Enantioselective Rhodium-Catalyzed Alkylative Desymmetrization of 3,5-Dimethylglutaric Anhydride

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Abstract: A rhodium-catalyzed enantioselective cross-coupling of sp^3 organozinc reagents and 3,5-dimethylglutaric anhydride has been developed to afford the corresponding products, *syn*-deoxypolypropionates, in excellent yields and enantioselectivities. This reaction has been developed so that both commercially available and in situ prepared organozinc reagents are competent coupling partners.

Key words: organozinc reagents, Grignard reagents, C–C bond formation, *syn*-deoxypolypropionates

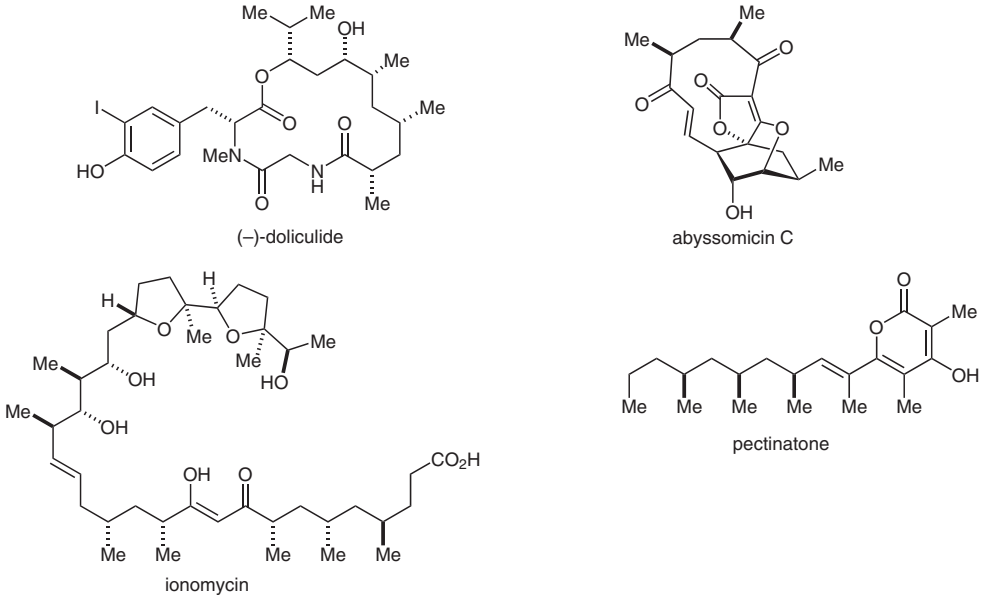

Figure 1 Examples of natural products containing *syn*-deoxypolypropionate motifs

The desymmetrization of achiral compounds into entities that bear one or more defined stereocenters is a powerful transformation.[1] Cyclic anhydrides are especially attractive substrates for these reactions as they are readily available as single *meso*-diastereomers. The products of such transformations are present in many fragments of natural products. The enantioselective desymmetrization of cyclic anhydrides has been achieved with heteroatom nucleophiles with impressive results;[2] however, the corresponding reaction with carbon-based nucleophiles is less explored. Building on our success of nickel-catalyzed cross couplings,[3,4] we have further expanded this approach to enantioselective carbon–carbon bond formation. We demonstrated that palladium was an efficient catalyst for the cross-coupling of succinic anhydrides with diphenylzinc.[5] Although high enantioselectivities were accomplished, this reaction was especially sensitive to the zinc reagent used with only diphenyl- and dimethylzinc being applicable. In some previous work from our group, this drawback was circumvented via the introduction of a rhodium-phosphoramidite complex for this reaction which allowed, for the first time, the use of in situ prepared arylzinc triflates as the nucleophile.[6]

We sought to extend this strategy to glutaric anhydrides and sp^3 nucleophiles, the products of which are *syn*-deoxypolypropionates, a ubiquitous structure in many natural products (see Figure 1).[7] Following a thorough catalyst and ligand screening, we discovered that the combination of chloronorbornadienylrhodium(I) dimer ($[Rh(nbd)Cl]_2$) and *tert*-butylphosphinooxazoline (*t*-Bu-PHOX)[8] was optimal. This catalyst system provides good yields and good to excellent enantioselectivities with commercially available Me_2Zn and Et_2Zn; however, the reaction was less efficient with Ph_2Zn and *i*-Pr_2Zn (Scheme 1, Table 1).

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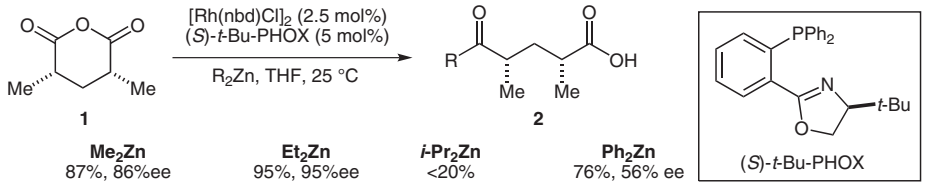
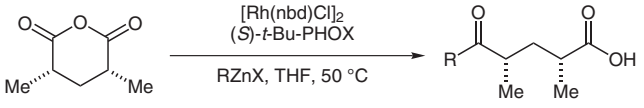
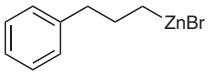
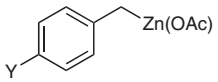
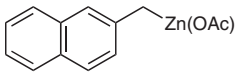
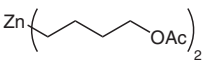
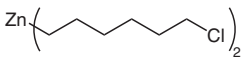
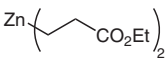


Scheme 1 Desymmetrization of 3,5-dimethylglutaric anhydride with commercially available zinc reagent

Table 1 Desymmetrization of 3,5-Dimethylglutaric Anhydride with In Situ Prepared Zinc Reagent



Entry	RZnX	Y =	Yield (%)	ee (%)
1	MeZnBr		85	95
2	EtZnBr		80	94
3	*n*-PrZnBr		62	88
4	*n*-BuZnBr		70	90
5			62	92
6		H	87	90
7		OMe	75	85
8		Me	74	88
9		F	78	90
10			68	90
11			66	89
12			76	94
13			78	95

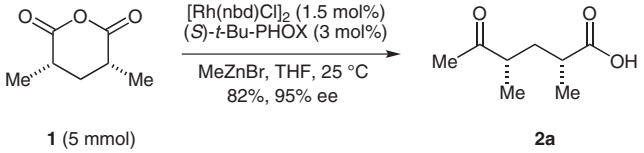
As these are the only commercially available diorganozinc reagents, this reaction was somewhat limited at this point. Therefore, a protocol was developed for the use of in situ prepared nucleophiles. Three distinct nucleophile classes were examined: alkyl, benzylic, and functionalized.

Alkyl nucleophiles were prepared using a Grignard–$ZnBr_2$ transmetalation protocol whereby the majority of the magnesium salts may be precipitated allowing for the alkyl transfer to occur in excellent yields and enantioselectivities. This sequence may be applied to a variety of unfunctionalized alkyl nucleophiles generated from their corresponding Grignard reagents.[9]

Benzylic nucleophiles can be generated from their Grignard reagent also. It is important to use freshly prepared Grignard reagent made from the corresponding benzyl chloride. Transmetalation with $Zn(OAc)_2$ affords the benzylic nucleophile, which provides the optimal results. This reaction is tolerant of a wide range of substituents on the benzene ring; however, electron-rich aromatics afford slightly diminished enantioselectivities due to an uncatalyzed background reaction.

Functionalized nucleophiles may be generated using Knochel's procedure[10] and the reaction is tolerant of both ester and halide functionalities.[11]

This chemistry is also amenable to scale-up; the reaction of dimethylglutaric anhydride and methylzinc bromide proceeds in excellent yields and enantioselectivities (Scheme 2). The catalyst loading may be reduced to 1.5 mol% rhodium dimer (3 mol% Rh atom) and 3 mol% of the ligand with little effect on yields or enantioselectivities.



Scheme 2 Large-scale desymmetrization of 3,5-dimethylglutaric anhydride with in situ prepared nucleophile

All reactions were carried out under argon in flame-dried glassware with magnetic stirring. Column chromatography was performed on EM Science silica gel 60 (230–400 mesh). TLC analyses were performed on EM Science 0.25 mm silica gel 60-F plates. For spectral and HPLC/GC data for all compounds described, see ref. 11.

In Situ Alkylzinc Reagent (0.15 M); General Procedure

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, removed from the glove box, and placed under a positive pressure of argon. To this was added anhyd THF (3 mL) and Et_2O (3 mL) and cooled to 0 °C. The alkylmagnesium bromide[9] (2 M in Et_2O; 0.5 mL,1 mmol) was added dropwise, then the resulting suspension was stirred at 0 °C for 30 min and at 25 °C for 1 h. The stirring was stopped and the precipitate was allowed to settle over 1 h. The supernatant was decanted via syringe and used directly.

In Situ Benzylzinc Reagent (0.15 M)

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, removed from the glove box, and placed under a positive pressure of argon. To this was added anhyd THF (3 mL) and Et_2O (3 mL) and cooled to 0 °C. Benzylmagnesium chloride (2 M in Et_2O; 0.5 mL, 1 mmol) was added dropwise, then the resulting suspension was stirred at 0 °C for 30 min and at 25 °C for 1 h. The stirring was stopped and the precipi-

tate was allowed to settle over 1 h. The supernatant was decanted via syringe and used directly.

In Situ Functionalized Zinc Reagent (0.15 M);[10] General Procedure

An oven dried Schlenk flask was charged with alkyl iodide (0.6 mmol), then sealed and treated to four cycles of evacuation using argon to backfill. This 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 MeOH to vacuum trap to quench the remaining Et_2Zn). Anhyd THF (1 mL) was added and the vessel evacuated again and this sequence was repeated further two times. Finally the mixture was allowed to cool to 25 °C, THF (2 mL) was added, and used directly.

Rhodium-Catalyzed Desymmetrization; General Procedure

To a flame-dried 10 mL round-bottomed 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. Anhyd 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 (**1**; 25 mg, 0.176 mmol) in THF (1 mL) was added. The mixture was stirred overnight at 50 °C and then subjected to either of the two workup procedures: To afford the free acid, the 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 aq sat. $NaHCO_3$ (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. To afford the methyl ester, the 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 organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in toluene–MeOH (1:1, 5 mL) and $TMSCHN_2$ (2 M in Et_2O, 0.5 mL) was added. After 10 min, the solution was concentrated in vacuo and chromatographed directly to afford the pure methyl ester.

(–)-(2*R*,4*S*)-2,4-Dimethyl-5-oxohexanoic Acid (2a); Large-Scale Procedure

A flame-dried 100 mL round-bottomed flak was charged with $ZnBr_2$ (2.25 g, 10 mmol) under an inert atmosphere in a glove box. The flask was sealed with a septum, removed from the glove box, and placed under a positive pressure of argon. To this was added anhyd THF (30 mL) and Et_2O (30 mL) and cooled to 0 °C. MeMgBr (3.3 mL, 3 M in THF, 10 mmol) was added dropwise, then the resulting suspension was stirred at 0 °C for 30 min and at 25 °C for 1 h. The stirring was stopped and the precipitate was allowed to settle over 1 h. To a separate 100 mL round-bottomed flask was added $[Rh(nbd)Cl]_2$ (35 mg, 0.0750 mmol) and (*S*)-*tert*-butylphosphinooxazoline (56 mg, 0.150 mmol) under an inert atmosphere in a glove box. The flask was sealed with a septum, removed from the glove box, and placed under a positive pressure of argon. To this was added anhyd THF (10 mL) followed, 5 min later, by the methylzinc bromide solution (48 mL) prepared earlier (which was decanted from the precipitate via syringe) and a pre-prepared solution of 3,5-dimethylglutaric anhydride (**1**; 710 mg, 5 mmol) in THF (5 mL). The mixture was allowed to stir at 25 °C for 36 h. The resulting dark brown solution was partitioned between Et_2O (50 mL) and aq 1 M HCl (50 mL) and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with aq sat. $NaHCO_3$ (2 × 25 mL). The aqueous layers were combined and acidified to pH 1 using aq 1 M HCl and the acidified layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$, 20 g), filtered, and concentrated in vacuo to afford the title compound (648 mg, 82%, 95% ee) as a colorless oil.[11] Chiral GC analysis (derived methyl ester) was performed using a Chiraldex BDM-2 column at 110 °C rising to 140 °C (2 °C/min) at 1 mL/min; peaks appeared at 13.15 (minor) and 13.33 min (major). The absolute stereochemistry was determined by comparison of optical rotation $[\alpha]_D^{23}$ –11.0 (*c* = 7.6, $CHCl_3$); {Lit.[12] $[\alpha]_D^{25}$ +14.7 (*c* = 7.6, $CHCl_3$) for the 2*S*,4*R*-enantiomer}. All other analytical data were consistent with those reported by Sih and co-workers.[12]

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References

(1) Reviews: (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) Rovis, T. *Recent Advances in Catalytic Asymmetric Desymmetrization Reactions,* In *New Frontiers in Asymmetric Catalysis*; Mikami, K.; Lautens, M., Eds.; Wiley: New York, **2007**, 275–312. (c) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.

(2) For reviews including the asymmetric alcoholysis of cyclic anhydrides, see: (a) Cheng, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. For asymmetric arylation of glutaric anhydrides using stoichiometric quantities of sparteine, see: (c) Shintani, R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1057.

(3) (a) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174. (b) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247. (c) Johnson, J. B.; Yu, R. T.; Fink, P.; Bercot, E. A.; Rovis, T. *Org. Lett.* **2006**, *8*, 4307. (d) Johnson, J. B.; Bercot, E. A.; Rowley, J. M.; Coates, G. W.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 2718. (e) Rogers, R. L.; Moore, J. L.; Rovis, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 9301. (f) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327.

(4) For other contributions to anhydride activation, see: (a) Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1986**, *42*, 1369. (b) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, 2316. (c) Goossen, L. J.; Ghosh, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3458. (d) Goossen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254. (e) Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiamani, A. *Org. Lett.* **2003**, *5*, 289. (f) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645. (g) Yamane, M.; Uera, K.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 424. (h) Kazmierski, I.; Bastienne, M.; Gosmini, C.; Paris, J.-M.; Perichon, J. *J. Org. Chem.* **2004**, *69*, 936. (i) Xin, B.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2006**, *71*, 5725. (j) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Organomet. Chem.* **2002**, *648*, 297. (k) Hong, Y.-T.; Barchuk, A.; Krische, M. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6885.

(5) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 10248.

(6) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4514.

(7) Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, 1057.

(8) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*,

3149. (d) Review: Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
(9) The reaction proceeds in a cleaner fashion if the Grignard is prepared in situ, to avoid by-products arising from oxidation of the organometallic.
(10) For nucleophiles formed by direct Zn–I exchange; see: Rozema, M. J.; Achyuta Rao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956.
(11) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302.
(12) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.