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A Mild and Efficient Catalytic Alkylative Monofunctionalization of Cyclic Anhydrides

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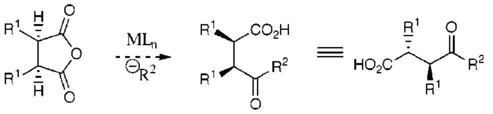
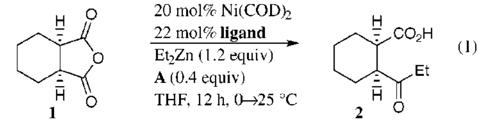
The ability of transition-metal complexes to mediate carbon−carbon bond construction renders them invaluable tools in organic synthesis.[1] When these processes are accompanied by the generation of new stereocenters, chiral complexes may be employed to introduce asymmetry into a molecule. A metal-catalyzed monoalkylation of cyclic *meso* anhydrides fulfills both criteria and would be an excellent complement to the established alcoholic[2] and reductive[3] methods for anhydride desymmetrization.[4] Although metal-catalyzed additions of organometallic reagents to acid derivatives are known, all involve the use of acid halides[5] or thioesters,[6] both of which are unsuitable for the introduction of stereochemistry into this process. The insertion of low-valent late transition metals into anhydride C−O bonds is precedented,[7] and a single report of a stoichiometric activation/alkylation of a cyclic anhydride has appeared.[7c] Herein we report the realization of a nickel-catalyzed anhydride monoalkylation leading to the formation of γ-keto acids[8] in high yield under mild conditions, and the first example of an asymmetric alkylative desymmetrization of *meso* anhydrides.

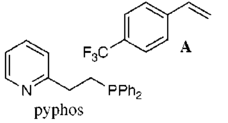


Investigations began with the known insertion of low-valent nickel complexes into cyclic anhydrides.[7] Organozinc reagents were chosen as the initial nucleophiles for two reasons: dialkylzinc reagents transmetalate to Ni alkoxides[9] and a control experiment revealed that the uncatalyzed addition of diethylzinc to cyclohexane dicarboxylic anhydride does not occur (THF, 23 °C, 6 h).[10] Anhydride **1** was subjected to a variety of nickel−ligand complexes at 0 °C in THF. In cases where the reactions were sluggish, they were allowed to warm to ambient temperature. To promote reductive elimination over the potentially competing β-hydride elimination from the presumed acyl ethyl nickel intermediate,[11] the electron-deficient alkene *p*-trifluoromethylstyrene (**A**) was employed, following the precedent of Knochel and co-workers.[12]

This reaction is extremely sensitive to ligand, eq 1. The use of monodentate phosphine ligands leads to poor results. The efficacy of bidentate phosphines seems to vary with bite angle: bis(diphenylphosphino)ethane (dppe) affords good yields whereas bis(diphenylphosphino)butane (dppb) provides a poor catalyst. Optimal ligands proved to be 2,2′-bipyridyl (bipy) and (2-diphenylphosphino)ethylpyridine (pyphos).[13] These ligands promoted this reaction at 0 °C to provide the coupled product in high yield, with most reactions complete in less than 3 h. The two ligands seem to be interchangeable with most substrates. We employed a simple acid−base workup to free the product acids of impurities, typically affording analytically pure material.

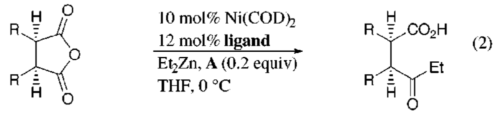


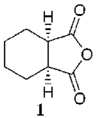
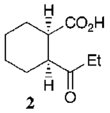
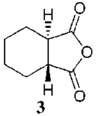
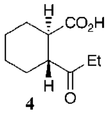
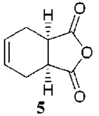
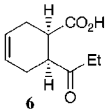
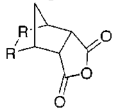
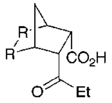
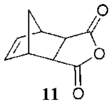
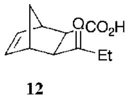
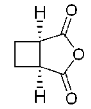
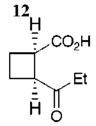
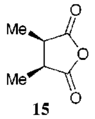
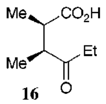
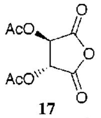
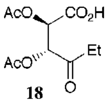
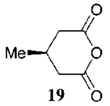
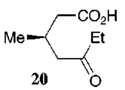
1 **2**



ligand	*yield (%)*
pyphos	80
bipy	92
PPh$_3$(2 equiv)	<5
dppb	20
dppe	78

Table 1. Substrate Scope in the Catalytic Alkylative Monofunctionalization of Cyclic Anhydrides



Entry[a]	Anhydride	Product	**ligand**	Yield (%)
1	 **1**	 **2**	bipy	95[b]
2	 **3**	 **4**	pyphos	86
3	 **5**	 **6**	bipy	95
				
4	**7** R = CH$_2$	**8** R = CH$_2$	pyphos	88
5	**9** R = CH	**10** R = CH	bipy	96
6	 **11**	 **12**	bipy	91
7	 **13**	 **14**	pyphos	61
8	 **15**	 **16**	bipy	93
9	 **17**	 **18**	bipy	88
10	 **19**	 **20**	pyphos	81

[a] All reactions conducted in the presence of 10 mol % Ni(COD)$_2$, 12 mol % ligand, 20 mol % *p*-trifluoromethylstyrene (**A**), and 1.2 equiv of Et$_2$Zn in THF for 3-12 h at 0 °C, unless otherwise stated. [b] Reaction conducted with 5 mol % Ni(COD)$_2$ and 6 mol % bipy.

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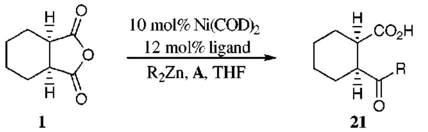
Table 2. Other Alkylzinc Nucleophiles



1 21 (3)

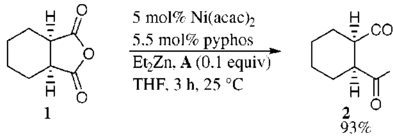
Entry^a	R$_2$Zn	R	ligand	Yield (%)
1	Me$_2$Zn	Me (**21a**)	pyphos	86
2	Ph$_2$Zn	Ph (**21b**)	pyphos	88
3	BuZnBr	Bu (**21c**)	dppe	67
4	BrZnCH$_2$CH$_2$CO$_2$Et	CH$_2$CH$_2$CO$_2$Et (**21d**)	dppe	53

[a] All reactions conducted in the presence of 10 mol % Ni(COD)$_2$, 12 mol % ligand, 1.2−1.5 equiv of R$_2$Zn, and 20 mol % **A** in THF, unless otherwise stated.

A variety of cyclic anhydrides undergo successful monoalkylation, Table 1. Cis Anhydride **1** provided ketoacid **2** in 93% yield under the optimized reaction conditions, entry 1 in Table 1, while the diastereomeric trans anhydride **3** afforded the complementary ketoacid **4** in 86% yield with no loss of stereochemical integrity, entry 2. The reaction of *cis*-cyclohexenedicarboxylic anhydride **5** proceeds well with the product **6** formed in 95% yield, entry 3. Tricyclic anhydride **7** and its two unsaturated analogues (**9** and **11**) lead to the bicyclic keto acids **8**, **10**, and **12** in 88, 96, and 91% yields, respectively. The strained cyclobutane-containing anhydride **13** underwent smooth monoalkylation affording ketoacid **14** in a moderate 61% yield. Monoalkylation of *meso*-dimethyl succinic anhydride **15** provides the ketoacid **16** in 93% yield, entry 8, while tartrate-derived anhydride **17** gave **18** in 88% yield. As is evident from entry 9, this procedure tolerates esters without difficulty. Last, glutaric anhydrides such as **19** are also suitable substrates: the corresponding δ-ketoacid is isolated in 81% yield, entry 10.

This reaction is not limited to ethyl nucleophiles. Treatment of anhydride **1** with Me$_2$Zn using the standard reaction conditions afforded the methyl ketone **21a** in 86% isolated yield, entry 1 in Table 2, whereas the use of Ph$_2$Zn provided the phenyl ketone **21b** in similar yield, entry 2. The latter reaction was significantly slower, requiring 13 h at ambient temperature to proceed to completion compared to only 15 min at 0 °C for Me$_2$Zn. Alkylzinc halides are also acceptable partners for this reaction, although they proceed in somewhat lower yields, entry 3 in Table 2. Functionalized zinc reagents are also compatible with this protocol, with a zinc homoenolate providing **21d** in moderate yield, entry 4.

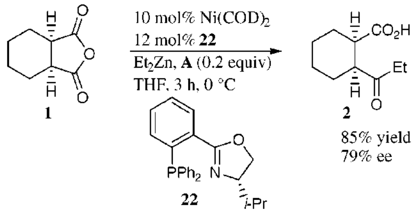
Although Ni(COD)$_2$ is commercially available,[14] its use requires strictly anaerobic conditions. In an effort to render this reaction more practical, air-stable Ni(II) catalyst precursors were investigated. With 5 mol % anhydrous Ni(acac)$_2$ and pyphos, **1** undergoes monoalkylation in identical yield, eq 4. As a further testament to the practicality of this protocol, we have conducted this reaction using 1 mol % Ni(acac)$_2$, 1.2 mol % bipy, and 30 mol % PhCF$_3$[15] on a 33 mmol scale to afford **2** in 96% yield after 48 h at room temperature.



1 2 93% (4)

In addition to the advantages conferred by a metal-catalyzed reaction (chemoselectivity and functional group compatibility), the presence of the transition metal allows the introduction of chiral ligands in an effort to provide absolute control over the bond-forming event. The sensitivity of this reaction to ligand was reflected in our initial survey: common chiral bis(phosphines) provided inactive catalysts (BINAP, DIOP, DuPHOS) or resulted in very low yields (CHIRAPHOS: 10% yield, albeit 88% ee).[16] The use of the phosphino-oxazoline ligand **22**[17] afforded an active catalyst for the desymmetrization of anhydride **1**, providing ketoacid **2** in 85% yield and 79% ee, eq 5.

In summary, we have developed a mild and efficient catalytic monoalkylation of cyclic anhydrides. The reaction is rapid and provides γ- and δ-keto acids in good yield and selectivity. We have also succeeded in effecting this transformation asymmetrically to provide the desymmetrized product in moderate ee. Efforts to improve selectivities and broaden the scope of this transformation are currently underway.



1 2 22 85% yield 79% ee (5)

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

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(15) Benzotrifluoride is a cheap alternative to styrene **A**, albeit somewhat less efficient as evidenced by a longer reaction time.
(16) Standard aqueous workup (acid/base extraction) provided >95% of the diacid when using commercially available chiral bis(phosphines) as ligands, with the desired ketoacid present in trace amounts at best. The single exception to this was the use of CHIRAPHOS which led to the isolation of the product ketoacid in 10% yield, 88% ee.
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