

Enantioselective Cross-Coupling of Anhydrides with Organozinc Reagents: The Controlled Formation of Carbon–Carbon Bonds through the Nucleophilic Interception of Metalacycles

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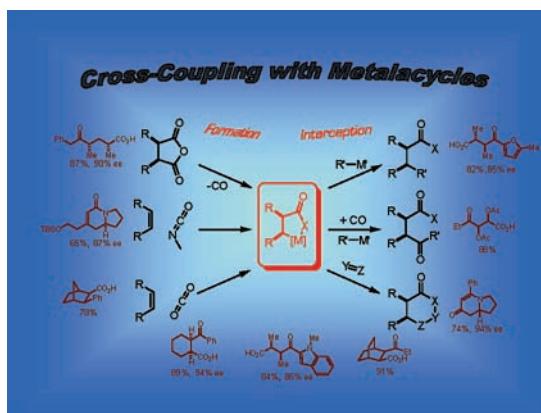
CON SPECTUS

The construction of carbon–carbon bonds, particularly with concomitant control of newly formed asymmetric centers, is of paramount importance for the development of synthetic routes to complex organic molecules. While cross-coupling reactions for the generation of sp^2 carbon centers are well established, similar methodology for the formation and control of sp^3 -hybridized carbon stereocenters is extremely limited. We suggest that the nucleophilic interception of metalacycles provides the means to achieve such a transformation, wherein the metal complex serves to activate electrophiles, facilitate nucleophile addition, and ultimately control stereochemistry. One means of accessing these intermediates is through the use of simple *meso*-carboxylic anhydrides, which upon reaction with transition metals readily generate the desired metalacycles. Interception of the metalacycle with an appropriate carbon-based nucleophile generates an enantioenriched ketoacid, the product of the asymmetric desymmetrization of achiral starting materials.

Early successes with achiral nickel catalysts and organozinc reagents provided the foundations for our approach. Alkylation of both succinic and glutaric anhydrides proceeds with a wide range of organozinc nucleophiles, forming 1,4- and 1,5-ketoacids in excellent yields. This reaction manifold has been extensively examined with a detailed kinetic study and mechanistic investigations utilizing mixed zinc reagents and alkene directing groups. This work has highlighted a number of unusual phenomena, including rate-limiting reductive elimination to form an sp^3 – sp^2 carbon–carbon bond. Despite excellent results with the achiral system, to date, all efforts to render the nickel-catalyzed reaction asymmetric have been limited to modest success.

Palladium and rhodium complexes, with the use of chiral P–P and P–N ligands, respectively, have been identified as competent catalysts for the enantioselective addition of organozinc reagents to anhydrides. The arylation of a series of succinic anhydrides with Ph_2Zn can be achieved in greater than 95% enantioselectivity using a Pd/Josiphos catalyst. Rhodium catalysts have proven amenable for the incorporation of *in situ* formed organozinc reagents, nucleophiles traditionally troublesome in transition metal catalysis due to the deleterious effects of residual halide ions. Highly functionalized organozinc nucleophiles, including those containing indole and furan, participate in this chemistry to provide the corresponding 1,4- and 1,5-ketoacids in excellent yield with greater than 85% enantioselectivity.

This metalacycle interception methodology is currently being expanded to the use of other systems, most notably the asymmetric [2 + 2 + 2] cycloaddition of alkenes, alkynes, and isocyanates. Ongoing studies promise the extension of existing methodology toward the development of modular, fully intermolecular three-component couplings in which both metalacycle formation and nucleophilic interception can be controlled. Ultimately, we envision the use of heterocumulenes in such methodology, providing a route to complex products utilizing CO_2 as an inexpensive C1 feedstock.

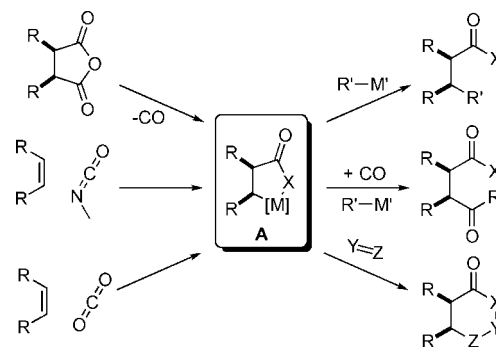


Introduction

The formation of carbon–carbon bonds through transition metal-mediated processes has transformed organic synthesis.¹ The advent of metal-catalyzed cross-coupling reactions some 35 years ago has led to a revolution in the assembly of sp^2 – sp^2 carbon–carbon bonds. Due to the ever increasing utility of carbon–carbon bond-forming methodologies, the identification of new manifolds and coupling partners is of continual interest. More specifically, the development of new cross-coupling methodology for the stereocontrolled formation of carbon–carbon bonds wherein one or both carbons are stereocenters is of paramount importance.

Despite the success of sp^2 – sp^2 cross-coupling methodologies, these advances have not translated to the formation of sp^3 – sp^3 or even sp^3 – sp^2 carbon–carbon bonds.² When we began our studies in the summer of 2000, the number of reports of cross-coupling reactions capable of the generation and control of stereocenters was minimal.^{3,4} In this vein, our interest was drawn to the potential of developing catalytic means of activating and functionalizing common electrophilic coupling partners through intermediate metalacycles bearing sp^3 hybridized C–M bonds, with particular emphasis upon the interception of these species with readily available nucleophilic partners for the formation of carbon–carbon bonds and simultaneous control of stereochemistry. Our vision relied heavily on the precedent of Hoberg, who demonstrated the generation of metalacycles of the general form **A** (Scheme 1) from the oxidative cyclization of alkenes with heterocumulenes such as isocyanates or carbon dioxide.⁵ The formation of similar metalacycles has been demonstrated by Yamamoto⁶ and Echavarren,⁷ while Trost,⁸ Yamamoto,⁹ and others¹⁰ have provided precedent for the generation of metalacycles via the insertion of low-valent transition metals into anhydrides. Interception of these metalacycles with a variety of carbon-based reagents provides the means of producing species of significant complexity from simple starting materials in a single transformation. In such methodology, the transition metal catalyst serves to activate the electrophilic partner, facilitate nucleophile addition, and ultimately control stereochemistry of the newly formed carbon–carbon bonds. The utility of metalacycles in catalytic methodology has developed greatly in recent years, and our work has benefited extensively from the previous and contemporary work in these areas, including that of Montgomery¹¹ and Jamison.¹²

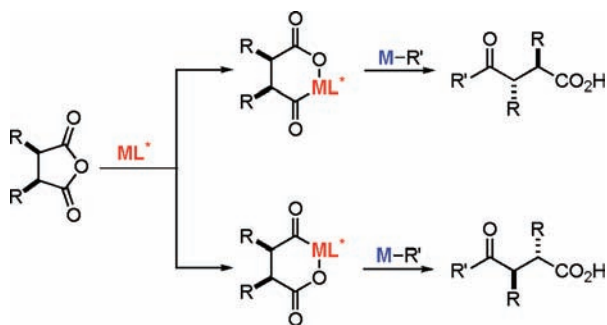
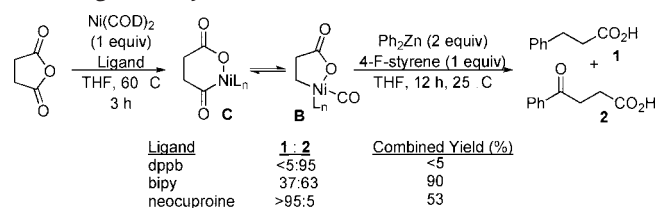
SCHEME 1. Potential Formation and Utility of Metalacycles



While our ultimate interest lies in the formation of metalacycles through the direct reaction of alkenes and CO_2 , this reaction lacks catalytic precedent outside of pyrone formation.^{13,14} This lack of precedent gave us significant trepidation, and we thus chose to initiate our studies into the catalytic formation and interception of metalacycles with the activation of cyclic anhydrides, with the added promise of generating synthetically useful ketoacids. To the present, our group has demonstrated several transition metal-catalyzed reaction manifolds utilizing cyclic anhydrides for the generation of metalacycles. Subsequent interception of these metalacycles with organozinc reagents leads to the enantioselective formation of δ - and γ -ketoacids. The development of this desymmetrization methodology is described herein. As methodology utilizing cyclic anhydrides has proceeded smoothly, we have initiated efforts toward the formation of metalacycles via the oxidative cyclization of alkynes with isocyanates. Early successes have utilized an intramolecular alkene to trap the nucleophile, producing bicyclic alkaloids in excellent yields and enantioselectivity. From the utilization of metalacycles generated from cyclic anhydrides to the use of π -components and isocyanates, our efforts are evolving toward the utilization of more readily available components. The successful realization and continued development of these methodologies have laid the groundwork for our ultimate goal, the formation and functionalization of metalacycles generated from alkenes and carbon dioxide.

Desymmetrization of *meso* Cyclic Carboxylic Anhydrides

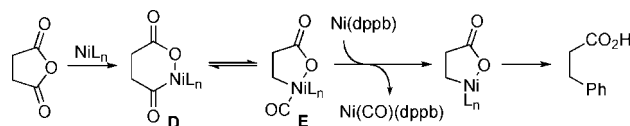
At the outset of our investigations in the summer of 2000, our efforts focused upon the functionalization of metalacycles generated from cyclic carboxylic anhydrides. While catalytic cross-coupling methodology exists for the formation of ketones from a variety of activated acyl species,¹⁵ only recently have anhydrides been investigated as acylating agents. In 2001 and 2002, respectively, Goossen¹⁶ and Yamamoto¹⁷ inde-

SCHEME 2. Metalacycles Generated from Oxidative Addition of Anhydride to Catalyst**SCHEME 3.** Product Mixtures from Early Reactions with Ni-Containing Metalacycles

pendently reported palladium-catalyzed couplings of mixed acyclic anhydrides with boronic acid nucleophiles, whereas in 2001 Frost described a rhodium-catalyzed analogue.¹⁸ Although these methodologies provide versatile means of forming ketones, each inherently lacks the ability to influence the formation or definition of stereocenters. In a recent advance, Krische and co-workers have demonstrated the rhodium-catalyzed, hydrogen-mediated coupling of styrenes and anhydrides with control of the newly formed stereocenter.¹⁹ The use of *meso* cyclic carboxylic anhydrides with backbone functionality provides the means to generate asymmetry in the ketoacid product through definition of the stereocenters within the anhydride backbone (Scheme 2).

The formation of enantioenriched acid species through the desymmetrization of cyclic carboxylic anhydrides has been previously demonstrated with a variety of heteroatom nucleophiles.²⁰ The use of carbon-based nucleophiles, however, has remained largely undeveloped. In an isolated example performed concurrently with our own work, Fu reports the use of stoichiometric sparteine to effect the asymmetric addition of Grignard reagents to *meso* glutaric anhydrides to form the corresponding ketoacids with excellent enantioselectivity.²¹

Our investigation of the nucleophilic interception of metalacycles began with the oxidative addition of cyclic anhydrides to nickel complexes. Nickel insertion into succinic anhydride generates five-membered metalalactone **B**, presumably via CO extrusion from metalacycle **C** (Scheme 3). Reaction of **B** with an organometallic reagent would result in the formation of a

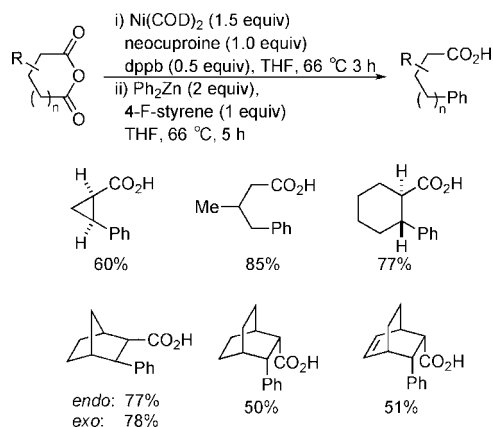
SCHEME 4. Proposed Mechanism of Ni-Mediated Decarbonylative Cross-Coupling

new carbon–carbon bond, yielding a carboxylic acid. We envisioned that with judicious choice of reaction conditions, we could also intercept metalacycle **C** prior to CO extrusion. Alkylation of this intermediate results in the formation of 1,4- or 1,5-ketoacids. Organozinc reagents quickly became the nucleophiles of choice, because these species are known to readily transmetalate to Ni complexes and both alkyl and aryl zinc reagents show no uncatalyzed reaction with cyclic anhydrides even after 6 h at 25 °C.

The reaction of succinic anhydride with Ph_2Zn in the presence of $\text{Ni}(\text{COD})_2$, bipy (2,2'-bipyridyl), and 4-F-styrene (*vide infra*) led to a 63:37 ratio of direct addition product **2** and decarbonylation product **1** in a combined 90% yield (Scheme 3).²² As envisioned, product selectivity can be controlled with judicious choice of ligand.

Despite the excellent product selectivity obtained with unsubstituted succinic anhydride, the use of more complex anhydrides led to product mixtures. Additional analysis led to the conclusion that upon decarbonylation, carbon monoxide remained complexed to the metal center, allowing reinsertion into the metalacycle and formation of the direct addition product. We reasoned that the addition of a CO sequestration agent could drive this equilibrium, thus yielding solely decarbonylative coupling product (Scheme 4). Due to the strength of Ni–CO bonds, estimated to be as high as 42 kcal/mol, we envisioned that the addition of sacrificial amounts of an electron-rich Ni complex should lead to a CO sink. As desired, the use of 1.5 equiv of $\text{Ni}(\text{COD})_2$ in the presence of 1.0 equiv of neocuproine and 0.5 equiv of 1,4-bis(diphenylphosphino)butane (dppb) led to complete selectivity for the desired product as a single diastereomer.²³ This methodology is compatible with a number of complex succinic and glutaric anhydrides, some of which are illustrated in Scheme 5.

Although the decarbonylative cross-coupling of anhydrides with diorganozinc reagents demonstrates the diastereoselective formation of carbon–carbon bonds, the nature of the CO sequestration agent made the catalytic reaction inordinately difficult. Furthermore, we envisioned that a more general approach to nucleophilic interception of metalacycles of type **A** would be via their formation from alkenes and CO_2 rather than via anhydride activation and CO extrusion. We thus

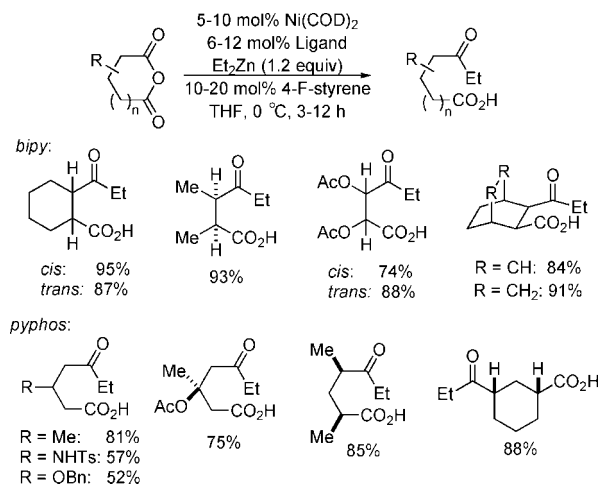
SCHEME 5. Scope of the Nickel-Mediated Decarbonylative Cross-Coupling

turned our attention to the direct interception of the metallocycles formed from transition metal insertion into cyclic anhydrides.

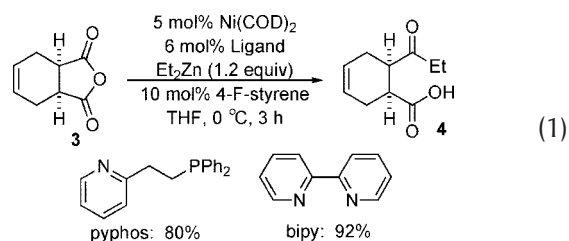
Catalytic Anhydride Alkylation Methodology

Simultaneously with the development of the decarbonylative coupling methodology, our group investigated the direct coupling reaction of diorganozinc reagents with cyclic carboxylic anhydrides.²⁴ The realization of such methodology provides ready access to a variety of δ - and γ -ketoacids from succinic and glutaric anhydrides, respectively. More promising, however, is the use of *meso* anhydrides, which upon transformation into the corresponding ketoacids contain backbone stereochemistry that can be defined by control of the carbon–carbon bond-forming event. These 1,4- and 1,5-dicarbonyl species with stereodefined backbones have been demonstrated as intermediates in the synthesis of a variety of heterocyclic systems,²⁵ and a facile formation of such synthons promises more expedient access to numerous natural products.

Utilizing *cis*-cyclohexenedicarboxylic anhydride **3** as a test substrate, we tested numerous ligands for reactivity with catalytic Ni(COD)₂, ligand, and 4-fluorostyrene with 1.2 equiv of Et₂Zn at 0 °C in THF. 4-Fluorostyrene was utilized following the precedent of Knochel,²⁶ who argued that it facilitates reductive elimination from bisalkyl nickel complexes.²⁷ While monodentate ligands provide limited reaction, some bidentate phosphines, such as 1,2-bis(diphenylphosphino)ethane (dppe), afford useful yields. Most efficient, however, are the bidentate N–N and P–N ligands, bipy and pyphos [(2-diphenylphosphino)ethylpyridine],²⁸ which provide the cross-coupling product, ketoacid **4**, in 80% and 92% yield, respectively (eq 1). These ligands are generally interchangeable for catal-

SCHEME 6. Selection of Nickel-Catalyzed Alkylation of Cyclic Carboxylic Anhydrides

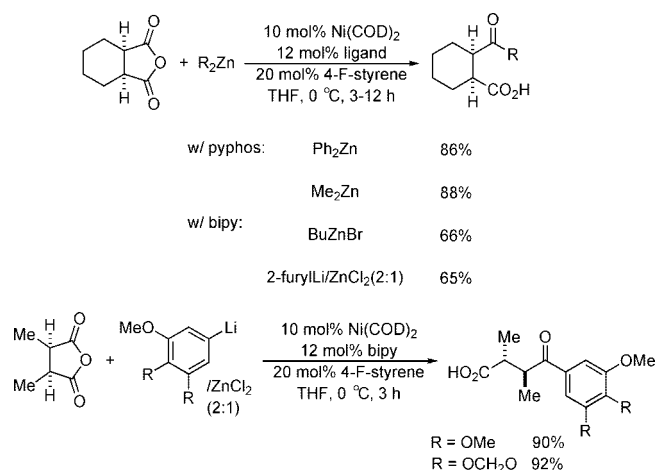
ysis of the alkylation of a wide variety of cyclic anhydride substrates (Scheme 6). Glutaric anhydrides also participate in this



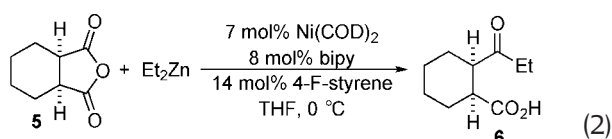
methodology, providing the desired 1,5-ketoacids in good to excellent yields in the presence of extensive substrate complexity and functionality. Even substrates containing β -alkoxy or -acetate substitution are compatible with this methodology, because the reaction conditions are neither acidic nor basic enough to induce elimination. It is also notable that in all cases the products are obtained as single diastereomers, because no epimerization occurs under the reaction conditions.

Because the availability of commercial organozinc reagents is quite limited, the extension of this methodology to *in situ* generated nucleophiles is of paramount importance. To this end, we have identified a diverse range of competent organozinc nucleophiles. In addition to commercially available diorganozinc reagents and organozinc halides, organozinc reagents prepared from the reaction of lithium or Grignard reagents with ZnCl₂ also perform well in this methodology (Scheme 7). It is notable that removal of byproducts from organozinc formation is not required, because the corresponding chloride salts and alkyl bromides have no deleterious effect on the reaction.

To address shortcomings in our Ni-catalyzed anhydride alkylation methodology, we initiated a mechanistic study to

SCHEME 7. Scope of Nucleophiles in the Nickel-Catalyzed Alkylation of Anhydrides

determine the catalytic cycle. *In situ* IR spectroscopy was utilized to obtain initial rate kinetics of the Ni(COD)₂/bipy-catalyzed reaction of anhydride **5** with Et₂Zn (eq 2).²⁹ While the reaction rate displays typical first-order dependence upon the concentration of the catalyst, the rate is independent of the

**Rate Law**

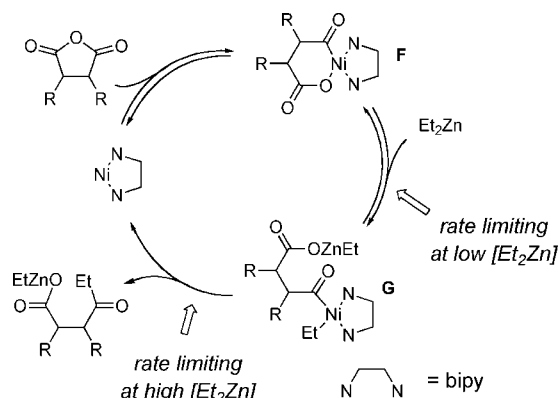
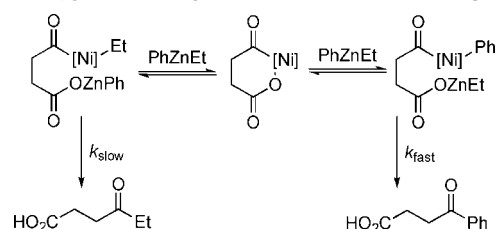
Low Et₂Zn concentration: $v = k[\mathbf{5}]^0[\text{Et}_2\text{Zn}]^1[\text{Ni/bipy}]^1[\text{4-F-sty}]^0$

High Et₂Zn concentration: $v = k[\mathbf{5}]^0[\text{Et}_2\text{Zn}]^0[\text{Ni/bipy}]^1[\text{4-F-sty}]^0$

concentrations of both anhydride **5** and 4-fluorostyrene. Variation of Et₂Zn concentration results in nearly first-order behavior at low concentrations, but little to no dependence at higher concentrations. This saturation behavior indicates a shift in the turnover-limiting step. These results suggest that at low Et₂Zn concentration, transmetalation is the turnover-limiting step, while at higher concentrations, the second-order process of transmetalation proceeds more rapidly, resulting in an equilibrium between intermediates **F** and **G** (Scheme 8). Reductive elimination, a first-order process that does not significantly accelerate with increasing Et₂Zn concentration, becomes rate-limiting under these conditions. This represents an unusual turnover-limiting step for catalytic cross-coupling and is particularly rare for the formation of carbon–carbon bonds.^{30,31}

Extensions of Reactivity

In our anhydride alkylation methodology, diorganozinc reagents provide optimal yields and reaction rates, yet only one of the two organic substituents is transferred. To address this deficiency, we followed the precedent of Knochel, who uti-

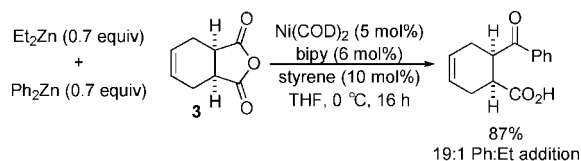
SCHEME 8. Mechanism of Ni/bipy-Catalyzed Alkylation of Succinic Anhydride with Et₂Zn**SCHEME 9.** Hypothetical Equilibria with Mixed Zinc Reagents

lized mixed zinc reagents for cross-coupling with primary alkyl iodides.³² Under typical reaction conditions, diorganozinc reagents readily exchange, providing equilibrium mixtures of the discreet starting materials with the mixed diorganozinc reagents. Because reductive elimination is rate-limiting within our Ni-catalyzed anhydride alkylation manifold, we envisioned that the selectivity of substituent addition from a mixed diorganozinc reagent to carboxylic anhydrides would be governed by the relative rate of reductive elimination of each substituent with the acyl group from the corresponding nickel-containing intermediate (Scheme 9).

To test our hypothesis, we utilized equimolar ratios of two diorganozinc reagents. Subjection of a mixture of Ph₂Zn and Et₂Zn to cyclohexenyl succinic anhydride **3** under standard conditions led to successful alkylation with nearly complete selectivity (19:1) for phenyl transfer.³³ Further studies have revealed a distinct continuum in the relative rate of substituent transfer: phenyl addition occurs with preference to alkyl addition, with small alkyl groups transferring more readily than sterically encumbered species (Scheme 10). While slight mixtures of products are observed with the use of ethyl- or methyl-based sacrificial substituents, use of *i*-propyl or trimethylsilylmethyl (TMSCH₂-) substituents results in selective transfer of the other organozinc substituent.

In addition to commercially available zinc reagents, this methodology is amenable for use with *in situ* formed nucleophiles. This concept is illustrated with the use of 0.55 equiv of

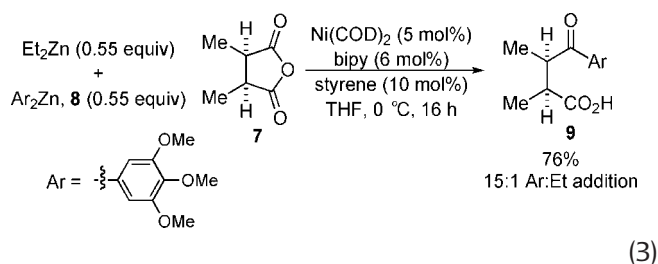
SCHEME 10. Utilization of Mixed Zinc Reagents



Rate of transfer from mixed reagent:

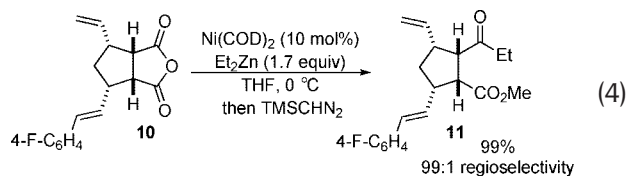
Ar > Me > Et >> *i*Pr ~ CH₂TMS

diorganozinc reagent **8**, derived from the corresponding aryl bromide, with 0.55 equiv of Et₂Zn. Under these conditions, dimethylsuccinic anhydride **7** reacts to provide desired ketoacid **9** in 76% yield in a 15:1 ratio with the ethyl adduct, thus representing the use of both equivalents of the desired nucleophile (eq 3).



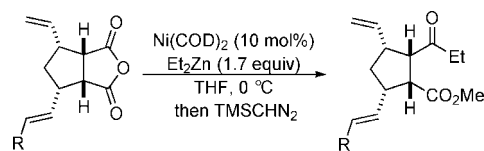
Because both early qualitative results and our mechanistic study indicate that the presence of styrene greatly influences the nickel-catalyzed cross-coupling of diorganozinc reagents with anhydrides, we rationalized that inclusion of an alkene in the substrate could be utilized to direct carboxylic anhydride alkylation. While numerous Lewis acidic and basic moieties, including alcohols, amines, and carbonyls, have been utilized to direct reactivity,³⁴ the use of alkenes as a directing functionality is quite limited.³⁵

We tested our hypothesis with the reaction of 4-fluorophenyl-substituted anhydride **10**, which contains both terminal and internal olefins. Alkylation proceeds with excellent selectivity utilizing Ni(COD)₂ as the catalyst, producing ketoester **11** in 99% yield with 99:1 selectivity for alkylation at the carbonyl proximal to the terminal olefin (eq 4).³⁶



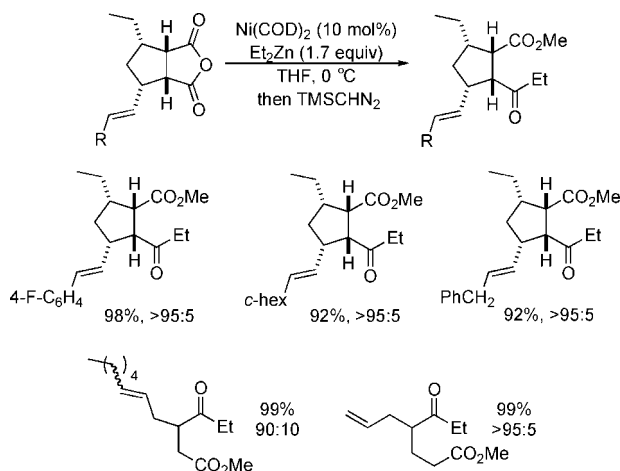
Regioselectivity of the cross-coupling remains high with a large variety of alkene substitution, with most substrates providing the desired product in good to excellent yields (Scheme 11). In addition to Et₂Zn, other commercially available and *in situ*-formed nucleophiles are also compatible with this methodology, generally providing the desired

SCHEME 11. Olefin-Directed Regioselective Anhydride Alkylation



R	Yield (%)	Regioselectivity
4-F-C ₆ H ₄	99	99:1
Ph	86	98:2
(CH ₂) ₃ CH ₃	99	98:2
<i>c</i> -Hex	92	98:2
<i>cis</i> -CH ₂ SiMe ₃	66	>95:5
<i>cis</i> -CH ₂ SnBu ₃	64	95:5
<i>trans</i> -CH ₂ SnBu ₃	68	85:15
<i>trans</i> -CH ₂ OTBS	73	76:24

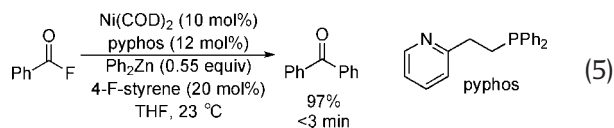
SCHEME 12. Regioselective Alkylation of Anhydrides Containing a Single Olefin



product in good to excellent yields with greater than 19:1 regioselectivity.

In the absence of terminal olefins, more weakly binding internal olefins also direct reactivity (Scheme 12). In cyclic anhydrides containing a single internal olefin, alkylation is successfully directed in excellent yield, typically with greater than 19:1 selectivity, even with a sterically hindered cyclohexyl-substituted olefin. Allyl-substituted glutaric anhydrides have also been identified as efficient substrates for olefin-directed alkylation.

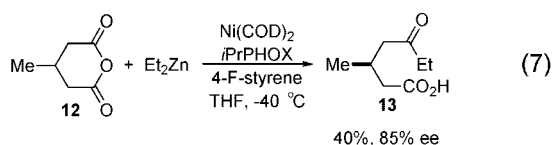
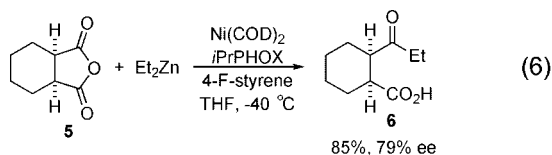
In a reaction closely related to the alkylation of carboxylic anhydrides, we have identified acid fluorides and organozinc reagents as competent cross-coupling partners in an extremely mild reaction methodology for the formation of ketones. Utilizing Ni(COD)₂ and pyphos in the presence of 4-fluorostyrene, we observed that only 0.55 equiv of the diorganozinc reagent is necessary for coupling of benzoyl fluoride with Ph₂Zn, indicating that both organic substituents are transferred from the organometallic reagent.³⁷ Under these conditions, benzophenone is obtained in 97% yield in less than 3 min (eq 5).



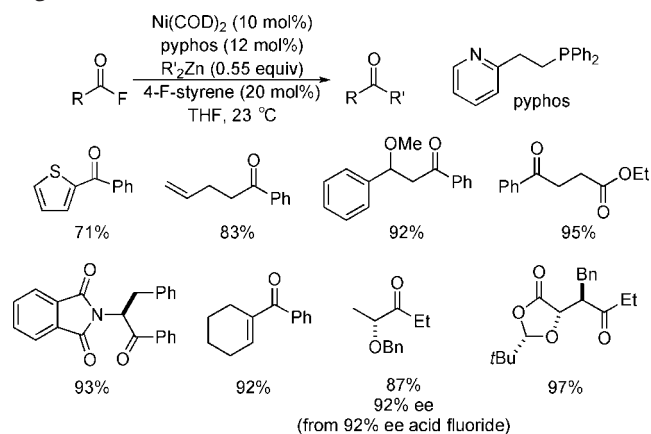
Optimized reaction conditions are tolerant of a wide range of functionality on the acid fluoride, including ethers, thiophene, alkenes, and acetals. Substrates containing β -alkoxide substitution undergo reaction without elimination, and those with a defined stereocenter, even in the α -position, are converted to the corresponding ketone with no loss of stereochemical integrity (Scheme 13). The identical reaction conditions can also be utilized for a number of other electrophilic coupling partners, including acid chlorides, acyl cyanides, anhydrides, thioesters, and even pyridyl esters, all of which produce the corresponding ketone in greater than 90% yield.

Enantioselective Desymmetrization with Ni

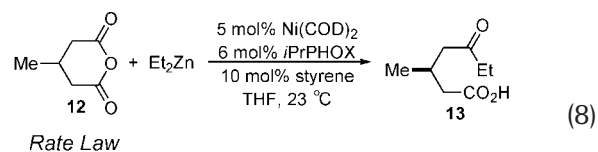
With the development of a general methodology for the nickel-catalyzed alkylation and arylation of *meso* cyclic succinic and glutaric anhydrides, we turned our attention to the development of an enantioselective variant of the reaction. Our initial results were quite promising: use of Ni(COD)₂ with *i*PrPHOX (*iso*-propylphosphinooxazoline) in the presence of 4-fluorostyrene affords active and selective catalysts for the alkylation of both succinic and glutaric anhydrides.²⁴ Alkylation of *cis*-cyclohexanedicarboxylic anhydride **5** with Et₂Zn proceeds in 85% yield and 79% ee at -40 °C (eq 6), while similar reaction with 4-methylglutaric anhydride (**12**) produces 1,5-ketoacid **13** in 40% yield and 85% ee (eq 7). We quickly realized, however, that such selectivity was not general, and that the presence of the additive had a profound influence upon both enantioselectivity and reactivity.³⁸ These observations countered those made earlier for the Ni(COD)₂/*bipy* catalyzed system, wherein styrene was absent from the rate law. In order to gain further knowledge of this system with the goal of developing a general asymmetric variant of this reaction, we extended our previously described mechanistic study to the Ni(COD)₂-*i*PrPHOX-catalyzed alkylation of glutaric anhydrides.



SCHEME 13. Acid Fluoride Cross-Coupling with Diorganozinc Reagents



In a manner similar to that described above, kinetic analysis of the reaction of 4-methylglutaric anhydride (**12**) with Et₂Zn utilizing Ni(COD)₂, *i*PrPHOX, and styrene was performed by *in situ* IR spectroscopy (eq 8).²⁹ The reaction displays first-order dependence upon catalyst and anhydride concentration but is independent of the concentration of Et₂Zn, suggesting rate-limiting oxidative addition of the metal center into the anhydride. Details of transmetalation and reductive elimination reactions remain hidden behind the turnover-limiting step. Further information was obtained upon variation of the styrene concentration. In the absence of styrene, the reaction proceeds slowly, producing ketoacid **13** in 4% ee. The reaction rate and enantioselectivity increase with styrene



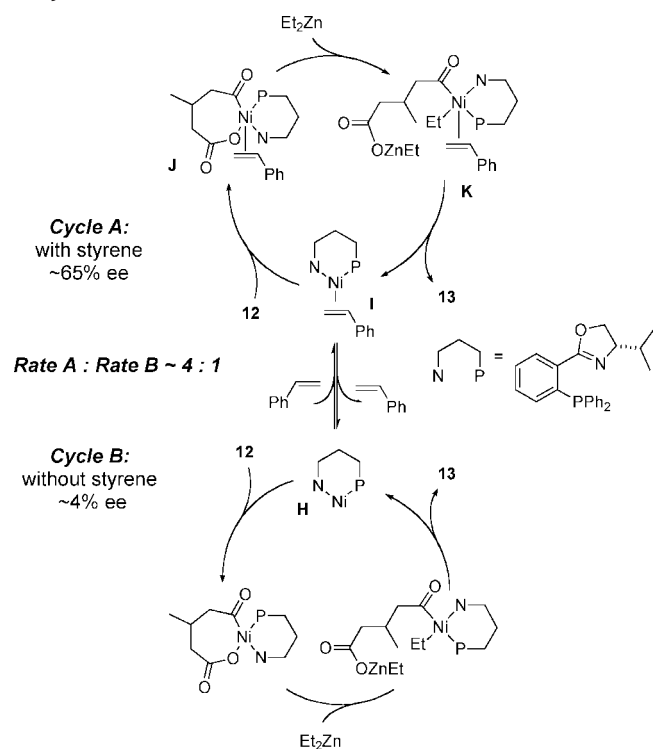
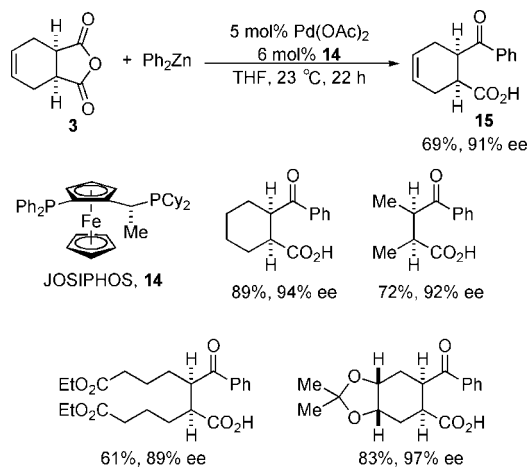
$$\text{Low styrene concentration: } v = k[\mathbf{12}]^1[\text{Et}_2\text{Zn}]^0[\text{Ni}/\text{PHOX}]^1[\text{4-F-sty}]^1$$

$$\text{High styrene concentration: } v = k[\mathbf{12}]^1[\text{Et}_2\text{Zn}]^0[\text{Ni}/\text{PHOX}]^1[\text{4-F-sty}]^0$$

concentration until saturating above 0.06 M styrene at 65% ee. These results suggest that two catalytic cycles are operational: catalysis in the absence of styrene results in slow turnover with low selectivity, while reaction in the presence of styrene provides a more selective reaction manifold (Scheme 14).

Enantioselective Desymmetrization of Cyclic Carboxylic Anhydrides

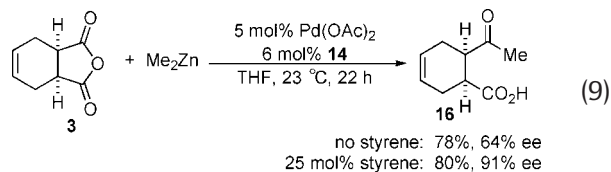
Due to the difficulties encountered in the development of a nickel-catalyzed asymmetric alkylation methodology,³⁸ other metals were explored for reactivity. In the course of these studies, we observed that Pd(OAc)₂, in the presence of a variety of bidentate phosphine ligands, is a competent desymme-

SCHEME 14. Proposed Catalytic Cycle for Ni(COD)₂-iPrPHOX Catalyzed Reaction**SCHEME 15.** Palladium-Catalyzed Desymmetrization of Succinic Anhydrides

trization precatalyst.³⁹ Optimum results are obtained utilizing Pd(OAc)₂ with ferrocene-based bisphosphine ligand Josiphos (**14**), which catalyzes the reaction of anhydride **3** with Ph₂Zn, producing ketoacid **15** in 69% yield and 91% ee. This system is similarly selective for a range of succinic anhydrides, producing arylated products in excellent yields and enantioselectivities near or above 90% (Scheme 15).

Extension of the reactivity to Et₂Zn and Me₂Zn led to several notable observations. While the desymmetrization of **3** with Me₂Zn yields ketoacid **16** in 64% ee, the addition of 25

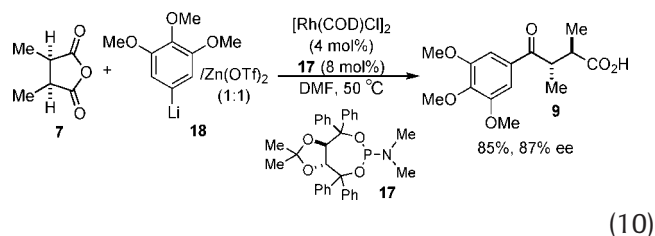
mol % of 4-fluorostyrene increases the enantioselectivity to 91% (eq 9). Unfortunately, similar effects are not observed for other diorganozinc reagents.



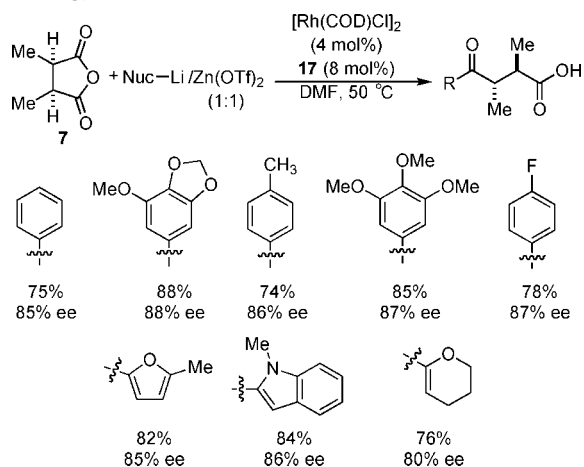
Although enantioenriched 1,4-ketoacids can be successfully generated from numerous anhydrides with commercially available diorganozinc reagents, all attempts to extend the reactivity to *in situ* prepared nucleophiles failed to produce the desired ketoacids in appreciable yields or enantioselectivities. Control experiments suggest that the presence of additional halide, present as byproducts of diorganozinc formation, inhibits the desired reactivity. In addition, desymmetrization, even with commercially available diorganozinc reagents, is limited to succinic anhydrides. For these reasons, we continued our pursuit of a more general solution.

Since rhodium complexes have been demonstrated to tolerate the presence of Lewis bases, as illustrated by rhodium-catalyzed conjugate addition reactions run in water,⁴⁰ we anticipated that these species would be less susceptible to complications due to the presence of halides. Furthermore, a Rh(I)/Rh(III) redox couple is anticipated for the desymmetrization reaction, potentially providing a mechanism distinct from previous Ni- and Pd-catalyzed reactions.

Because previous methodology is ineffective with *in situ* formed organozinc reagents, our investigation of rhodium-catalyzed desymmetrization focused upon nucleophiles formed via reaction of aryl lithium reagents with various ZnX₂ salts.⁴¹ After a number of rhodium sources were screened with various ligands, the combination of [Rh(COD)Cl]₂ with phosphoramidite **17** proved an efficient and selective catalyst system. In the presence of a 1:1 ratio of Zn(OTf)₂ and aryl lithium **18**, *cis*-dimethylsuccinic anhydride **7** was arylated in 85% yield and 87% ee (eq 10). It is notable that optimal conditions include the use of the organozinc triflate, formed from 1 equiv of aryl lithium, rather than the more reactive diorganozinc reagent that requires 2 equiv while utilizing only 1 equiv.



SCHEME 16. Nucleophiles Compatible with Rh/(-)-*trans*- α,α' -(Dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) (TADDOL)–PNMe₂-Catalyzed Anhydride Desymmetrization Methodology

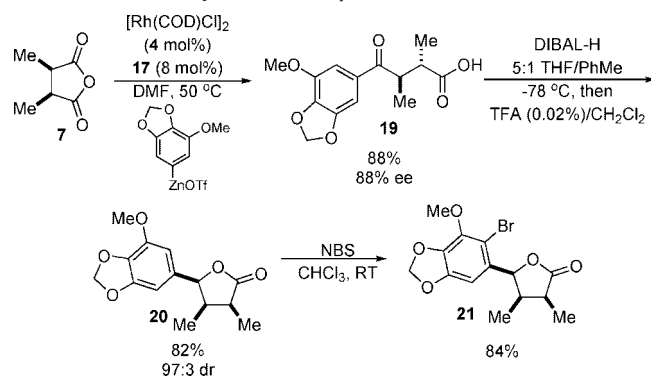


While several alkyl- and alkenyl-substituted anhydrides are compatible in this reaction, the strength of this methodology is demonstrated with the diversity of organozinc reagents, which includes nucleophiles formed from functionalized aryl bromides, as well as from 2-methyl furan, dihydropyran, and *N*-methylindole. Products from the reactions of these nucleophiles with anhydride **7** are shown in Scheme 16. Yields range from 74% to 88%, and enantioselectivities are typically in excess of 85%. It is notable that in the preparation of these organozinc triflates, no purification is necessary. All components remain present, including Li and halide salts yet have no deleterious influence upon the reaction. Attempts to utilize alkyl analogues under these conditions result in complex product mixtures.

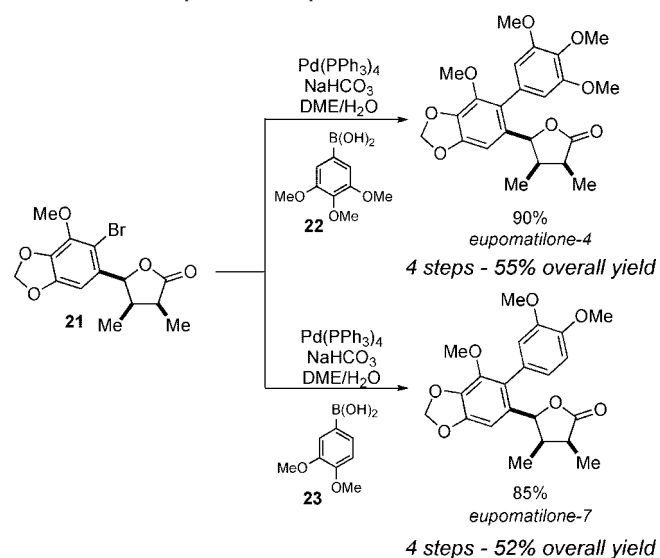
The concise synthesis of three lignans, eupomatilones **4** and **7**, and the reported structure of eupomatilone **6**, illustrates the utility of this methodology. The members of the eupomatilone family are characterized by oxygenated biaryl systems connected to a highly substituted γ -lactone core.⁴² Ketoacid **19**, obtained from desymmetrization of **7**, was subjected to Frenette's reduction protocol and cyclized, providing the desired all *syn* lactone **20**.⁴³ Subsequent bromination affords aryl bromide **21** as the exclusive regioisomer (Scheme 17).

Suzuki cross-coupling of **21** with the appropriate boronic acid was accomplished utilizing Pd(PPh₃)₄. Use of 3,4,5-trimethoxyphenylboronic acid **22** results in the formation of eupomatilone **4**, completing the four step synthesis in an overall yield of 55% from readily available starting materials (Scheme 18). Likewise, coupling of 3,4-dimethoxyphenylboronic acid **23** with aryl bromide **21** produces eupomatilone **7** in an overall yield of 52% in four steps.

SCHEME 17. Core Synthesis of Eupomatilones **4** and **7**

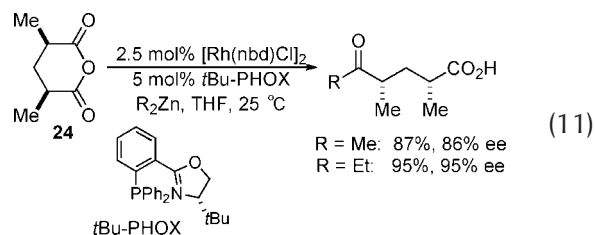


SCHEME 18. Completion of Eupomatilones **4** and **7**



Despite the success of the rhodium-catalyzed desymmetrization of succinic anhydrides, these conditions are unfit for the use of alkyl nucleophiles or glutaric anhydrides. A series of additional optimization studies identified [Rh(nbd)Cl]₂ (nbd = norbornadiene) with *t*BuPHOX (*t*-butyl phosphinooxazoline) as a competent catalyst for the desymmetrization of glutaric anhydrides with alkyl nucleophiles.⁴⁴ Under these conditions, Me₂Zn and Et₂Zn nucleophiles alkylate 3,5-dimethylglutaric anhydride (**24**) in 86% and 95% ee, respectively, providing the first catalytic enantioselective desymmetrization of glutaric anhydrides with carbon nucleophiles (eq 11). This asymmetric formation of 1,5-ketoacids represents a means of generating enantioenriched synthons of *syn*-deoxypropionate, a structural motif common to natural products.

Similar reaction conditions are also amenable to the use of alkyl zinc halide nucleophiles generated from the corresponding Grignard or lithium reagents with ZnX₂ salts. A range of nucleophile functionality is tolerated, and in all cases, the desymmetrization of glutaric anhydride **24** proceeds with



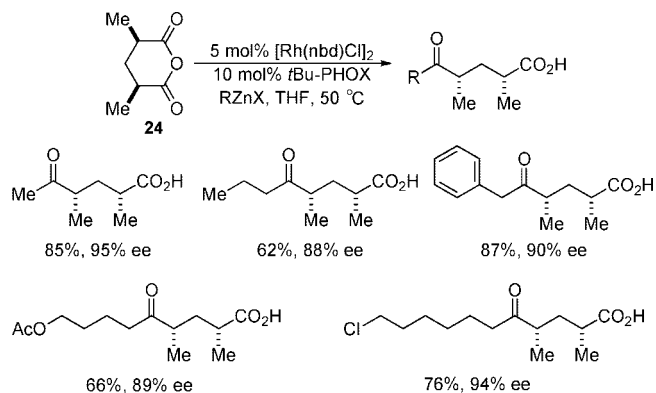
enantioselectivities near 90% (Scheme 19). Notably, the use of *in situ* formed MeZnBr provides significantly higher enantioselectivity than commercially available Me₂Zn.

Overview and Outlook

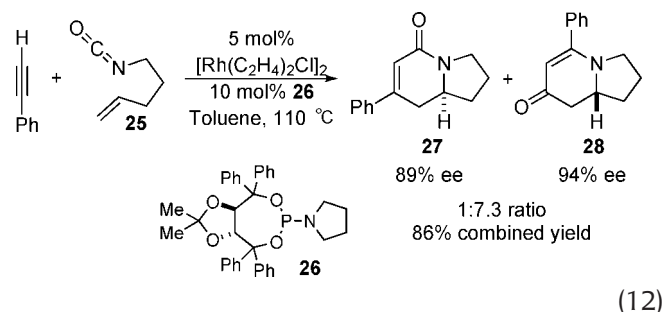
The development of carboxylic acid desymmetrization methodology has provided the means for the enantioselective construction of 1,4- and 1,5-ketoacids. Reaction manifolds enable the selective alkylation of succinic and glutaric anhydrides, using commercially available and *in situ* generated nucleophiles. Mechanistic understanding of the parent reaction systems has led to the use of mixed zinc reagents and the development of the olefin-directed anhydride alkylation methodology. The utility of anhydride desymmetrization has been demonstrated with concise asymmetric syntheses of several members of the eupomatilone family of lignans and the establishment of a versatile means of producing enantioenriched *syn*-deoxy-polypropionate synthons. Despite these advances, the methodology is inherently limited by the availability of substrates; the symmetrical nature of *meso* cyclic anhydrides makes them very specialized species. From the outset, we viewed anhydride desymmetrization as the foundation for future work into the generation of metalacycles via the cyclization of alkenes or alkynes with heterocumulenes.

To this end, our group has recently described the initial developments of a rhodium-catalyzed [2 + 2 + 2] coupling of an alkenyl isocyanate with an alkyne for the rapid construction of

SCHEME 19. Nucleophile Scope for Rh/*t*BuPHOX-Catalyzed Desymmetrization of 3,5-Dimethylsuccinic Anhydride



alkaloidal heterocycles.⁴⁵ Although similar heterocumulene couplings have been demonstrated, this work represents a rare example of the successful inclusion of an alkenyl π -system⁴⁶ and thus formation of a stereocenter. While this methodology remains in its infancy, early results are promising: the cyclization of alkenyl isocyanate **25** with phenyl acetylene, catalyzed by [Rh(COD)Cl]₂ and phosphoramidite **26**, produces bicycle **27** and rearrangement product **28**, both in excellent enantioselectivity (eq 12). Efforts are currently focusing upon identification of the reaction mechanism, as well as means to control regio- and stereoisomer selectivity. These rapidly developing studies will be reported in due course.



The continued evolution of these methodologies promises the means to readily synthesize complex molecules through previously unavailable routes. Despite these advances in the use of metalacycles, additional frontiers remain. We believe that our efforts to date provide the foundation for the utilization of more versatile means of metalacycle formation, with the goal of developing a fully modular, completely intermolecular three-component cycloaddition compatible with numerous π components. Ultimately, we envision the extension of this asymmetric methodology to include other heterocumulenes, including carbon dioxide. Realization of this goal would provide a route to complicated carboxylic acid containing products while utilizing CO₂ as an inexpensive C1 feedstock.

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BIOGRAPHICAL INFORMATION

Jeffrey B. Johnson was born and raised in Grand Forks, North Dakota, and received his B.A. in chemistry in 2000 from Gusta-

vus Adolphus College. He earned his Ph.D. in 2004 under the direction of Prof. Charles P. Casey from the University of Wisconsin—Madison, where he was an ACS Division of Organic Chemistry Fellow, and served as an NIH postdoctoral fellow under the direction of Prof. Tomislav Rovis. He is currently an assistant professor at Hope College.

Tomislav Rovis was born in Zagreb in the former Yugoslavia but was raised in Southern Ontario, Canada. Following his undergraduate studies at the University of Toronto, he earned his Ph.D. degree at the same institution in 1998 under the direction of Professor Mark Lautens. From 1998 to 2000, he was an NSERC postdoctoral fellow at Harvard University with Professor David A. Evans. He has served at Colorado State University since 2000 and has been named a GlaxoSmithKline Scholar, an Amgen Young Investigator, a Lilly Grantee, an Alfred P. Sloan Fellow, and a Monfort Professor at Colorado State University.

FOOTNOTES

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