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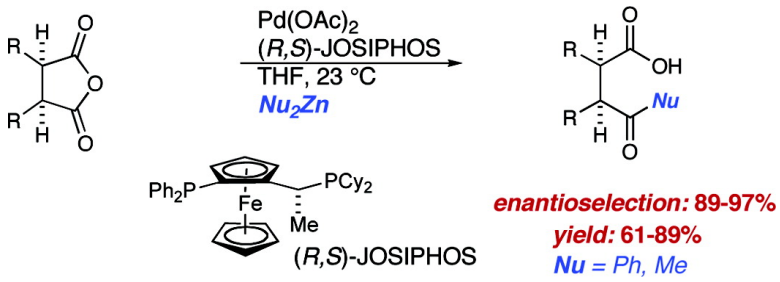

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A Palladium-Catalyzed Enantioselective Alkylative Desymmetrization of *meso*-Succinic Anhydrides

Eric A. Bercot and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

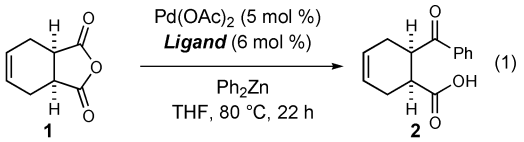
Received June 11, 2004; E-mail: rovis@lamar.colostate.edu

The asymmetric desymmetrization of prochiral meso compounds represents a powerful strategy for the expedient synthesis of two or more contiguous stereogenic centers in one operation.[1] Cyclic anhydrides have been of particular interest, providing fertile ground for the development of a host of both diastereo- and enantioselective desymmetrization methods.[2] Although much of the focus has been centered on the addition of heteroatom-based nucleophiles,[3] surprisingly little attention has been paid to the addition of carbon nucleophiles. Fu and Shintani recently reported the enantioselective addition of aryl Grignard reagents to glutaric anhydrides in the presence of stoichiometric amounts of (−)-sparteine, representing, to our knowledge,[4] the only general method for enantioselective alkylation of cyclic anhydrides.[5] We have previously reported that nickel complexes catalyze the monoalkylation of cyclic anhydrides and showed one example of an enantioselective desymmetrization proceeding in 79% ee.[6] Herein, we report the development of a palladium-catalyzed alkylation of *meso*-succinic anhydrides providing the corresponding keto acids in good yields and enantioselectivity at ambient temperature.

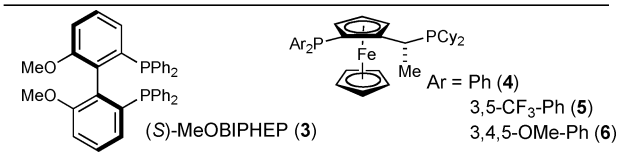
As part of our ongoing interest in transition metal-mediated reactions of anhydrides,[7] we envisioned that palladium catalysis could be applied to the desymmetrization of prochiral cyclic anhydrides. The synthesis of ketones via metal-mediated processes is well-known.[8] However, only recently have anhydrides been used as electrophilic coupling partners under traditional palladium catalysis, with all of these reports describing the alkylation of acyclic anhydrides.[9] The use of meso cyclic anhydrides as electrophilic partners in this chemistry has the additional advantage of allowing backbone stereochemistry to be controlled in the alkylation event, with the caveat that cyclic anhydrides are more electrophilic and competing processes could be problematic. Our initial studies focused on the addition of diphenylzinc to cyclohexenyldicarboxylic anhydride (**1**) in the presence of a palladium catalyst. To our gratification, treatment of anhydride **1** with 1.1 equiv of diphenylzinc in the presence of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) at 80 °C provided the desired phenyl ketone **2** in 57% isolated yield.[10]

Having established the viability of palladium-catalyzed arylzinc addition to cyclic anhydrides, we turned our attention to the ultimate goal of rendering the process enantioselective. Optimization was initially undertaken by exploiting chiral, bidentate aromatic phosphines. Use of (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP] as ligand and $Pd(OAc)_2$ as a palladium source provided the desired keto-acid **2** in good yield and 77% enantiomeric excess (Table 1, entry 1). The enantioselectivity was further increased by use of the electron-rich chiral biphenyl ligand **3** (MeOBIPHEP), providing the product in 63% yield and 80% ee (Table 1, entry 2). The use of JOSIPHOS (**4**) as a ligand provided the desired product in good yield and excellent enantioselectivity (Table 1, entry 3). Further manipulation of the electronic nature of the aromatic phosphine portion of the ligand failed to increase selectivity (Table 1, entries 4 and 5).[11]

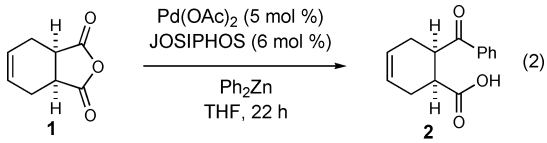
Table 1. Ligand Screen for the Enantioselective Arylation



Entry	*Ligand*	Yield (%)	ee (%)
1	(*S*)-BINAP	67	-77
2	(*S*)-MeOBIPHEP (**3**)	63	-80
3	(*R, S*)-JOSIPHOS (**4**)	67	90
4	(*R, S*)-**5**	70	77
5	(*R, S*)-**6**	71	80



Although the reaction conditions provide a good yield of the desired product in excellent selectivity, we sought to improve selectivity by carrying out the process at lower temperatures. To our surprise, substrate **1** underwent smooth arylation even at room temperature, providing the desired product **2**[12] in improved yield and comparable selectivity (eq 2).[13]



A variety of succinic anhydrides undergo successful arylation under optimized conditions (Table 2). Anhydrides **7** and **9**, both bearing unsaturation in the cyclohexyl backbone, efficiently provide the corresponding desymmetrized products **8** and **10** in 90 and 95% ee, respectively (entries 1 and 2). Cyclohexanedicarboxylic anhydride **11** affords the product keto acid **12** in 89% yield and 94% ee (entry 3). Substrate **13** provides the desired phenyl ketone **14** containing four stereocenters in good yield and excellent selectivity (entry 4). The cyclohexyl backbone is not a required motif, as illustrated by the smooth monoarylation of cyclopentanedicarboxylic anhydride **15**, supplying ketone **16** in good yield and selectivity at slightly elevated temperatures (entry 5). Monocyclic succinic anydrides are also viable substrates for this reaction manifold. Arylation of dimethylsuccinic anhydride **17** affords acyclic keto acid **18** in 72% yield and 92% ee (entry 6). Monocyclic anhydride **19** undergoes addition uneventfully to provide the ester containing

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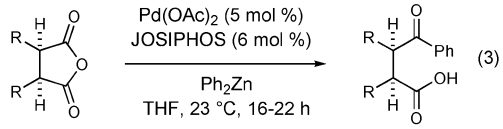
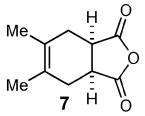
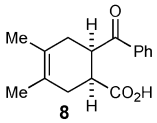
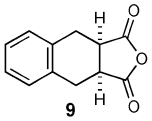
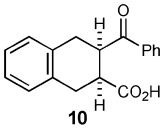
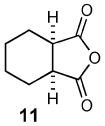
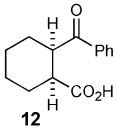
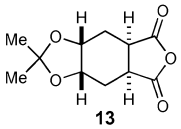
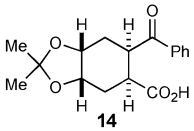
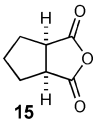
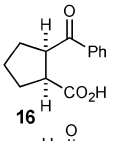
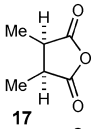
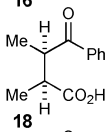
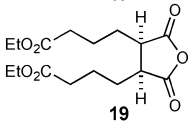
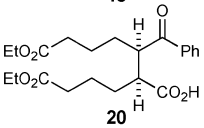
Table 2. Substrate Scope of Catalytic Asymmetric Anhydride Arylation



Entry[a]	Anhydride	Product	Yield (%)	ee (%)
1	 **7**	 **8**	87	90
2	 **9**	 **10**	84	95
3	 **11**	 **12**	89	94
4	 **13**	 **14**	83[b]	97
5	 **15**	 **16**	74[b,c]	89
6	 **17**	 **18**	72[d]	92
7	 **19**	 **20**	61[b,d]	89

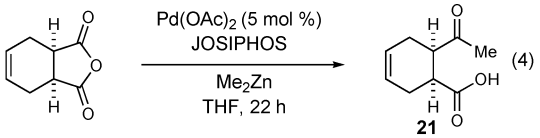
[a] All reactions conducted in the presence of 5 mol % $Pd(OAc)_2$, 6 mol % (*R*,*S*)-JOSIPHOS, and 1.1 equiv of Ph_2Zn at 23 °C for 18 h unless otherwise stated. [b] Isolated as the methyl ester. [c] Reaction conducted at 40 °C. [d] Reaction conducted at 80 °C.

ketone **20** in modest yield and good selectivity, a testament to the mild nature of the reaction conditions (entry 7).

With the realization of an effective asymmetric anhydride arylation method we sought to expand the reaction scope with respect to the nucleophilic coupling partner (Table 3). Exploitation of dimethylzinc as a coupling partner provided the desired methyl ketone **21** in good yield and modest selectivity (entry 1). In an effort to increase the selectivity of methyl addition we examined the effect of varying the ratio of palladium and ligand as well as using an olefinic additive.[14] To our delight, addition of a catalytic amount of 4-fluorostyrene provided the desired product in 80% yield and 91% ee (entry 2). Furthermore, the efficiency of the reaction is highly dependent on the palladium-to-ligand ratio, although the selectivity is virtually unaffected. The reaction fails to provide any product in the presence of more than 1 equiv of ligand to palladium (entry 3), but the use of less than 1 equiv of ligand to palladium provides highly enantioeriched products (entries 4 and 5), an example of ligand-accelerated catalysis.[15]

In conclusion, we have developed a room-temperature catalytic asymmetric anhydride desymmetrization reaction which provides

Table 3. Desymmetrization Using Dimethylzinc



Entry[a]	Pd : Lig	4-F-sty (mol %)	Yield (%)	ee (%)
1	1 : 1.0	--	78	64
2	1 : 1.0	25	80	91
3	1 : 1.2	25	NR	--
4	1 : 0.8	25	60	90
5	1 : 0.5	25	<25	84

[a] All reactions conducted in the presence of 5 mol % $Pd(OAc)_2$, indicated amount of (*R*,*S*)-JOSIPHOS, and 1.2 equiv of Me_2Zn at 23 °C for 22 h.

the product γ-keto acids containing up to four stereocenters in excellent yields and selectivities. Efforts to extend the scope and probe the mechanism of this transformation are currently underway.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A study revealed that THF is superior; Et_2O = 40% ee, CH_2Cl_2 = 38% ee.
(12) The absolute configuration of **2** is as shown and was determined by X-ray analysis of the corresponding iodolactonized ketone; all other compounds are assigned by analogy: see Supporting Information.
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