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

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ABSTRACT

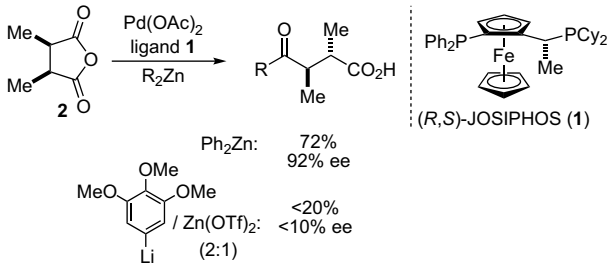
Two distinct systems for the rhodium-catalyzed enantioselective desymmetrization of *meso*-cyclic anhydrides have been developed. Each system has been optimized and are compatible with the use of in situ prepared organozinc reagents. Rhodium/PHOX species efficiently catalyze the addition of alkyl nucleophiles 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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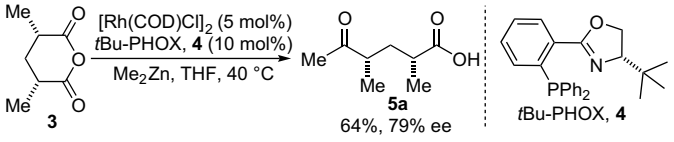
In efforts to develop methodology to expand the utility of the enantioselective desymmetrization of cyclic anhydrides, we turned to the use of rhodium. These catalysts promise to be less susceptible to complications from in situ prepared nucleophiles, specifically the presence of halides, as rhodium 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).

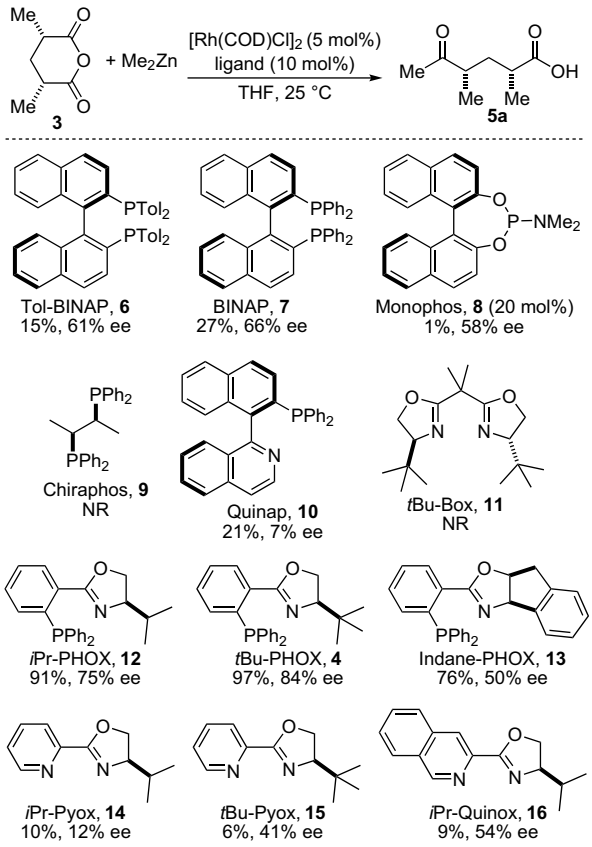


Scheme 2. Initial results for rhodium-catalyzed desymmetrization with commercially available diorganozinc reagents. COD=1,5-cyclooctadiene.

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