Enantioenriched Keto Acids

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A Concise Synthesis of Eupomatilones 4, 6, and 7 by Rhodium-Catalyzed Enantioselective Desymmetrization of Cyclic *meso* Anhydrides with Organozinc Reagents Generated In Situ**

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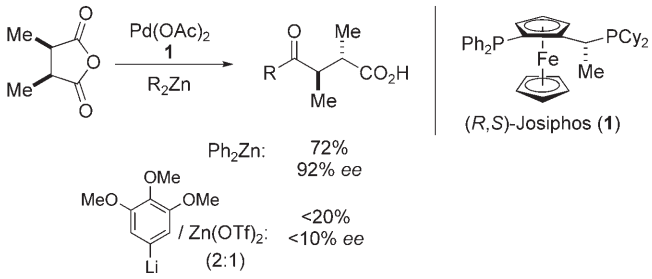
Cross-coupling methodology, as a subset of transition-metal-catalyzed reactions, has revolutionized the means by which complex molecules are constructed.[1] Despite recent advances, significant challenges remain in this area, including the selective construction and definition of stereocenters.[2] Although numerous activated acyl species have been utilized in the formation of ketones,[3] carboxylic acid anhydrides have only recently been investigated as acylating agents in metal-mediated reactions.[4] Our group is engaged in the development of the transition-metal-catalyzed cross-coupling reactions of carboxylic anhydrides and has reported the nickel-catalyzed alkylation of cyclic anhydrides with organozinc nucleophiles to produce 1,4- or 1,5-keto acids.[5]

The power of this methodology lies in the ability to transform cyclic carboxylic anhydrides into keto acid derivatives with stereodefined backbones. We have recently disclosed the enantioselective desymmetrization of succinic anhydrides catalyzed by $Pd(OAc)_2$ and Josiphos (**1**) (Scheme 1).[6] As part of an effort to utilize this reaction for the rapid assembly of complex molecules, we targeted the enantioselective desymmetrization of 2,3-dimethylsuccinic anhydride utilizing functionalized organozinc nucleophiles. Despite the excellent results obtained with commercially available diorganozinc reagents, the use of zinc nucleophiles formed in situ is not compatible with the palladium-catalyzed methodology, an observation not uncommon in asymmetric catalysis involving organozinc reagents.[7,8] Organozinc nucleophiles also fail to produce the desired keto acids in appreciable yields, further limiting the number of available nucleophiles.



Scheme 1. Palladium-catalyzed enantioselective desymmetrization of succinic anhydrides. Tf = trifluoromethanesulfonyl.

Rhodium complexes have been documented to tolerate the presence of Lewis bases, as illustrated by rhodium-catalyzed asymmetric conjugate addition reactions run in water,[9] and thus they promise to be less susceptible to complications arising from the presence of halides. Furthermore, the use of the Rh^I/Rh^{III} redox couple holds the promise of a mechanism distinct from that of the nickel- and palladium-catalyzed reactions.[10] Herein, we present the development of the rhodium-catalyzed desymmetrization of succinic anhydrides with a variety of zinc nucleophiles formed in situ. The utility of this methodology is demonstrated with the concise synthesis of three members of the eupomatilone family of natural products.

Organozinc nucleophiles, formed from the corresponding arylbromide by lithium–halogen exchange and subsequent reaction with various ZnX_2 salts, were utilized in the identification of Rh^I sources capable of catalyzing the addition to cyclic carboxylic anhydrides (Table 1). Further screening revealed the currently optimized conditions for the enantioselective desymmetrization of *meso* succinic anhydrides: $[\{Rh(cod)Cl\}_2]$ (4 mol%) (cod = cyclooctadiene), used in conjunction with phosphoramidite ligand **2** (8 mol%), catalyzes the coupling of ArZnOTf nucleophile **3** (1.4 equiv) with dimethylsuccinic anhydride **4** (1 equiv) in DMF at 50 °C over 16 h. These conditions provide the corresponding keto acid, **5**, in 85% yield and 87% *ee*.[11] Table 1 illustrates the impact of changing several components of these standard conditions. While the reaction proceeds in a number of different solvents and with numerous ZnX_2 salts, all alternatives to DMF and $Zn(OTf)_2$ produce inferior results.

In addition to representing the first example of the application of organozinc reagents formed in situ in the enantioselective desymmetrization of anhydrides, it is also notable that optimum conditions include the use of ArZnOTf nucleophiles. Formation of these nucleophiles requires only a single equivalent of the aryl lithium precursor. This constitutes a significant advance over earlier studies that often required the more reactive diorganozinc reagents, which results in the transfer of only one of the two zinc substituents.[12]

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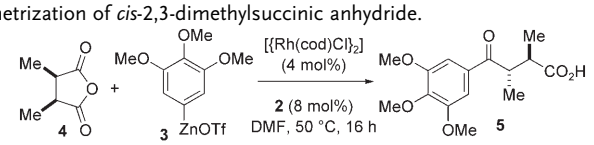
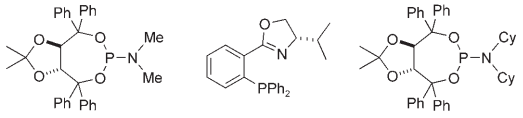
Table 1: Optimization of conditions for the rhodium-catalyzed desymmetrization of *cis*-2,3-dimethylsuccinic anhydride.



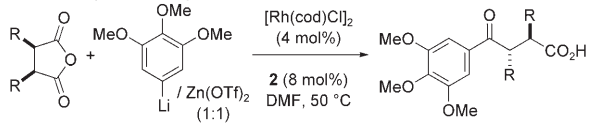


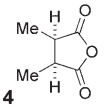
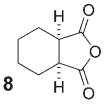
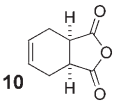
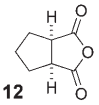
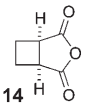
Taddol-PNMe$_2$, **2** *i*Pr-PHOX, **6** Taddol-PNCy$_2$, **7**

Entry	Deviation from standard conditions[a]	Yield [%]	*ee* [%][c]
1	no change	85	87
2	THF, instead of DMF	68	47
3	toluene, instead of DMF	<10	–
4	25 °C, instead of 50 °C	58	70
5	80 °C, instead of 50 °C	73	74
6	$ZnCl_2$, instead of $Zn(OTf)_2$	74	78
7	$ZnBr_2$, instead of $Zn(OTf)_2$	71	72
8	ZnI_2, instead of $Zn(OTf)_2$	32	60
9	ArLi/$Zn(OTf)_2$ 2:1	30	68
10	*i*Pr-Phox[b] (**6**), instead of **2**	23	32
11	Taddol-PNCy$_2$ (**7**) instead of **2**	32	42
12	$[Rh(cod)_2]BF_4$	76	46

[a] Standard conditions: Anhydride **4** (1 equiv) and ArZnOTf (1.4 equiv) with [{Rh(cod)Cl}$_2$] (4 mol%) and ligand **2** (8 mol%) in DMF at 50 °C for 20 h. [b] *i*Pr-Phox (**6**) = isopropylphosphinooxazoline. [c] Determined by HLPC of corresponding methyl ester utilizing a chiral stationary phase.

Table 2: Anhydride scope.



Entry[a]	Anhydride	Product	Yield [%]	*ee* [%][b]
1	 **4**	**7**	85	87
2	 **8**	**9**	72	83
3	 **10**	**11**	77	82
4[c]	 **12**	**13**	61	77
5[c]	 **14**	**15**	56	76

[a] Standard reaction conditions. [b] Determined by HLPC of corresponding methyl ester utilizing a chiral stationary phase. [c] Reactions run at 25 °C.

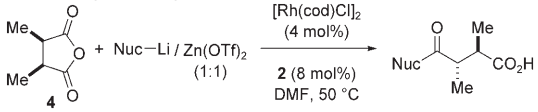
To further extend the utility of this methodology, standard reaction conditions were utilized to examine the reactivity of a series of cyclic *meso* succinic anhydrides (Table 2).[13] Various anhydrides are compatible in this chemistry, including substrates that possess backbone olefins and strained rings. Although enantioselectivities in this reaction are slightly diminished relative to those observed with the Pd/Josiphos methodology, the scope is equally diverse, tolerating a range of succinic anhydrides.

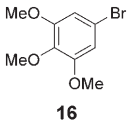
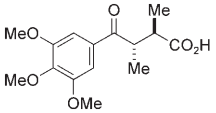
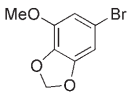
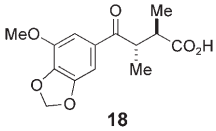
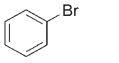
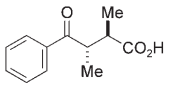
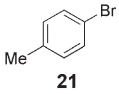
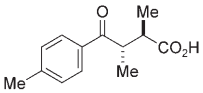
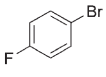
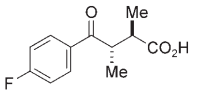
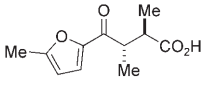
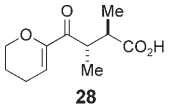
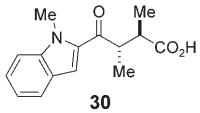
The strength of this methodology is demonstrated with the scope of the organozinc nucleophiles, which was determined to be quite general (Table 3). The arylzinc triflate nucleophiles are formed from the reaction of the nucleophile precursor with *n*BuLi or *t*BuLi, and the corresponding aryl lithium species is subsequently added to a suspension of $Zn(OTf)_2$ in THF. Following a solvent switch to DMF, these nucleophiles are utilized in the desymmetrization methodology without isolation or additional purification. Noteworthy is that no effort is made to liberate the organozinc triflate nucleophile from any salt byproducts—all components remain present, yet have no deleterious influence upon the asymmetric reaction. The functional-group tolerance of this reaction is illustrated by the use of arylzinc triflates formed from a series of functionalized aryl bromides, as well as products formed from 2-methylfuran (**26**), dihydropyran (**28**) and *N*-methylindole (**30**) (entries 6–8, Table 3).[14] Yields range from 74 to 88%, and enantioselectivities are typically greater than 85% *ee*. It is notable that the enantioselectivity is quite similar for most nucleophiles, suggesting that the enantioselectivity-determining step occurs independently of nucleophile involvement.

To demonstrate the synthetic utility of the asymmetric desymmetrization methodology, we sought to prepare three members of the eupomatilone family of lignans. Eupomatilones 1–7, natural products isolated from the Australian shrub *Eupomatia bennettii*, are a structurally unique subset of the broader lignan family.[15] These species are characterized by highly oxygenated biaryl systems connected to a trisubstituted γ-lactone core. While several members of this family have been prepared in racemic form,[16,17] only recently have the research groups led by Buchwald and Gurjar accomplished the asymmetric synthesis of eupomatilone lignans.[18,19] We envisioned that our desymmetrization methodology could be utilized to develop a general, asymmetric approach to the synthesis of eupomatilone 4, eupomatilone 7, and the originally assigned structure of eupomatilone 6.

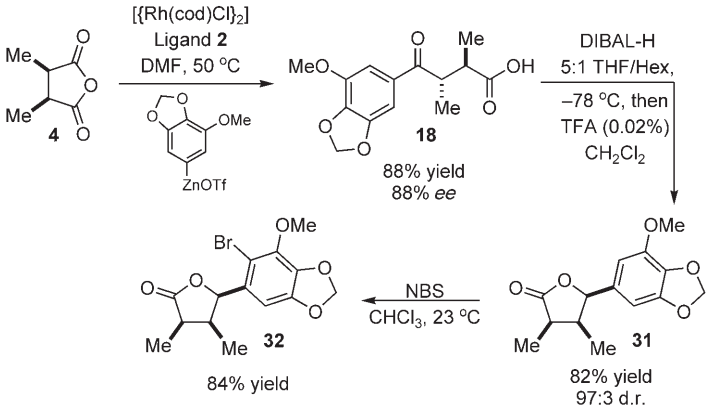
The *syn*-dimethyl relationship present in the backbone of the eupomatilones can be readily accessed by the coupling of the appropriate arylzinc triflate with *cis*-dimethyl succinic anhydride (**4**). Substrate-controlled reduction of the resulting keto acid followed by cyclization results in the formation of the desired all-*syn* lactone.[20] Subsequent biaryl installation by a halogenation/Suzuki-coupling sequence then provides ready access to these three natural products. This route presents numerous attractive features, including rapid assembly of the stereochemically complex core and a structurally flexible sequence in which each component can be tailored for the desired product.

Table 3: Nucleophile scope.

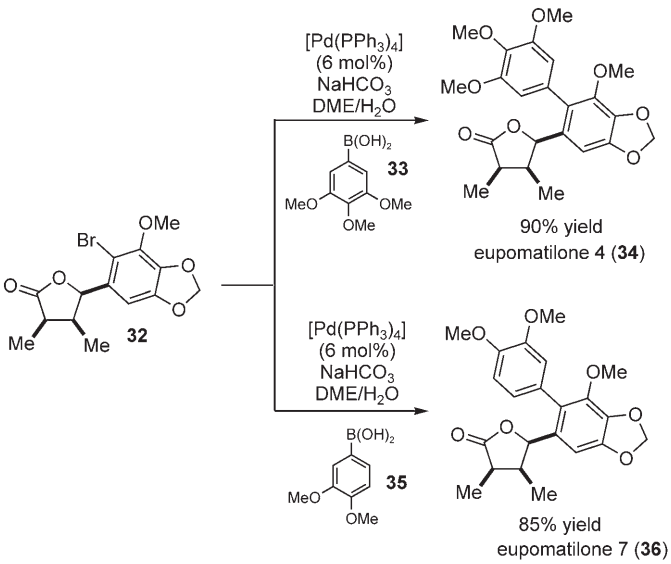


Entry[a]	Nucleophile precursor	Product	Yield [%]	*ee* [%][b]
1	 **16**	 **7**	85	87
2	 **17**	 **18**	88	88
3	 **19**	 **20**	75	85
4	 **21**	 **22**	74	87
5	 **23**	 **24**	78	87
6	 **25**	 **26**	82	85
7	 **27**	 **28**	76	80
8	 **29**	 **30**	84	86

[a] Standard reaction conditions [b] Determined by HPLC of corresponding methyl ester using a chiral stationary phase.



Scheme 2. Core synthesis of eupomatilones 4 and 7. DIBAL-H = diisobutylaluminum hydride, TFA = trifluoroacetic acid, NBS = *N*-bromosuccinimide.

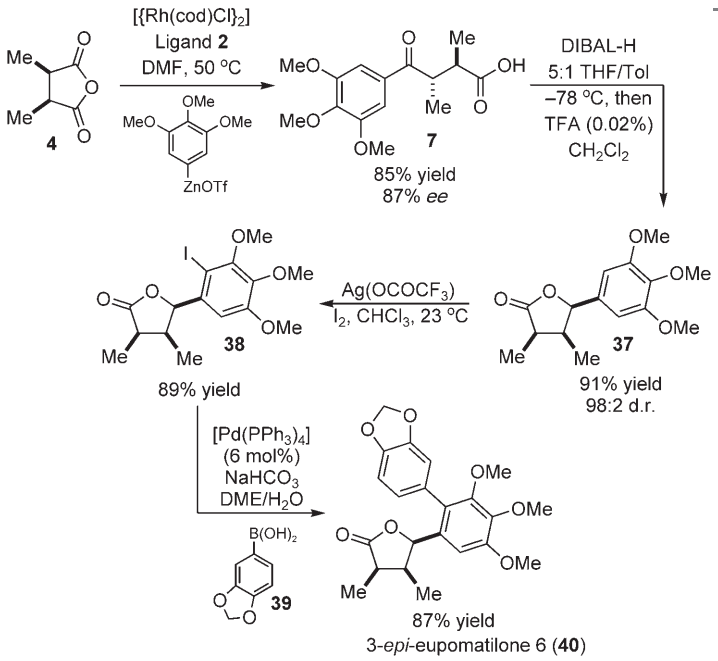


Scheme 3. Completion of eupomatilones 4 and 7. DME = dimethoxyethane.

The syntheses of eupomatilones 4 and 7 followed the same sequence, which began with the preparation of keto acid **18**, in 88% yield and 88% *ee*, on a 250-mg scale using the methodology described above (Scheme 2). Using Frenette's protocol,[20] treatment of **18** with 2.4 equiv of DIBAL-H at −78 °C produced the hydroxy acid, which was cyclized with TFA to produce the desired all-*syn* lactone **31** in 82% yield in a 97:3 ratio of diastereomers. Bromination of electron-rich aromatic **31** was accomplished by treatment with NBS in $CHCl_3$ at 23 °C, providing aryl bromide **32** as the exclusive regioisomer.[21]

Suzuki cross-coupling of **32** was performed using [Pd-$(PPh_3)_4$] in refluxing DME/H_2O (10:1) in the presence of $NaHCO_3$.[22] Use of 3,4,5-trimethoxyphenylboronic acid (**33**) provides the coupling product, eupomatilone 4 (**37**), in 90% yield[23]—an overall yield of 55% in four steps from readily available starting materials **4** and **17** (Scheme 3). Similarly, Suzuki coupling of 3,4-dimethoxyphenylboronic acid (**35**) with **32** provides eupomatilone 7 (**36**) as a 1:1 mixture of atropisomers in 85% yield, and an overall yield of 52% in four steps.[24] The lactone core of eupomatilones 4 and 7 contains 3*R*,4*S*,5*R* absolute stereochemistry which was determined through correlation with the previously reported crystallographic analysis of keto acid **11**.[6] This work represents the first asymmetric synthesis of eupomatilone 4 and the first synthesis of any type for eupomatilone 7.

The initially proposed structure of eupomatilone 6 was prepared in an analogous manner (Scheme 4). Coupling of the arylzinc triflate from **16** with *cis*-dimethylsuccinic anhydride **6** proceeds in 85% yield and 87% *ee* to form keto acid **7**. Diastereoselective reduction and cyclization of **7** provides γ-lactone **37** in 91% yield and in a 98:2 diastereomeric ratio. Iodination of **37** was accomplished by treatment with I_2 in the presence of a silver salt, providing aryl iodide **38** in 89% yield. Suzuki coupling of boronic acid **39** under Pd catalysis proceeded in 87% yield, providing **40**, the putative structure



Scheme 4. Synthesis of 3-*epi*-eupomatilone 6. Tol = toluene.

of eupomatilone 6, in four steps from **4** and **16** in 60% overall yield.[25]

As previously described by Gurjar et al.[19] and Coleman et al.,[17c] this structure is in fact 3-*epi*-eupomatilone 6, which contains the 3*R*,4*S*,5*R* backbone sequence. Natural eupomatilone 6, which contains the 3*S*,4*S*,5*R* sequence, can be obtained from this material by subjection of **40** to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in hot toluene and separation of the resulting epimers.[19]

Herein, we have described the enantioselective rhodium-catalyzed cross-coupling of *meso* cyclic carboxylic anhydrides with arylzinc reagents and the total syntheses of three members of the eupomatilone family of lignan natural products. The cross-coupling reaction proceeds with selectivities in excess of 80% *ee* with a variety of nucleophiles formed from corresponding lithium reagents and used without purification. Synthetic routes, which include the definition or construction of three contiguous stereocenters with excellent control, have been developed for eupomatilones 4 and 7, as well as the originally proposed structure of eupomatilone 6. Each species is prepared in a concise four-step sequence with greater than 50% overall yield. The flexible synthetic route provides rapid stereoselective formation of the γ-lactone core and allows ready manipulation of the biaryl functionality.

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[2] For asymmetric cross-coupling reactions, see: T. Hayashi, *J. Organomet. Chem.* **2002**, *653*, 41, and references therein.
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[24] Eupomatilone 7 (**36**, 88% *ee*): $[\alpha]_D = +24.3\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.6\ g\,cm^{-3}$, $CHCl_3$), Lit.: Ref. [15b]; $[\alpha]_D = +35.8\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.5\ g\,cm^{-3}$, $CHCl_3$).
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