1448, 1234, 1198 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 254.1539, found 254.1543.

4-(2-phenylpropanoyl)Benzaldehyde (18l)



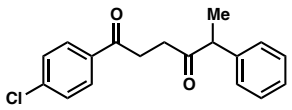
Prepared from *S*-phenyl 4-formylbenzothioate (**17l**, 48.5 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 20:80 EtOAc:hexanes) to yield 33.7 mg (71% yield) of **18l** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.11 – 7.98 (m, 2H), 7.95 – 7.75 (m, 2H), 7.45 – 7.12 (m, 5H), 4.67 (q, *J* = 6.8 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 191.5, 140.7, 138.6, 129.7, 129.2, 128.9, 127.7, 127.2, 126.8, 48.6, 19.3; IR (NaCl/thin film): 3060, 3026, 2975, 2929, 1700, 1684, 1606, 1452, 1219 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 237.0921, found 237.0909.

1-(4-fluorophenyl)-5-Phenylhexane-1,4-dione (18m)



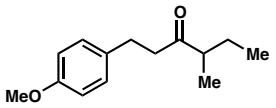
Prepared from *S*-phenyl 4-(4-fluorophenyl)-4-oxobutanethioate (**17m**, 57.7 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 10:90 EtOAc:hexanes) to yield 50.3 mg (88% yield) of **18m** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.92 (m, 2H), 7.41 – 7.33 (m, 2H), 7.30 – 7.21 (m, 3H), 7.16 – 7.05 (m, 2H), 3.90 (q, *J* = 7.0 Hz, 1H), 3.28 (ddd, *J* = 18.1, 7.6, 5.8 Hz, 1H), 3.06 (dt, *J* = 18.1, 6.0 Hz, 1H), 2.88 (ddd, *J* = 18.2, 7.6, 5.7 Hz, 1H), 2.72 (dt, *J* = 18.2, 6.0 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 197.0, 165.7 (d, *J*C-F = 254.4 Hz), 140.6, 133.1, 130.7 (d, *J*C-F = 9.1 Hz), 128.9, 127.9, 127.2, 115.6 (d, *J*C-F = 21.8 Hz), 53.1, 34.8, 32.5, 17.4; IR (NaCl/thin film): 2975, 2913, 1714, 1685, 1597, 1506, 1410, 1231 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 283.1140, found 283.1141.

1-(4-chlorophenyl)-5-Phenylhexane-1,4-dione (18n)



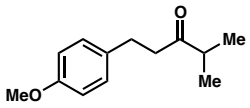
Prepared from *S*-phenyl 4-(4-chlorophenyl)-4-oxobutanethioate (**17n**, 61.0 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (2:98 to 10:90 EtOAc:hexanes) to yield 52.8 mg (88% yield) of **18n** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 2H), 7.48 – 7.22 (m, 7H), 3.89 (q, *J* = 7.0 Hz, 1H), 3.26 (ddd, *J* = 18.1, 7.5, 5.8 Hz, 1H), 3.04 (dt, *J* = 18.2, 5.9 Hz, 1H), 2.87 (ddd, *J* = 18.2, 7.6, 5.6 Hz, 1H), 2.72 (dt, *J* = 18.2, 6.0 Hz, 1H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 197.4, 140.6, 139.5, 134.9, 129.4, 128.9, 128.8, 127.9, 127.2, 53.1, 34.8, 32.5, 17.4; IR (NaCl/thin film): 3062, 3026, 2974, 2913, 1713, 1685, 1590, 1493, 1452, 1400, 1199 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 299.0844, found 299.0870.

1-(4-methoxyphenyl)-4-Methylhexan-3-one (18o)



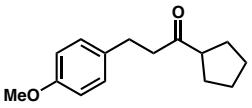
Prepared from *S*-phenyl 3-(4-methoxyphenyl)propanethioate (**17a**, 54.5 mg, 0.2 mmol) and Rieke organozinc **113b** (0.5 M THF, 0.56 mL, 0.28 mmol). The crude residue was purified by silica gel chromatography (5:95 EtOAc:hexanes) to yield 41.4 mg (94% yield) of **18o** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.05 (m, 2H), 6.87 – 6.76 (m, 2H), 3.78 (s, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.81 – 2.66 (m, 2H), 2.41 (h, *J* = 6.9 Hz, 1H), 1.71 – 1.58 (m, 1H), 1.44 – 1.29 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 157.3, 133.4, 129.2, 113.8, 55.2, 48.0, 43.0, 28.8, 25.82, 15.7, 11.6; IR (NaCl/thin film): 2964, 2933, 2875, 2835, 1710, 1612, 1513, 1462, 1300, 1247 cm^{-1}; HRMS (MM) calc'd for $[M]^+$ 220.1458, found 220.1414.

1-(4-methoxyphenyl)-4-Methylpentan-3-one (18p)



Prepared from *S*-phenyl 3-(4-methoxyphenyl)propanethioate (**17a**, 54.5 mg, 0.2 mmol) and Rieke organozinc **113c** (0.5 M THF, 0.56 mL, 0.28 mmol). The crude residue was purified by silica gel chromatography (5:95 EtOAc:hexanes) to yield 38.2 mg (92% yield) of **18p** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 2H), 6.87 – 6.78 (m, 2H), 3.78 (s, 3H), 2.87 – 2.78 (m, 2H), 2.78 – 2.68 (m, 2H), 2.56 (hept, *J* = 7.0 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.0, 157.8, 133.4, 129.2, 113.8, 55.2, 42.2, 41.0, 28.9, 18.1; IR (NaCl/thin film): 2968, 2933, 2873, 2835, 1710, 1612, 1513, 1465, 1300, 1246 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 205.1234, found 205.1575.

1-Cyclopentyl-3-(4-methoxyphenyl)propan-1-one (18q)



Prepared from *S*-phenyl 3-(4-methoxyphenyl)propanethioate (**17a**, 54.5 mg, 0.2 mmol) and Rieke organozinc **113d** (0.5 M THF, 0.56 mL, 0.28 mmol). The crude residue was purified by silica gel chromatography (5:95 EtOAc:hexanes) to yield 41.0 mg (88% yield) of **18q** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.05 (m, 2H), 6.87 – 6.78 (m, 2H), 3.78 (s, 3H), 2.88 – 2.76 (m, 3H), 2.78 – 2.69 (m, 2H), 1.84 – 1.49 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4, 157.8, 133.4, 129.2, 113.8, 55.2, 51.5, 43.6, 29.0, 28.7, 25.9; IR (NaCl/thin film): 2953, 2868, 1707, 1612, 1513, 1300, 1247 cm^{-1}; HRMS (MM) calc'd for $[M–H]^-$ 233.1536, found 233.1530.

2.5.4 Procedure for Acid Chloride Cross-Coupling

In a glovebox, a vial was charged with $Pd_2(dba)_3$ (0.002 mmol, 0.01 equiv), PCy_3 (0.004 mmol, 0.02 equiv), and THF (1 mL). The deep purple solution was stirred at 28 °C for 10 min. Acid chloride **117** (0.2 mmol, 1 equiv) and Rieke organozinc bromide **113a** (0.5 M THF, 0.56 mmol, 1.4 equiv) were added to the reaction. The reaction was stirred at 28 °C for 12 h, after which time it was removed from the glovebox, quenched with 0.1 mL sat. NH_4Cl, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

2.6 NOTES AND REFERENCES

(1) For reviews on alkyl halides in cross-couplings: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. & Catal.* **2004**, *346*, 1525. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. For a review on alkyl organometallics in cross-couplings: (d) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011,** *111*, 1417.

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