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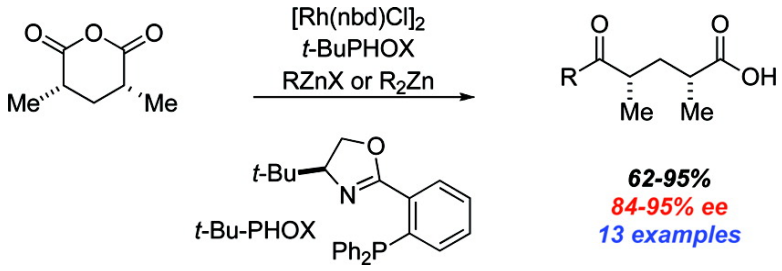
J. Am. Chem. Soc., **2007**, 129 (30), 9302-9303• DOI: 10.1021/ja073269s • Publication Date (Web): 10 July 2007



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Rhodium-Catalyzed Enantioselective Desymmetrization of *meso*-3,5-Dimethyl Glutaric Anhydride: A General Strategy to *syn*-Deoxypolypropionate Synthons

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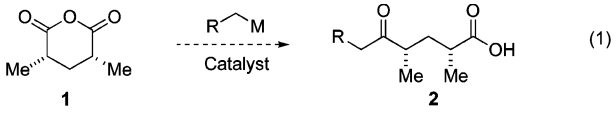
The *syn*-deoxypolypropionate motif is a ubiquitous structure within nature. Numerous iterative methods exist for its construction, mainly involving stereoselective enolate alkylations and conjugate additions in the presence of a chiral auxiliary.[1] More recent methods include Burgess' enantioselective hydrogenation of polyene systems[2] and Negishi's sequential carboalumination/vinylation protocols.[3] The enantioselective monoalkylation of *meso*-3,5-dimethyl glutaric anhydride **1** would provide a unique and rapid entry into *syn*-deoxypolypropionate systems such as **2** (eq 1). We and others have previously reported catalytic anhydride activation,[4,5] as well as asymmetric sp^2-sp^2 cross-couplings.[6] Dimethyl glutaric anhydride **1** is readily available in molar quantities,[7] and while the enantioselective desymmetrization with heteroatom nucleophiles is well-established,[8] no general methods for direct enantioselective carbon−carbon bond formation is known.[9] Herein we report a rhodium-catalyzed enantioselective alkylative desymmetrization of **1** with in situ prepared carbon nucleophiles to generate a series of *syn*-deoxypolypropionate synthons.



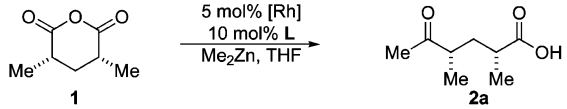
(1)

We discovered that Rh(I) sources efficiently catalyze the addition of dimethyl zinc to 3,5-dimethyl glutaric anhydride.[10] Through optimization studies (Table 1 and Supporting Information), we identified phosphinooxazoline ligands (PHOX)[11] as the optimal scaffold with *tert*-butyl PHOX **3d** in the presence of $[Rh(nbd)Cl]_2$ at 25 °C providing the best results.[12,13]

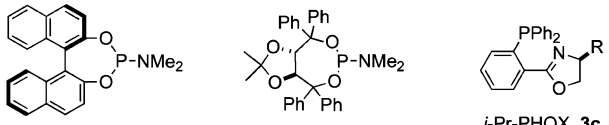
The use of commercially available dimethyl and diethyl zinc reagents allows the desymmetrization to proceed with excellent yields and enantioselectivities. When the sterically encumbered *i*-Pr_2Zn is used, only trace amount of product is observed. The enantioselectivity is dramatically reduced when Ph_2Zn is used under these conditions. In this case, the Rh/TADDOL−P−NMe_2 system[6b] provides products of higher ee possibly indicating a change in mechanism between sp^3 and sp^2 nucleophiles. In situ prepared aryl nucleophiles are not compatible.

With the intent of expanding this reaction to accommodate more diverse nucleophiles, we began to examine the use of in situ prepared organozinc reagents.[14] These conditions proved fully compatible with a wide range of alkyl zinc reagents easily prepared from their Grignard reagents[15] or via other protocols[16] (Table 2). The reaction is tolerant of a wide range of functionality. Alkyl substituents are well-suited affording compounds **2a**−**2f**. The enantioselectivity is augmented (86−95% ee) when in situ generated MeZnBr is used (Scheme 1 vs Table 2). Esters and alkyl chlorides are well-tolerated in this reaction to provide functionalized products **2g** and **2h**. Benzylic nucleophiles are excellent coupling partners, providing compounds **2i**−**2m**. An apparent correlation between the

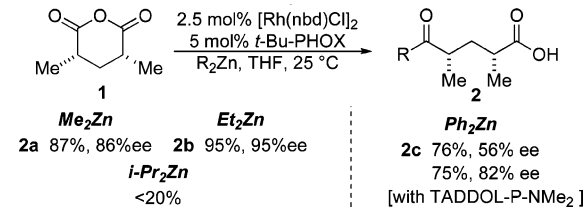
Table 1. Catalyst and Ligand Optimization



Entry	[Rh]	L	T/ °C	Yield (%)	ee (%)
1	$[Rh(COD)Cl]_2$	MONOPHOS **3a**	40	4	15
2	$[Rh(COD)Cl]_2$	TADDOL-P-NMe_2 **3b**	40	n.r.	-
3	$[Rh(COD)Cl]_2$	*i*-Pr-PHOX **3c**	40	68	72
4	$[Rh(COD)Cl]_2$	*t*-Bu-PHOX **3d**	40	64	79
5	$[Rh(nbd)Cl]_2$	*t*-Bu-PHOX **3d**	40	97	80
6	$[Rh(nbd)Cl]_2$	*t*-Bu-PHOX **3d**	25	90	86

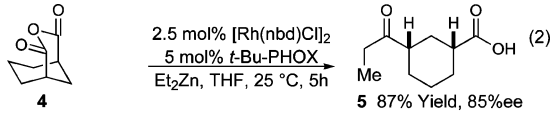


Scheme 1. Commercial Diorganozinc Nucleophile Scope

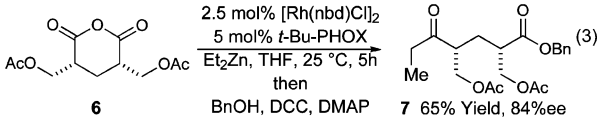


electronics of the benzylic nucleophile and the ee is observed: electron-rich benzylic zinc reagents, such as in **2j**, provide lower enantioselectivities due to an uncatalyzed background reaction.

Other 3,5-disubstituted glutaric anhydrides[17] are also competent partners in this chemistry. For example, bicyclic anhydride **4** provides product **5** in 85% ee, while bisacetate anhydride **6** affords ketoacid **7** in 84% ee (eqs 2 and 3).[18]



(2)



(3)

The use of a zinc homoenolate produces keto bisester **2n** in good yield and excellent enantioselectivity. The use of this nucleophile is complicated with formation of a significant byproduct arising from isomerization of the homoenolate to the corresponding enolate (eq 4). The amount of this byproduct may be reduced if the reaction is conducted at higher concentrations, a finding that strongly suggests that initial interaction occurs between the nucleophile and Rh, prior to addition to anhydride (eq 5). At lower concentrations,

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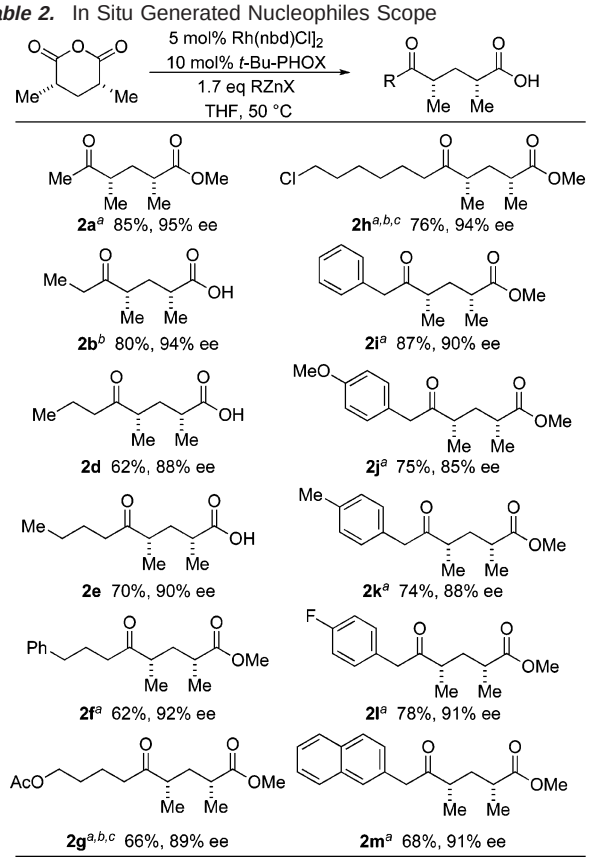
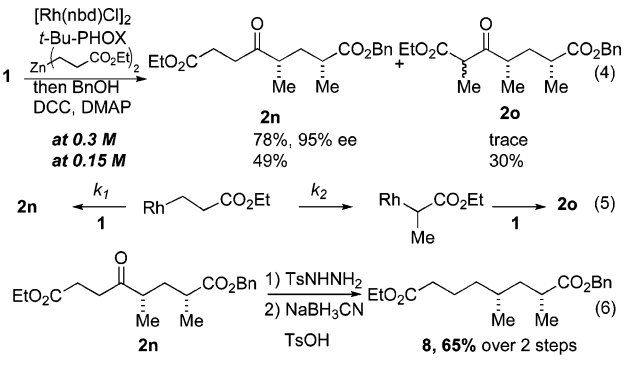
Table 2. In Situ Generated Nucleophiles Scope

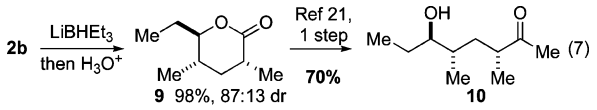


[a] Treated with $TMSCHN_2$. [b] Reaction performed at 25 °C. [c] R_2Zn was used.

the unimolecular isomerization reaction is competitive with the second order addition to anhydride. It is also worth noting that other ligands, including *i*-Pr-PHOX **3c**, lead to exclusive formation of the isomerized product **2o**, suggesting that the steric bulk associated with *t*-Bu-PHOX is responsible for inhibiting this isomerization reaction. Compound **2n** can be further elaborated through a two-step deoxygenation protocol[19] to afford bisester **8** (eq 6), a potentially useful synthon in polypropionate synthesis.



Ketoacid **2b** undergoes a diastereoselective reduction with $LiBHEt_3$, which upon acidic workup affords lactone **9**.[20] This compound is an intermediate in Mori's synthesis of beetle pheromone **10** which was prepared in 12 steps from dimethyl glutaric anhydride **1**,[21] allowing for the synthesis of **10** in 57% overall yield and three steps (eq 7).



In conclusion, we have developed a highly enantioselective alkylative desymmetrization of 3,5-substituted *meso*-glutaric anhydrides, providing rapid access into substituted *syn*-deoxypolypropionate fragments in a single transformation.

Acknowledgment. M.J.C. acknowledges the American Heart Association for a postdoctoral fellowship. T.R. thanks Johnson and Johnson, Merck, Eli Lilly, and Boehringer Ingelheim for support. T.R. is a fellow of the A.P. Sloan Foundation and thanks the Monfort Family Foundation for a Monfort Professorship.

Supporting Information Available: Experimental information, compound characterization and starting material synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Catalyst loading may be reduced to 2.5 mol % (87%, 86% ee, 5 h) and 1 mol % (56%, 85% ee, 24 h).
(13) For catalyst optimization and absolute stereochemistry assignment, see Supporting Information.
(14) For the majority of substrates, elevated temperatures (50 °C) were required for reactivity (e.g., for **2d** 25 °C, 26% yield, 86% ee; 50 °C, 70% yield, 90% ee).
(15) The reaction proceeds in a cleaner fashion if the Grignard is prepared in situ to avoid byproducts arising from oxidation of the organometallic.
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(17) 4-Substituted glutaric anhydrides are not competent partners in this chemistry; for example, 4-methyl glutaric anhydride + Et_2Zn = 90%, 9% ee; 4-phenyl glutaric anhydride + Et_2Zn = 40%, 53% ee.
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JA073269S