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Ligand differentiated complementary Rh-catalyst systems for the enantioselective desymmetrization of *meso*-cyclic anhydrides

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ABSTRACT

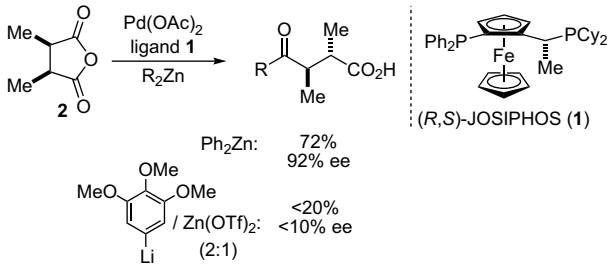
Two distinct systems for the rhodium-catalyzed enantioselective desymmetrization of *meso*-cyclic anhydrides have been developed. Each system has been optimized and are compatible with the use of in situ prepared organozinc reagents. Rhodium/PHOX species efficiently catalyze the addition of alkyl nucleophiles to glutaric anhydrides, while a rhodium/phosphoramidite system is effective in the enantioselective arylation of succinic and glutaric anhydrides.

1. Introduction

The formation of carbon–carbon bonds through transition metal-catalyzed cross-coupling methodology continues to revolutionize the synthesis of complex organic molecules.[1] New combinations of electrophilic and nucleophilic coupling partners present myriad options for bond construction, and mild conditions are tolerant of a wide range of functional groups. Despite the constant advances in this area, significant challenges remain, including the selective construction and definition of stereocenters and the use of sp^3 hybridized coupling partners.[2]

Although activated acyl species have long been utilized in the formation of ketones,[3] only recently has the use of carboxylic acid anhydrides as acylating agents been investigated in metal mediated reactions.[4] While the process of acylation does not in itself result in the construction of a stereogenic center, acylation utilizing a prochiral anhydride results in desymmetrization and definition of backbone stereocenters. While there are several reports of such efforts with heteroatom nucleophiles,[5] the use of carbon-based nucleophiles in similar efforts is quite limited.[6]

The power of this methodology lies in the use of organozinc reagents to transform substituted *meso*-cyclic anhydrides into enantioenriched ketoacid derivatives with stereodefined backbones. Our group has focused on the transition metal-catalyzed desymmetrization of *meso*-cyclic anhydrides with organozinc nucleophiles. Early efforts with nickel-catalyzed reactions were quite promising, although the development of an enantioselective reaction remained elusive.[7] More recently, the enantioselective desymmetrization of succinic anhydrides became a reality with the development of a $Pd(OAc)_2$ and Josiphos (**1**) catalyst system.[8] Reaction of *meso*-cyclic succinic anhydrides with Ph_2Zn provides the corresponding ketoacids in excellent yields with enantioselectivities typically above 92% (Scheme 1). Despite this success, efforts to extend this methodology were problematic. Reactions with glutaric anhydrides and dialkylzinc reagents are largely ineffective, and in situ prepared organozinc nucleophiles are incompatible with the palladium-catalyzed methodology, an issue not uncommon in asymmetric catalysis with organozinc reagents.[9]



Scheme 1. Palladium-catalyzed enantioselective desymmetrization of 2,3-dimethylsuccinic anhydride (**2**). Tf=trifluoromethanesulfonyl.

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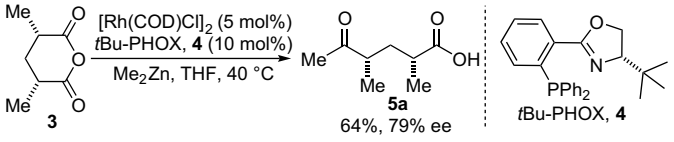
In efforts to develop methodology to expand the utility of the enantioselective desymmetrization of cyclic anhydrides, we turned to the use of rhodium. These catalysts promise to be less susceptible to complications from in situ prepared nucleophiles, specifically the presence of halides, as rhodium complexes have demonstrated tolerance to Lewis bases in asymmetric conjugate addition reactions run in water.[10] Furthermore, employment of the Rh(I)/Rh(III) redox couple presents the possibility of a mechanism distinct of that observed in the Ni(0)/Ni(II) and Pd(0)/Pd(II) systems. The use of a new metal also provides the opportunity to introduce ligand scaffolds that are ineffective with earlier systems. Herein we describe the development of two complementary Rh-catalyzed systems, utilizing phosphinooxazoline (PHOX) and phosphoramidite ligands, for the enantioselective desymmetrization of succinic and glutaric anhydrides with sp^2- and sp^3-hybridized in situ prepared nucleophiles.[11]

2. Results and discussion

2.1. Rh/^{t}Bu-PHOX catalyst system

Early studies into the enantioselective desymmetrization of *meso*-3,5-dimethylglutaric anhydride **3** focused on the use of dialkylzinc reagents, with the intent of generating *syn*-deoxypolypropionate synthons, a motif common in natural products. While nickel and palladium catalysts were generally ineffective for the addition of alkyl nucleophiles to glutaric anhydrides, initial success was uncovered with a rhodium(I) catalyst, with bidentate phosphine–nitrogen ligands such as *tert*-butylphosphinooxazoline (^{t}Bu-PHOX, **4**) in THF. Efforts with commercially available Me_2Zn and Et_2Zn nucleophiles were successful, resulting in the generation of the corresponding sp^2–sp^3 cross coupled *syn*-deoxypolypropionate synthons (Scheme 2).

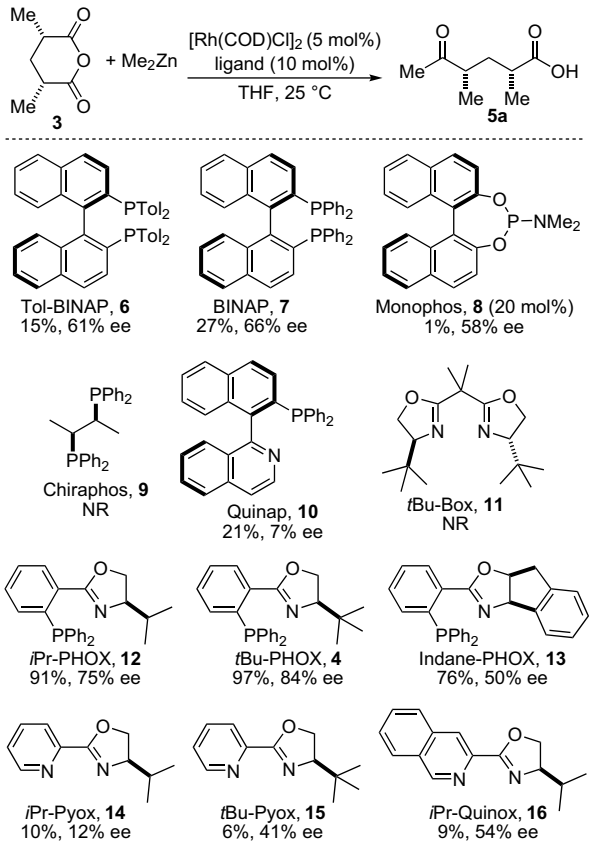


Scheme 2. Initial results for rhodium-catalyzed desymmetrization with commercially available diorganozinc reagents. COD=1,5-cyclooctadiene.

A series of studies were performed in order to develop optimized conditions for the enantioselective alkylation of 3,5-disubstituted glutaric anhydrides. In turn, effects of the ligand, catalyst precursor, temperature, and nucleophile source and preparation were each examined for impact upon the efficiency and selectivity of the reaction. The results of these efforts, and the insight gained into the reaction mechanism, are described below.

An extensive screen of ligands was performed using dimethylglutaric anhydride **3** and Me_2Zn in THF at 25 °C. These results, an abbreviated portion of which is provided in Scheme 3, illustrate the efficacy of phosphorus-nitrogen bidentate ligands within this reaction manifold.[12] Under the screening conditions, the use of *i*Pr-PHOX (isopropylphosphinooxazoline, **12**) and ^{t}Bu-PHOX (**4**) ligands generates the desired product in 75% and 84% ee, respectively. Several bis-phosphine ligands, such as BINAP derivatives (**6**,**7**), produce ketoacid **5a** in enantioselectivities up to 66%, although yields are quite low. Bis-nitrogen and phosphoramidite ligands also fail to generate the ketoacid in appreciable yields. The results of this screen led us to utilize PHOX-based ligands for further reaction optimization.

A screen of rhodium catalyst precursors, including $[Rh(COD)Cl]_2$, $[Rh(COE)Cl]_2$ (COE=cyclooctene), and $[Rh(CO)_2Cl]_2$ demonstrated that while the rhodium source has a significant impact on the yield of the transformation, the effect on the enantioselectivity is quite



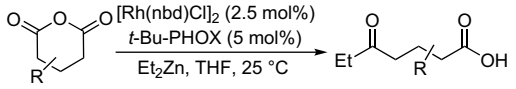
Scheme 3. Examination of ligands for rhodium-catalyzed alkylation of 3,5-dimethylglutaric anhydride (**3**).

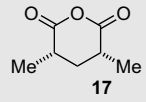
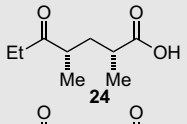
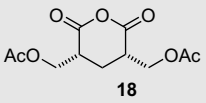
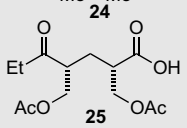
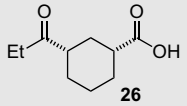
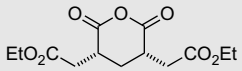
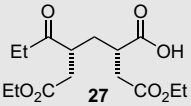
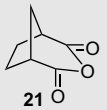
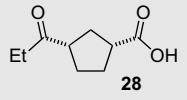
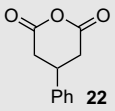
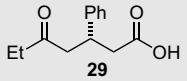
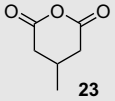
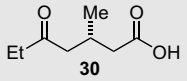
modest.[12] The most selective catalysis was achieved with the use of $[Rh(nbd)Cl]_2$ (nbd=norbornadiene) and ^{t}Bu-PHOX. With this catalyst, glutaric anhydride **3** is alkylated with Me_2Zn to generate **5b** in 87% yield and 86% ee. Notably, cationic precursor $Rh(COD)_2BF_4$ also generates a competent catalyst with some loss of selectivity (68% ee).

Upon development of these reactions conditions, we focused upon expansion of the scope of anhydrides. A series of 3,5-disubstituted glutaric anhydrides were prepared and tested for reactivity with mixed results (Table 1). Bisacetate **18** provides ketoacid **25** in 65% yield and 84% enantioselectivity using ^{t}Bu-PHOX, while bicyclic anhydride **19** provides corresponding alkylated product **26** in higher yield and similar enantioselectivity with *i*Pr-PHOX. Unfortunately, efforts to further extend the substrate scope through variation of substitution patterns provided few promising results. Although a variety of 3,5-disubstituted glutaric anhydrides undergo alkylation with good enantioselectivity, 4-monosubstituted glutaric anhydrides **22** and **23** undergo facile reaction, albeit with significantly reduced enantioselectivity.

As the range of commercially available diorganozinc reagents is quite limited, efforts shifted toward the use of in situ prepared nucleophiles. A variety of methods of generating and purifying organozinc reagents were explored. Scheme 4 includes the results of the desymmetrization of **3** run with several of these methods. Without additional purification, alkylations run with nucleophiles prepared from either lithium or Grignard reagents fail to produce ketoacid **5b**, suggesting that the presence of lithium or magnesium halide salts has a deleterious effect upon the reaction. To circumvent this difficulty, the desired organozinc halide was decanted away from residual salts. This simple purification procedure led to dramatic increases in yield and enantioselectivity. Ultimately, the use of a 1:1 ratio of freshly prepared butyl magnesium bromide

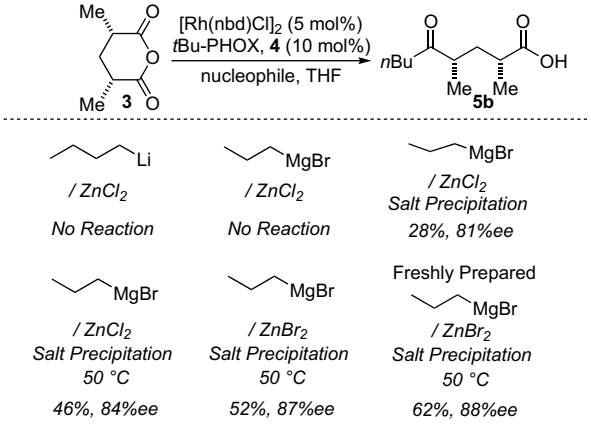
Table 1
Scope of glutaric anhydrides



Entry[a]	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	 **17**	 **24**	95	95
2	 **18**	 **25**	65	84
3	 **19**	 **26**	87	85
4	 **20**	 **27**	56	52
5	 **21**	 **28**	81	40
6	 **22**	 **29**	40	53
7	 **23**	 **30**	90	9

[a] Standard conditions: 2.5 mol % $[Rh(nbd)Cl]_2$, 5 mol % ^{t}Bu-PHOX, 1.5 equiv Et_2Zn in THF at 25 °C.
[b] Isolated yields.
[c] Enantioselectivity determined by HPLC analysis of corresponding benzyl or methyl esters.

with zinc bromide generates a butyl zinc bromide nucleophile capable of producing the desired ketoacid in 62% yield and 88% ee. In addition, successfully utilized functionalized diorganozinc nucleophiles were also prepared from the reaction of alkyl iodides with Et_2Zn following the precedent of Knochel,[13] or through the reaction of (1-ethoxycyclopropoxy)trimethylsilane with $ZnCl_2$ to generate the bis(homoenolate)zinc species.



Scheme 4. Preparation of organozinc nucleophiles and use in the desymmetrization of glutaric anhydride **3**.

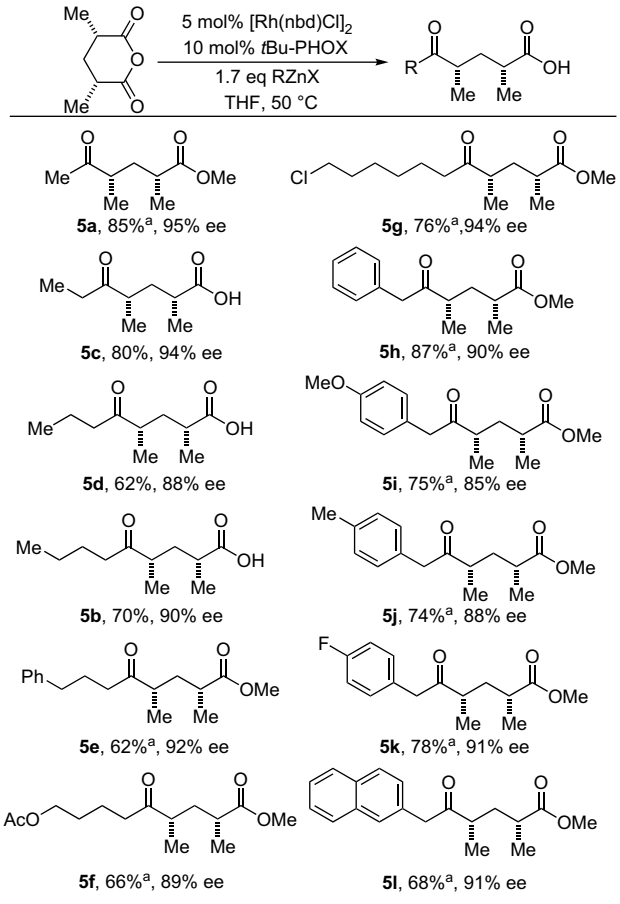
Table 2
Screen of zinc salts for preparation of organozinc reagents

Entry[a]	ZnX_2	Yield (%)[b]	ee (%)[c]
1	ZnF_2	32	30
2	$ZnCl_2$	56	89
3	$ZnBr_2$	72	90
4	ZnI_2	85	84
5	$Zn(OTf)_2$	85	7
6	$Zn(OAc)_2$	87	90

[a] Standard conditions: 0.175 mmol anhydride, 2.5 mol % $[Rh(nbd)Cl]_2$, 5 mol % ^{t}Bu-PHOX, RZnX (1.7 equiv) in THF at 50 °C.
[b] Isolated yields.
[c] Enantiomeric excess (ee) determined by HPLC analysis of corresponding benzyl ester.

As studies have shown that the presence of seemingly innocuous halides can have significant impact upon the course of transition metal-catalyzed reactions,[14] a series of zinc salts were examined for the formation of the organozinc reagent. Utilizing benzyl magnesium chloride to form the organozinc reagent, the corresponding nucleophile was then purified by precipitation and reacted with 3,5-dimethylglutaric anhydride **3** with $[Rh(nbd)Cl]_2$ and ^{t}Bu-PHOX. While each reaction produced the desired product, enantioselectivities of 90% were obtained using $ZnBr_2$ and $Zn(OAc)_2$ (Table 2).

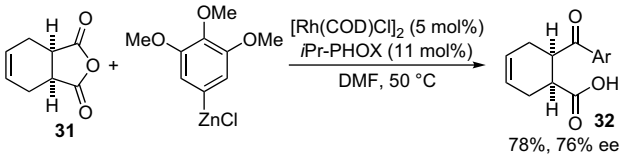
The scope of nucleophiles amenable for use in the desymmetrization reaction is shown in Scheme 5. When run in THF at 50 °C with $[Rh(nbd)Cl]_2$ (5 mol %), ^{t}Bu-PHOX (10 mol %), and 1.7 equiv of



Scheme 5. Scope of organozinc halide nucleophiles in Rh/^{t}Bu-PHOX catalyzed desymmetrization. (a) Isolated as methyl ester after treatment with $TMSCHN_2$.

RZnX, alkyl and benzylic nucleophiles perform well in the reaction. Ethers, esters, and halides are among tolerated functionality, and yields generally exceed 70% while enantioselectivities range from 85% to 95%. We have observed a slight correlation between the nucleophilicity of the benzylic nucleophile and enantioselectivity (**5h**–**5l**): the selectivity increases with decreasing electron density, perhaps suggesting that an uncatalyzed background reaction of the zinc reagent with 3,5-dimethylglutaric anhydride.

While this methodology works selectively and efficiently for alkyl nucleophiles, it is quite inconsistent with the use of arylzinc nucleophiles. While commercially available Ph_2Zn produces the desired arylated product in reasonable yields and enantioselectivity (76%, 56% ee), no general methodology for the use of in situ prepared arylzinc nucleophiles has been developed using PHOX-based ligands. A recent result, however, holds promise for the use of arylzinc nucleophiles in this reaction manifold: In DMF, with an arylzinc chloride nucleophile prepared from the corresponding aryl lithium and 1 equiv of $ZnCl_2$, the desymmetrization of cyclohexenedicarboxylic anhydride **31** proceeds in 78% yield and 76% ee (Scheme 6).



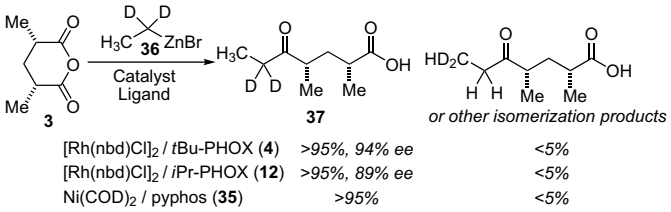
Scheme 6. Arylation of succinic anhydride **31** with an in situ prepared nucleophile with Rh/*i*Pr-PHOX in DMF.

An interesting observation was made when the reaction was performed with bis(homoenolate)zinc nucleophile **33**. When run with a substrate concentration of 0.15 M, the desired alkylation product **5m** was obtained in 49% and 95% ee (Scheme 7). In addition, **34**, presumably obtained by rearrangement of the nucleophile, was also isolated in 30% yield. This product, however, is racemic. Additional studies indicated that at higher reaction concentrations, such as 0.30 M substrate, no rearrangement product is observed, and the desired product is obtained in 75% yield and 95% ee. When the reaction is run with *i*Pr-PHOX or (2-diphenylphosphino)ethylpyridine (pyphos, **35**) as the ligand, the rearrangement product is the sole isolated species.

The observation of rearrangement product **34** led us to a deeper examination of the mechanism. Initial mechanistic hypotheses were loosely based upon kinetic studies of the Ni-catalyzed desymmetrization of cyclic anhydrides,[7d] in which the catalytic cycle begins with nickel insertion into the anhydride. As we proposed when selecting rhodium as a potential catalyst, it appears that while the starting materials and products are the same, the reaction may occur through a new mechanistic pathway.

Qualitative observations, including color changes visible upon addition of reagents, suggest that no reaction occurs prior to addition of the organozinc reagent. This is consistent with initial reaction of the organozinc reagent with the rhodium catalyst prior to interaction with the anhydride.

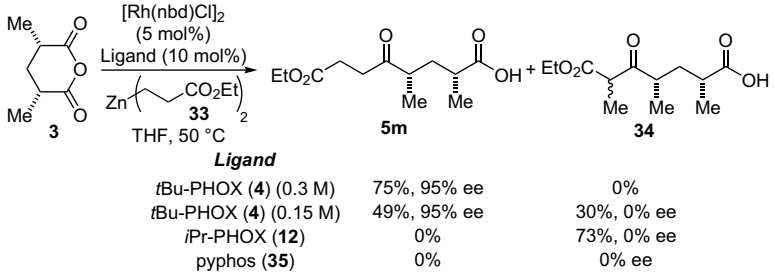
To further examine the mechanism of anhydride alkylation, deuterated organozinc halide, 1,1-dideuteroethyl zinc bromide (H_3CD_2CZnBr, **36**) was prepared via a Grignard reaction from the commercially available ethyl bromide. Under standard reaction conditions (5 mol % $[Rh(nbd)Cl]_2$, 10 mol % ligand, 1.7 equiv of RZnBr in THF at 50 °C), the alkylation of 3,5-dimethylglutaric anhydride occurred with no sign of deuterium scrambling with either *i*Pr-PHOX or ^{t}Bu-PHOX (Scheme 8). The enantioselectivities obtained in each reaction, 89% and 94%, respectively, are comparable with that obtained using unlabeled nucleophile.



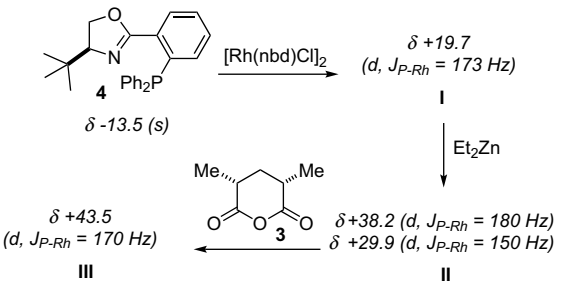
Scheme 8. Enantioselective desymmetrization with deuterium-labeled diorganozinc reagent.

To more quantitatively examine the catalytic cycle of anhydride alkylation, a series of ^{31}P NMR spectroscopic studies were performed. In these experiments, each component of the reaction was added sequentially, and the change in the ^{31}P NMR spectrum was noted at each stage. Free ^{t}Bu-PHOX (**4**) displays a chemical shift of −13.5 ppm. Upon addition of 0.5 equiv of $[Rh(nbd)Cl]_2$ (1:1 Rh/ligand), the initial signal disappeared and a new doublet was observed at +19.7 ppm with a coupling constant of 173 Hz (intermediate **I**), consistent with the formation of a rhodium–ligand complex. Addition of 1 equiv of Et_2Zn to this solution resulted in the disappearance of the resonance at +19.7 and the appearance of doublets at +38.2 (J_{P-Rh}=180 Hz) and +29.9 (J_{P-Rh}=150 Hz) (intermediate **II**). Finally, the addition of 3,5-dimethyl glutaric anhydride **3** resulted in the slow disappearance of these two phosphine peaks and the simultaneous appearance of a resonance at +43.5 (J_{P-Rh}=170 Hz), which has been tentatively assigned to the rhodium carboxylate product (intermediate **III**), (Scheme 9).

Analysis of the combined mechanistic data suggests that the mechanism for rhodium/PHOX-catalyzed cyclic anhydride desymmetrization proceeds via a mechanism distinct from that observed in the nickel-catalyzed reaction. Rather than interaction of the metal center with the anhydride, the ^{31}P NMR data indicates initial reaction of rhodium with an alkyl zinc species, presumably to generate alkyl-rhodium intermediate **IV** (Scheme 10). This species

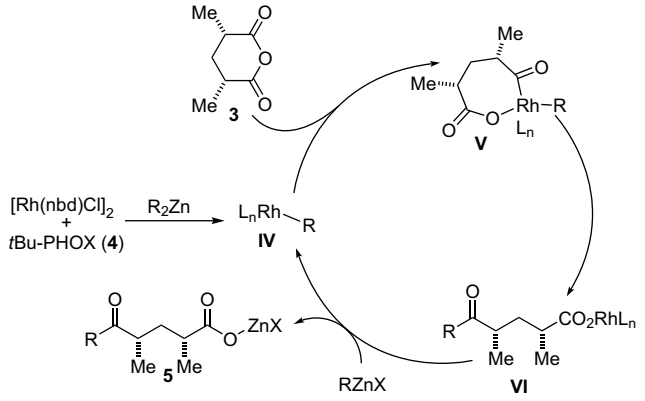


Scheme 7. Examination of rearrangement product observed with the use of bis(homoenolate)zinc reagent (**33**).



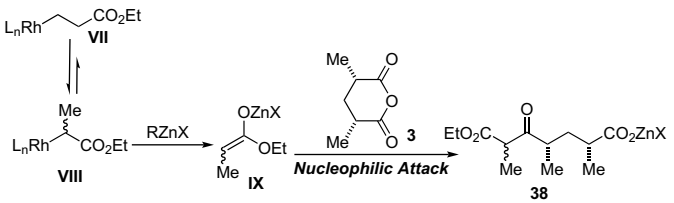
Scheme 9. ^{31}P NMR examination of potential reaction intermediates.

then reacts with the anhydride via insertion to form metalacycle **V** in the enantioselectivity defining step. Subsequent reductive elimination yields rhodium carboxylate **VI**, which reacts with another equivalent of RZnX to regenerate catalytic intermediate **IV** and release the desired product as a zinc carboxylate.



Scheme 10. Proposed catalytic cycle for the Rh/^{t}BuPHOX-catalyzed anhydride alkylation with standard diorganozinc reagents.

The rearrangement product observed in the reaction of bis(homoenolate) zinc species **33** provides additional information regarding the mechanism (Scheme 11). With this nucleophile, it is believed that the rhodium-homoenolate species **VII** undergoes reversible β-hydride elimination, resulting in a mix of the α- and β-rhodium substituted esters (**VII** and **VIII**). As noted previously, only activated organozinc substrates undergo β-hydride elimination—nucleophiles such as the deuterium-labeled EtZnBr do not undergo the rearrangement. Upon isomerization, the α-rhodium substituted species **VIII**, behaves as an enolate. As rearrangement product **38** is racemic, it is believed that the isomerized rhodium-alkyl complex exchanges with RZnBr to generate zinc enolate **IX** prior to undergoing uncatalyzed nucleophilic attack on the anhydride.



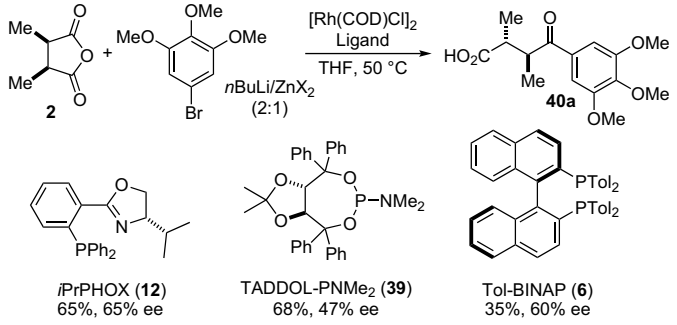
Scheme 11. Secondary pathway accessible by substituents prone to β-hydride elimination.

This proposed mechanism accounts for the combination of desired optically active alkylation product as well as the racemic isomeric product. Furthermore, the lack of rearrangement product under higher reaction concentrations is consistent with alkyl-rhodium intermediate **IV** reacting with anhydride faster than it undergoes elimination. It is also believed that the steric bulk of ^{t}Bu-PHOX retards the β-hydride elimination isomerization process, as the racemic rearrangement product is the sole isolated species when other phosphine–nitrogen chelating ligands, including *i*Pr-PHOX, are used.

2.2. Rh/phosphoramidite catalyst system

Simultaneously with efforts to develop the means of generating the *syn*-deoxypolypropionate motif through the alkylative enantioselective desymmetrization of 3,5-disubstituted glutaric anhydrides, similar efforts focused on the addition of sp^2-hybridized organozinc nucleophiles to cyclic anhydrides. As described above, the use of arylzinc nucleophiles was relatively unsuccessful using rhodium with PHOX-based ligands. We sought a general methodology that would allow the efficient enantioselective desymmetrization of cyclic anhydrides with in situ formed nucleophiles, preferably without the need for purification. Toward this end, a complementary system has been developed, in which succinic and glutaric anhydrides are readily arylated to generate 1,4- and 1,5-dicarbonyl compounds with stereochemically defined backbone substitution.

While a large range of metal sources and ligands have been screened in the reaction of 2,3-dimethylsuccinic anhydride **2** with arylzinc nucleophiles, initial studies identified [Rh(COD)Cl]$_2$ with *i*Pr-PHOX (**12**), taddol-derived phosphoramidite **39**, and Tol-BINAP (**6**) as competent ligands worthy of additional study. As described previously, PHOX ligands have proven a moderate success, as have BINAP ligands (Scheme 12). The most fruitful area of study came with examination of phosphoramidite ligands.

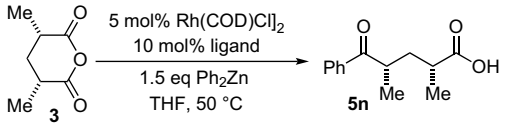


Scheme 12. Initial results in desymmetrization of succinic anhydrides with in situ prepared nucleophiles.

Initial studies utilized the reaction of commercially available Ph_2Zn and 3,5-dimethylglutaric anhydride to examine the impact of solvent upon the yields and enantioselectivity of the desymmetrization reaction catalyzed by [Rh(COD)Cl]$_2$ and phosphoramidite **39** at 50 °C (Table 3). While little reaction is observed in nonpolar solvents, the use of polar aprotic solvents results in the efficient formation of desired ketoacid **5n**, the best of which occurs in DMF (75% yield and 82% ee).

As described above, the use of in situ prepared arylzinc reagents is vital for the development of a general methodology, and thus various solvents were also used in the reaction of succinic anhydride **2** with arylzinc chloride and diarylzinc nucleophiles prepared from the corresponding aryl lithium reagent. As observed for the reaction of glutaric anhydrides, it was observed that reaction proceeds most efficiently in DMF, providing **40a** in 74% yield and 78% ee. Most importantly, the yield and enantioselectivity were obtained without precipitation or other means of purification of the nucleophile.

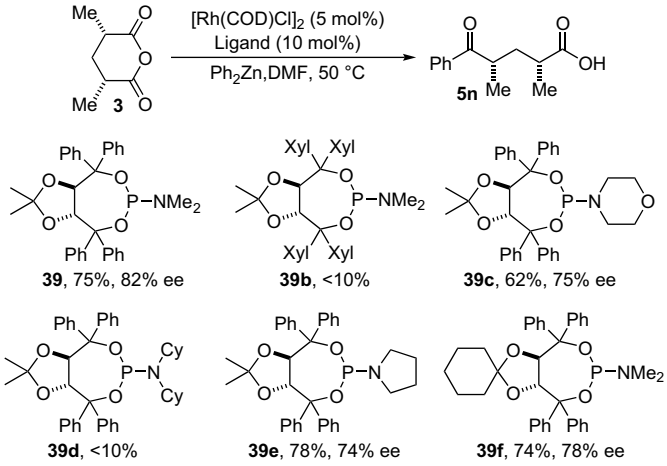
Table 3
Screen of solvents for desymmetrization with Rh/phosphoramidite catalyst



Entry[a]	Solvent	Yield (%)[b]	ee (%)[c]
1	DMF	75	82
2	MeCN	50	64
3	DMA	62	15
4	DMSO	56	3
5[d]	CH_2Cl_2	20	12
6	Toluene	NR	—
7	THF	<10	—
8	1,4-Dioxane	35	0

[a] Standard conditions: 5 mol % $[Rh(COD)Cl]_2$, 10 mol % phosphoramidite **39**, Ph_2Zn (1.5 equiv) at 50 °C.
[b] Isolated yield.
[c] Enantiomeric excess (ee) determined by HPLC analysis of corresponding benzyl ester.
[d] Reaction performed at 40 °C.

Use of taddol-derived phosphoramidite **39** with $[Rh(COD)Cl]_2$ results in the efficient catalysis of the addition of Ph_2Zn to 3,5-dimethylglutaric anhydride. To examine increases in selectivity with related ligands, a series of phosphoramidites were utilized in the reaction. Examples from this screen are provided in Scheme 13.[12] Unfortunately, modifications to the aryl groups, the amine, and the acetal failed to produce a significant increase in selectivity.



Scheme 13. Examination of phosphoramidite ligands in the desymmetrization of 3,5-dimethylglutaric anhydride.

Rhodium precursors were also examined for reactivity. For the arylation of glutaric anhydride **3** with Ph_2Zn, an initial screen indicated little difference in reactivity for catalysts generated from alkene stabilized rhodium chloride complexes (entries 1–3, Table 4). Notably, the use of cationic complex $[Rh(COD)_2]BF_4$ resulted in no reaction, unlike the Rh/PHOX methodology (vide supra).

Upon identification a promising rhodium source, ligand and solvent for reaction, arylzinc nucleophiles were prepared from a variety of zinc salts and utilized in the desymmetrization of 2,3-dimethylsuccinic anhydride (**2**) (Table 5). While a variety of zinc salts are compatible, formation of the arylzinc nucleophile from $Zn(OTf)_2$ resulted in the efficient and selective generation of ketoacid **40a** in 82% yield and 85% ee.[15]

Table 4
Screen of rhodium precursors in conjunction with phosphoramidite **39** for enantioselective arylation of **3** with Ph_2Zn

Entry[a]	Rh source	Yield (%)[b]	ee (%)[c]
1	$[Rh(COD)Cl]_2$	75	82
2	$[Rh(nbd)Cl]_2$	78	78
3	$[Rh(C_2H_4)_2Cl]_2$	79	82
4	$[Rh(COE)Cl]_2$	52	70
5	$[Rh(CO)_2Cl]_2$	20	60
6	$[Rh(COD)_2]BF_4$	NR	—

[a] Standard conditions: 5 mol % $[Rh(COD)Cl]_2$, 10 mol % phosphoramidite **39**, Ph_2Zn (1.5 equiv) in DMF at 50 °C.
[b] Isolated yield.
[c] Enantiomeric excess (ee) determined by HPLC analysis of corresponding methyl ester.

Optimization of the reaction continued with examination of the temperature dependence of the reaction. Using Ph_2Zn and 3,5-dimethylgluataric anhydride **3**, the reaction was performed at several temperatures between 25 °C and 80 °C. While yields are relatively consistent, the enantioselectivity peaks at 50 °C and decreases with higher or lower temperatures. Likewise, the reaction of 2,3-dimethylsuccinic anhydride (**2**) with in situ prepared arylzinc triflates provides the greatest enantioselectivity at 50 °C and results in lower selectivities at room temperature and 80 °C.

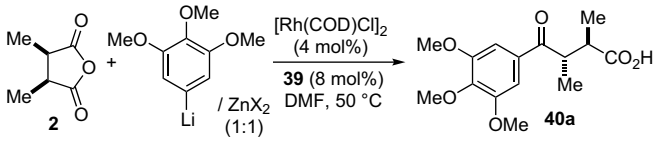
With the identification of conditions amenable for the enantioselective desymmetrization of 3,5-dimethylglutaric anhydride and 2,3-dimethylsuccinic anhydride, efforts shifted to the examination of the reactivity of a series of *meso*-cyclic anhydrides. The use of commercially available Ph_2Zn is compatible with a number of anhydrides, including those containing strained rings, esters and alkene functionality. While good yields and selectivities are obtained with 3,5-disubstituted glutaric anhydrides, the use of 4-substituted glutaric or succinic anhydrides results in a significant loss of enantioselectivity (Table 6).

The use of in situ prepared arylzinc triflates with *meso*-succinic anhydrides is also quite promising. While the functional group tolerance is less than that observed with Ph_2Zn, substrates containing backbone olefins and strained rings are efficiently converted to the corresponding ketoacids in good yields and enantioselectivities (Table 6).

For strained rings such as **42** and **43**, it was also observed that a decrease in reaction temperature provides higher enantioselectivity.

The strength of the rhodium/phosphoramidite-catalyzed methodology lies in the use of in situ prepared arylzinc nucleophiles (Table 7). The scope of compatible nucleophiles is quite general, and

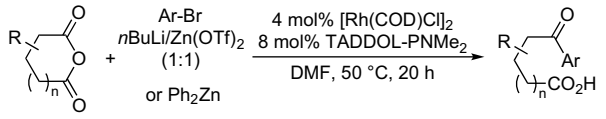
Table 5
Examination of zinc salts for preparation of organozinc nucleophile

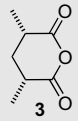
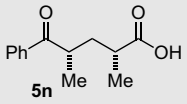
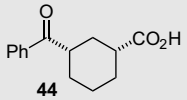
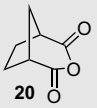
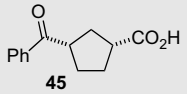
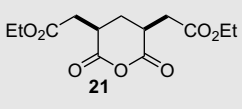
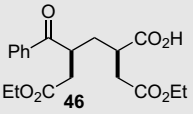
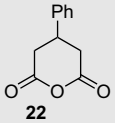
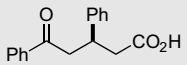
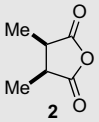
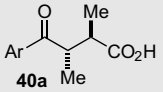
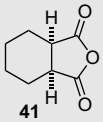
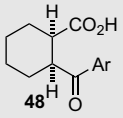
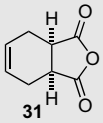
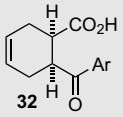
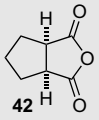
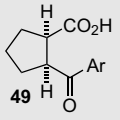
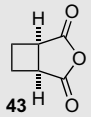
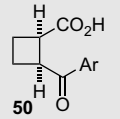


Entry[a]	ZnX_2	Yield (%)[b]	ee (%)[c]
1	ZnF_2	<10	—
2	$ZnCl_2$	74	78
3	$ZnBr_2$	71	72
4	ZnI_2	32	60
5	$Zn(OTf)_2$	82	85
6	$Zn(OAc)_2$	61	36

[a] Standard conditions: 1.5 equiv ArZnX, 4 mol % $[Rh(COD)Cl]_2$, 8 mol % phosphoramidite **39**, in DMF at 50 °C for 20 h.
[b] Isolated yield.
[c] Enantiomeric excess (ee) determined by HPLC analysis of corresponding methyl ester.

Table 6
Scope of anhydrides compatible with Rh/phosphoramidite catalyzed arylation methodology

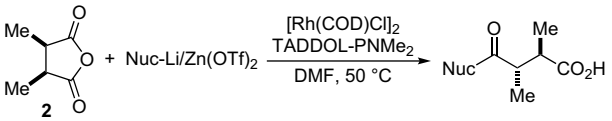


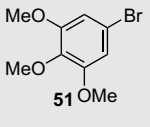
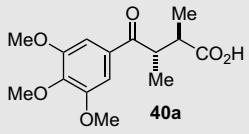
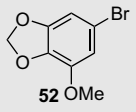
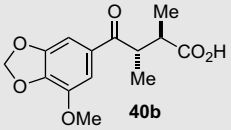
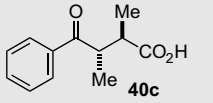
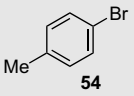
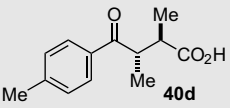
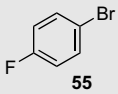
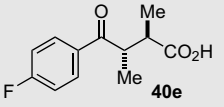
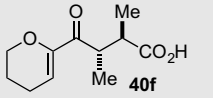
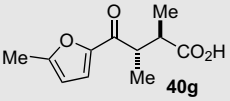
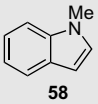
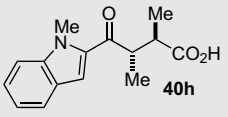
Entry[a]	Anhydride	Product	Yield (%)[b]	ee (%)[c]
1	 **3**	 **5n**	75	82
2	 **19**	 **44**	78	73
3	 **20**	 **45**	69	48
4	 **21**	 **46**	56	82
5	 **22**	 **47**	81	51
6[d]	 **2**	 **40a**	85	87
7[d]	 **41**	 **48**	72	83
8[d]	 **31**	 **32**	77	82
9[d,e]	 **42**	 **49**	61	77
10[d,e]	 **43**	 **50**	56	76

[a] Standard reaction conditions: 1.5 equiv nucleophile, 4 mol % $[Rh(COD)Cl]_2$, and 8 mol % phosphoramidite **39** in DMF at 50 °C for 16 h.
[b] Isolated yield.
[c] Enantiomeric excess (ee) measured by HPLC analysis of methyl ester.
[d] Ar=3,4,5-$(MeO)_3C_6H_2$.
[e] Reaction performed at 23 °C.

includes arylzinc triflates derived from a variety of bromine substituted aryl bromides as well 2-methyl furan, dihydropyran and *N*-methylindole. Difficulties were encountered with more sterically hindered 2-substituted aryl nucleophiles, which produced the desired ketoacids albeit in significantly lower yields, and with simple vinyl ethers. For successful substrates, yields are above 75%, while

Table 7
Scope of nucleophiles amenable to Rh/phosphoramidite catalyzed arylation of succinic anhydrides



Entry[a]	Nucleophile precursor	Product	Yield (%)[b]	ee (%)[c]
1	 **51**	 **40a**	85	87
2	 **52**	 **40b**	88	88
3	 **53**	 **40c**	75	85
4	 **54**	 **40d**	74	87
5	 **55**	 **40e**	78	87
6	 **56**	 **40f**	76	80
7	 **57**	 **40g**	82	85
8	 **58**	 **40h**	84	86

[a] Standard conditions: 1.5 equiv nucleophile, 4 mol % $[Rh(COD)Cl]_2$, 8 mol % phosphoramidite **39** in DMF at 50 °C for 16 h.
[b] Isolated yield.
[c] Enantiomeric excess (ee) determined by HPLC analysis of methyl ester.

enantioselectivities are typically in excess of 85%. It appears that enantioselectivity is independent of the nucleophile, suggesting that the enantioselectivity determining step occurs independently of the transmetallation process.

2.3. Comparison of complementary systems

In the process of expanding the methodology for enantioselective desymmetrization of *meso*-cyclic anhydrides, we have developed complementary systems differentiated by the ligands utilized in reaction.

The rhodium/PHOX system is efficient for the desymmetrization of anhydrides, particularly 3,5-dimethylglutaric anhydride, with alkyl zinc halide nucleophiles in THF. When a precipitation protocol is used, alkyl and benzyl nucleophiles prepared from corresponding Grignard reagents produce the corresponding ketoacids in high

yields and enantioselectivities. Despite preliminary results that suggest the intermediacy of a rhodium-alkyl complex, evidence for β-hydride elimination exists with only a single substrate. Also of note is that for reasons that remain unclear, arylzinc reagents are ineffective in this methodology.

In contrast, the rhodium/phosphoramidite system efficiently catalyzes the enantioselective desymmetrization of succinic anhydrides with in situ prepared arylzinc triflate reagents. Notably, these nucleophiles can be generated and utilized without purification and form the desired products in good yields and enantioselectivities. Alkyl zinc reagents, however, are incompatible with this catalyst system.

These results suggest that there are obvious mechanistic differences between the metal/ligand systems. Differences in coordination number, ligand electronic character, and solvent may play significant roles in differentiating between catalytic cycles. Detailed studies to ascertain the mechanistic variations and to utilize these differences remain underway.

3. Conclusion

Herein we have described the development and optimization of complementary rhodium-catalyzed reaction manifolds for the enantioselective desymmetrization of *meso*-cyclic anhydrides. Advances in reaction methodology now allow the general use of glutaric and succinic anhydrides, in situ prepared nucleophiles, and both sp^3- and sp^2-hybridized organozinc nucleophiles for the formation of ketoacids with multiple stereocenters in high yields and enantioselectivities.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) and dimethylformamide (DMF) were purged with argon and passed through two columns of neutral alumina. Column chromatography was performed using EM Science silica gel 60 (230–400 mesh). Thin layer chromatography was performed using EM Science 0.25 mm silca gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, or bromocresol green dips followed by heating. All products described in this work match the corresponding published spectral data for existing compounds.[11]

Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard (tetramethylsilane [TMS] or deuterated chloroform [$CDCl_3$]), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br s=broad singlet), integration, and coupling constant (Hz). Chemical shifts are reported in parts per million from ($CDCl_3$) taken as 77.0 ppm.

4.2. General procedure for the preparation of in situ alkyl zinc reagents

The procedure will be illustrated with a specific example. A flame-dried 10 mL round bottom flask was charged with $ZnBr_2$ (225 mg, 1 mmol) under an inert atmosphere in a glove box. The flask was sealed with a septum and removed from the glove box and placed under a positive pressure of argon. To this was added anhydrous THF (3 mL) and Et_2O (3 mL) and cooled to 0 °C. Alkyl magnesium bromide[9] (0.5 mL, 2 M in Et_2O, 1 mmol) was added dropwise. The resulting suspension was stirred at 0 °C for 30 min and then for 25 °C for 1 h. Following agitation, the precipitate was allowed to settle for 1 h. The supernatant was decanted via syringe and used directly.

4.3. General procedure for the preparation of in situ benzyl zinc reagents

The procedure will be illustrated with a specific example. A flame-dried 10 mL round bottom flask was charged with $Zn(OAc)_2$ (183 mg, 1 mmol) under an inert atmosphere in a glove box. The flask was sealed with a septum and removed from the glove box and placed under a positive pressure of argon. To this was added anhydrous THF (3 mL) and Et_2O (3 mL) and cooled to 0 °C. Benzyl magnesium chloride (0.5 mL, 2 M in Et_2O, 1 mmol) was added dropwise. The resulting suspension was stirred at 0 °C for 30 min and then for 25 °C for 1 h. Following agitation, the precipitate was allowed to settle for 1 h. The supernatant was decanted off via syringe and used directly.

4.4. General procedure for the preparation of in situ functionalized zinc reagent

The procedure will be illustrated with a specific example. An oven-dried Schlenk flask was charged with alkyl iodide (0.6 mmol), then sealed and degassed four times. The flask was then cooled to 0 °C and neat Et_2Zn (307 μL, 366 mg, 3 mmol) was added. Following 10 min at 0 °C the mixture was heated to 40 °C for 12 h. The excess Et_2Zn and EtI were removed under vacuum (CAUTION: evacuate using Schlenk techniques and add methanol to vacuum trap to quench remaining Et_2Zn). Anhydrous THF (1 mL) was added and the vessel evacuated. This sequence was repeated a further two times. The mixture was allowed to cool to ambient temperature and THF (2 mL) was added and used directly.

4.5. General procedure for the rhodium/PHOX-catalyzed enantioselective desymmetrization of *meso*-cyclic anhydrides

The procedure will be illustrated with a specific example. To a flame-dried 10 mL round bottom flask was added $[Rh(nbd)Cl]_2$ (4 mg, 0.0088 mmol) and ^{t}Bu-PHOX (6.5 mg, 0.0176 mmol) in a glove box. The flask was sealed with a septum, removed from the glove box and purged with argon for 15 min. Anhydrous THF (2 mL) was added and then the nucleophile solution (0.3 mmol) was added via syringe. The solution was heated to 50 °C and dimethylglutaric anhydride **3** (25 mg, 0.176 mmol) in THF (1 mL) was added. The reaction was stirred at 50 °C overnight then subjected to the workup procedure.

To afford the free acid, the reaction mixture was partitioned between Et_2O (5 mL) and HCl (1 M, 5 mL) and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic washings were extracted with $NaHCO_3$ (saturated, 2×5 mL) and the combined aqueous phases were acidified (pH 1) and extracted with Et_2O (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the pure free acid.

4.6. General procedure for the preparation of organozinc triflates

The procedure will be illustrated with a specific example. An oven-dried round bottom flask was charged with 3,4,5-trimethoxy-1-bromobenzene (124 mg, 0.5 mmol) and purged with Ar. The solid was subsequently dissolved in 1.5 mL THF and cooled to −78 °C in a dry ice/acetone bath. To this solution *n*BuLi (1.6 M in hexanes, 0.31 mL, 0.5 mmol) was slowly added and the mixture was allowed to stir for 30 min. Meanwhile, an oven-dried Schlenk flask was charged with $Zn(OTf)_2$ (182 mg, 0.5 mmol) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, this solid was suspended in 1 mL THF. The aryl lithium formed in the initial step was then added via syringe to the suspension of $Zn(OTf)_2$ over blowing Ar. The mixture was stirred at ambient temperature for 2 h,

at which time the THF was evaporated under reduced pressure. Addition of 1 mL DMF over blowing Ar to the resulting residue provided a solution (0.5 M) of the desired organozinc triflate.

4.7. General procedure for the rhodium/phosphoramidite-catalyzed enantioselective desymmetrization of *meso*-cyclic anhydrides

The procedure will be illustrated with a specific example. An oven-dried round bottom flask was charged with $[Rh(COD)Cl]_2$ (6.0 mg, 0.012 mmol) and (−)-TADDOL-$PNMe_2$ (13.1 mg, 0.024 mmol) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, the flask was purged with Ar and 1.0 mL DMF was added. The desired organozinc triflate (0.5 mmol), prepared according to the above procedure, was added to the catalyst solution. A solution of 2,3-dimethylsuccinic anhydride (38 mg, 0.3 mmol) in 1 mL DMF was added via syringe and the reaction mixture was heated at 50 °C in an oil bath. After 20 h, the reaction mixture was diluted with 10 mL of Et_2O and quenched with 10 mL 1 M aq HCl. The layers were separated and the aqueous layer extracted with Et_2O (2×10 mL). The combined organic layers were extracted with 1 M aq Na_2CO_3 (2×5 mL), and the combined aqueous layers were brought to pH ~1 with concentrated HCl. The acidified aqueous layer was then extracted with Et_2O (3×10 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield desired ketoacid **7**. For analysis of enantioselectivity, the corresponding methyl ester was generated by treatment of the ketoacid with $TMSCHN_2$ (2.0 M in Et_2O) in 3 mL of MeOH/PhH (1:1) at 23 °C for 5 min followed by quenching with AcOH.

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Supplementary data

Supplementary data includes general methods for the procedures described herein, and full results of the screens performed in this work. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.075.

References and notes

1. Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998.
2. For asymmetric cross-coupling reactions, see: (a) Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41 and references therein; See also (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482; (c) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4595.
3. Use of acid chlorides: (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423; (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636; (c) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613; Thioesters: (d) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189; (e) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260; (f) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033; Aryl trifluoroacetates: (g) Kakin, R.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 371; Acyl cyanides: (h) Duplais, C.; Bures, F.; Sapountzis, I.; Korn, T. J.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2968; Acid fluorides: (i) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964.
4. (a) Real, S. D.; Kronenthal, D. R.; Wu, H. Y. *Tetrahedron Lett.* **1993**, *34*, 8063; (b) Goossen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458; (c) Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, *19*, 3254; (d) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, R. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333; (e) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137; (f) Yamamoto, A. *J. Organomet. Chem.* **2002**, *653*, 5; (g) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, 2316; (h) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645; (i) Hong, Y.-T.; Barchuk, A.; Krische, M. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 6885.
5. See Ref. 4. See also (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131; (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965; (c) Willis, M. C. *J. Chem. Soc., Perkins Trans. 1* **1999**, 1765; (d) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621; (e) Bolm, C.; Atodiresei, I.; Schiffers, I.; Kanai, M.; Shibasaki, M. *Org. Synth.* **2005**, *82*, 120.
6. Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1057.
7. (a) O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498; (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174; (c) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247; (d) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718; (e) Johnson, J. B.; Yu, R. T.; Fink, P.; Bercot, E. A.; Rovis, T. *Org. Lett.* **2006**, *8*, 4307; (f) Rogers, R. L.; Moore, J. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 9301; (g) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327.
8. Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248.
9. For a recent solution to this problem, see: Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175.
10. Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829 and references therein.
11. Portion of this work have been communicated: See (a) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514; (b) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302.
12. The full results of this screen are provided in Supplementary data.
13. (a) Rozema, M. J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956; (b) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229; (c) Stadtmueller, H.; Knochel, P. *Organometallics* **1995**, *14*, 3163.
14. Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.
15. Formation of the organozinc reagent was performed in THF. The solvent was removed under vacuum and redissolved in DMF prior to use in reaction.