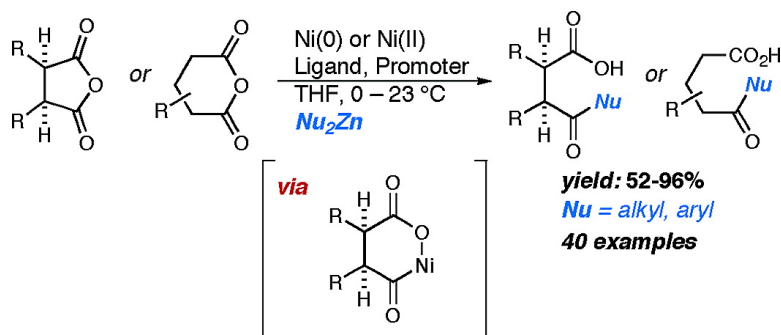


## Highly Efficient Nickel-Catalyzed Cross-Coupling of Succinic and Glutaric Anhydrides with Organozinc Reagents

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## Highly Efficient Nickel-Catalyzed Cross-Coupling of Succinic and Glutaric Anhydrides with Organozinc Reagents

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**Abstract:** A nickel-catalyzed alkylation of succinic and glutaric anhydrides with alkyl- and arylzinc reagents has been developed. A dramatic olefin effect has been investigated resulting in the identification of several styrene-based promoters which show pronounced enhancements in reaction rate. The substrate scope with respect to electrophilic and nucleophilic coupling partners has been examined and found to be remarkably broad, allowing for rapid introduction of molecular complexity through the use of functionalized coupling partners. Regioselective alkylation of an unsymmetrical succinic anhydride and a profound effect of pendent coordinating olefins on reaction rate suggest a mechanism involving discrete oxidative addition of the nickel complex into the cyclic anhydride followed by a transmetalation event.

### Introduction

Transition metal-catalyzed carbon–carbon bond forming reactions have become a lynchpin in modern synthetic organic chemistry.<sup>1</sup> Due to the mild nature of reaction conditions employed, a variety of functional groups are well-tolerated, making transition metal-catalyzed reactions invaluable in the context of complex molecule synthesis. In light of the ever-expanding application of these reaction manifolds, the exploitation of new electrophilic and nucleophilic coupling partners continues to be of interest.<sup>2</sup> New methods for the synthesis of ketones through the exploitation of novel electrophilic coupling partners have been of particular interest,<sup>3</sup> providing the desired products without the use of harsh reaction conditions.<sup>4</sup>

A variety of activated acyl species have seen extensive application in transition metal-catalyzed synthesis of ketones. The palladium catalyzed acylation of organostannanes using acid chlorides,<sup>5</sup> first reported by Migita<sup>6</sup> and later extensively developed by Stille,<sup>7</sup> represented the first example of the utilization of acid halides as electrophilic coupling partners. Following Migita and Stille's pioneering work, a multitude of metal-catalyzed methods have been developed employing activated esters including thioesters<sup>8</sup> and aryl trifluoroacetates.<sup>9</sup>

Anhydrides have only recently garnered attention as competent acylating agents in metal-mediated reaction manifolds.<sup>10</sup> A particularly convenient method for the palladium catalyzed cross-coupling of boronic acids and mixed acyclic anhydrides, generated in situ from the parent carboxylic acids, was reported by Goossen<sup>11</sup> and Yamamoto<sup>12</sup> independently, providing the product ketones in good yields. Although the aforementioned methods represent powerful approaches to the ketone functionality, they inherently lack the ability to incorporate stereochemical information during the carbon–carbon bond forming event.

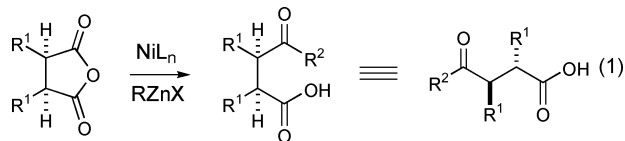
The use of succinic or glutaric anhydride derivatives as electrophilic coupling partners would provide access to  $\gamma$ - and  $\delta$ -keto acid derivatives possessing stereochemically defined backbones. The realization of this approach would represent a very efficient entry into 1,4- and 1,5-dicarbonyl systems, intriguing synthons with a demonstrated importance as intermediates in the synthesis of a variety of heterocyclic systems.<sup>13</sup>

The desymmetrization of cyclic meso anhydrides by the addition of heteroatom nucleophiles has been extensively investigated.<sup>14</sup> In contrast, the addition of carbon based nucleophiles is less developed. Addition of aromatic nucleophiles to

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cyclic anhydrides under Friedel–Crafts acylation conditions provides the product aromatic ketones in moderate to good yields.<sup>15</sup> However, this manifold is inherently limited to aromatic nucleophiles bearing the proper substitution patterns. The corresponding alkylation of meso cyclic anhydrides has received little attention from the synthetic community. Addition of strongly nucleophilic species such as Grignard reagents to meso cyclic anhydrides may lead to mixtures of products including Meerwein–Ponndorf–Verley reduction, over alkylation, and epimerization.<sup>16</sup> Fu and Shintani reported the alkylation of meso-glutaric anhydride derivatives by aryl Grignard reagents in the presence of stoichiometric amounts of (–)-sparteine to provide the corresponding enantioenriched keto acids in good yields and selectivities.<sup>17</sup> The combination of a transition metal-catalyzed carbon–carbon bond forming process with concurrent desymmetrization of a meso compound would represent a powerful method for the synthesis of keto acid derivatives.



We recently reported an alkylation of cyclic anhydrides in the presence of catalytic amounts of a nickel catalyst providing the product keto acids in good yields under mild conditions (eq 1).<sup>18</sup> Herein, we detail a full account of the nickel catalyzed anhydride alkylation including expansion of the substrate scope with respect to both nucleophilic and electrophilic coupling partners, the further refinement of a nickel (II) precatalyst obviating the need for the use of air-sensitive nickel(0) compounds, and the results of mechanistic investigations which shed light on some steps of the catalytic cycle.

**Initial Ligand Screen.** Our initial survey began with the known insertion of low-valent nickel complexes into cyclic anhydrides.<sup>19</sup> We envisioned that in the presence of a suitable nucleophilic coupling partner the initial oxidative addition adduct could be intercepted, providing the desired keto acid under mild conditions. Organozinc reagents were chosen for several reasons: alkyl zinc reagents are known to transmetalate cyclic nickel alkoxide intermediates,<sup>20</sup> alkyl zinc reagents are easily

**Table 1.** Initial Ligand Survey

Entry	Ligand	M : L	Yield (%)
1	PPh <sub>3</sub>	1 : 1	50–60
2	PPh <sub>3</sub>	1 : 2	< 5
3	PCy <sub>3</sub>	1 : 1	< 5
4	PCy <sub>3</sub>	1 : 2	< 5
5	DPPE	1 : 1.2	78
6	DPPB	1 : 1.2	20
7	bpy	1 : 1.2	92
8	pyphos	1 : 1.2	80

prepared and functional group tolerant,<sup>21</sup> and control experiments revealed that diethylzinc does not add to cyclohexanedicarboxylic anhydride (THF, 23 °C, 6 h).<sup>22</sup> Cyclohexanedicarboxylic anhydride **1** was subjected to a catalytic amount of a variety of nickel–ligand complexes in the presence of diethylzinc in THF at 0 °C. For instances in which the reaction was slow as indicated by TLC, it was allowed to warm to ambient temperature. Catalytic amounts of electron-deficient styrene **3** were added to accelerate reductive elimination in lieu of potential β-hydride elimination from the presumed acyl-alkyl nickel intermediate (vide infra), following the precedent of Knochel.<sup>23</sup>

The efficiency of the reaction is highly dependent on the ligand employed (Table 1). Trialkyl- and triarylmonodentate phosphines proved rather ineffective under the prescribed reaction conditions (entries 1–4). Bidentate phosphine complexes are more efficient than adducts derived from monodentate phosphine ligands and also exhibit a dependence on bite angle. Bis(diphenylphosphino)ethane (DPPE) furnishes the desired product in good yield while bis(diphenylphosphino)butane (DPPB) is less effective (entries 5 and 6). The most competent ligands are 2,2'-bipyridyl (bpy) and (2-diphenylphosphino)ethylpyridine (pyphos)<sup>24</sup> each efficiently supplying the desired addition product **2** in less than 3 h at 0 °C (entries 7 and 8). Each of these ligand–metal complexes deliver analytically pure material upon acid–base workup.

**Promoter Effects.** Our working hypothesis regarding the reaction mechanism involved the initial oxidative addition of the low-valent nickel catalyst to the electron-deficient C–O bond of the anhydride followed by a transmetalation event providing an acyl-alkyl nickel intermediate which upon reductive elimination provides the desired alkylation product (vide infra, Scheme 2, Pathway A). Electron-deficient olefins have been

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Table 2. Promoter Survey

Entry <sup>a</sup>	Promoter	Time (min.)	Yield (%)
1	none	1260	76
2		< 5	82
3	R = H (4)	25	68
4	R = F (5)	30	80
5	acrylonitrile	2880	<10
6	Ph-CF <sub>3</sub>	2880	~50

<sup>a</sup> All reactions run in the presence of Ni(COD)<sub>2</sub> (5 mol %), bpy (6 mol %), and Et<sub>2</sub>Zn (1.2 eq.) at 0 °C for indicated time.

shown to facilitate the reductive elimination of dialkyl nickel intermediates.<sup>25</sup> The acceleration of reductive elimination is thought to proceed through initial coordination of the olefin to the metal center resulting in a  $\pi$ -back-bonding interaction leading to weakening of the carbon-metal  $\sigma$ -bonds.<sup>26</sup> Knochel and co-workers have exploited the use of catalytic amounts of electron-deficient olefins in the context of Csp<sup>3</sup>-Csp<sup>3</sup> cross-coupling, resulting in dramatic enhancements of reaction rate and efficiency.<sup>27</sup> We had noted the benefit of these olefinic additives in our reaction manifold and sought to quantify this effect. Therefore, a systematic study of the reductive elimination promoter was undertaken to probe its effect on reaction rate and efficiency.

The nature of the promoter has a dramatic effect on reaction rate and conversion (Table 2).<sup>28</sup> The reaction proceeds smoothly in the absence of promoter at 0 °C to provide a good yield of addition product **2** although the reaction requires 21 h to proceed to completion (entry 1). The addition of 10 mol % (2 equiv to catalyst) of 4-trifluoromethyl styrene (**3**) results in a dramatic rate acceleration, providing the product acid **2** in 80% isolated yield in less than 5 min (entry 2). Variation of the electronic properties of the styrene-based promoter has little effect on the efficiency of the transformation, but a small effect on the reaction rate was observed. Styrene (**4**) provides the product keto acid in 68% yield in 25 min. while the more electron deficient 4-fluorostyrene (**5**) provides **2** in 80% yield in 30 min (entries 4 and 5). The use of trifluorotoluene or acrylonitrile seems to suppress reactivity providing poor yields of **2**

contaminated with byproducts<sup>29</sup> even after extended reaction times (entries 5 and 6).<sup>30</sup>

**Anhydride Substrate Scope.** A variety of succinic anhydride derivatives undergo alkylation (Table 3). Both *cis*- and *trans*-cyclohexanedicarboxylic anhydride provide the desired products **2** and **7** with no loss of stereochemical integrity (entries 1 and 2). Cyclohexenedicarboxylic anhydride derivatives **8**, **10** and **12** undergo smooth alkylation providing keto acids **9**, **11**, and **13** in good yield (entries 3–5). Substituents at the  $\beta$ -position of the anhydride are well tolerated, as typified by anhydride **14**, the Diels–Alder adduct of 2,4-hexadiene and maleic anhydride, which upon alkylation provides acid **15** containing 4 contiguous stereocenters (entry 6). Tricyclic anhydride adducts efficiently participate in this reaction manifold providing ready access to *endo*- and *exo*-bicyclic keto acids (entries 7–12). Anhydride **28**, readily available in one step from cycloheptatriene and maleic anhydride,<sup>31</sup> provides the desymmetrized product **29**, giving access in two steps to a stereochemically defined hexasubstituted cyclohexane core (entry 13). Fused cyclopentane and cyclobutane anhydrides **30** and **32** offer products **31** and **33** in 71 and 61% yield respectively with no evidence of epimerization (entries 14 and 15). Monocyclic succinic anhydrides also take part in the chemistry. Tartaric acid derived anhydrides **34** and **36** afford acyclic keto acids **35** and **37** in good yield with no evidence of elimination of the potentially labile acetates (entries 16 and 17). *meso*-Dimethylsuccinic anhydride **38** as well as the homologated ester-containing derivative **40** each furnish the corresponding 1,4-dicarbonyl compounds **39** and **41** with no evidence of epimerization or ester hydrolysis (entries 18 and 19).

With the catalytic alkylation applied to succinic anhydride derivatives we sought to further expand the scope of the current method to glutaric anhydrides. Although the bpy-derived nickel catalyst was quite effective in the context of succinic anhydride electrophiles, glutaric anhydrides failed to provide product under identical conditions. However, the use of the pyphos-derived nickel catalyst provides for an effective alkylation of glutaric anhydrides (Table 4).<sup>32</sup> Glutaric anhydrides bearing a variety of substitution at the 4-position participate in this transformation. Methyl glutaric anhydride **42** as well phenyl glutaric anhydride **44** each afford good yields of the corresponding ethyl ketones **43** and **45** (entries 1 and 2). Heteroatom substituents at the 4-position are also well tolerated providing  $\beta$ -benzyloxy acid **47** and N-protected  $\beta$ -amino acid derivative **49** in modest yields (entries 3 and 4). The HMGA derived anhydride **50**, bearing a potentially labile  $\beta$ -acetate group, efficiently provides keto acid **51** in 75% yield (entry 5). Substitution at the  $\alpha$ -position of the anhydride does not adversely affect the reaction with anhydride **52** smoothly providing acyclic keto acid **53** containing a skipped 1,3-*syn*-dimethyl relationship in the backbone (entry 6). Bridged bicyclic glutaric anhydrides **54** and **56** afford 1,3-*syn*-cyclopentane **55** and 1,3-*syn*-cyclohexane **57** in 90 and 88% yield

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(28) Reaction times were determined by the disappearance of starting material as observed by TLC. Each reaction was assayed every 5 min for the first 30 min, then every 30 min for an additional 3 h. After 3 h each reaction was assayed every 6 h to an ultimate time of 42 h.

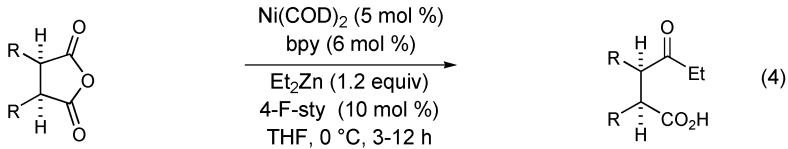
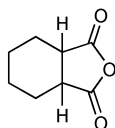
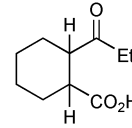
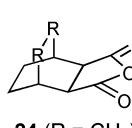
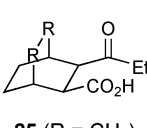
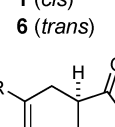
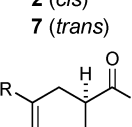
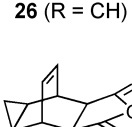
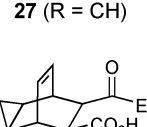
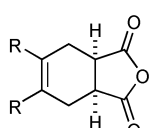
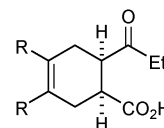
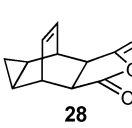
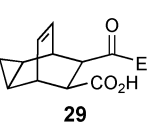
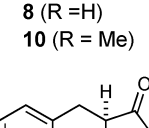
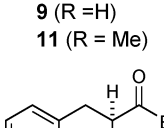
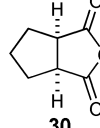
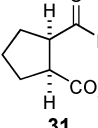
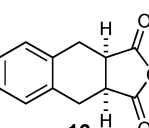
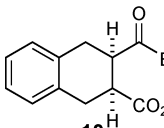
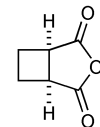
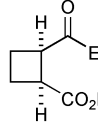
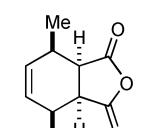
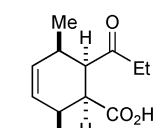
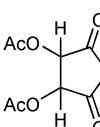
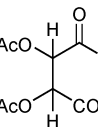
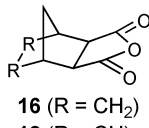
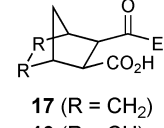
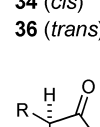
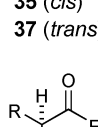
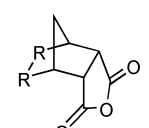
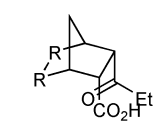
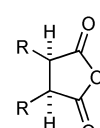
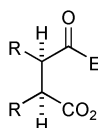
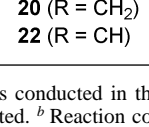
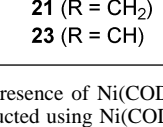
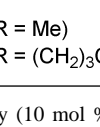
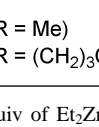
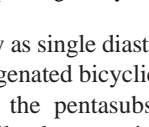
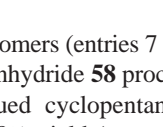
(29) Reactions that are sluggish often result in the formation of ester byproducts presumably arising from the slow oxidation of the alkyl zinc reagent by adventitious oxygen; for a similar example, see: Katritzky, A. R.; Luo, Z. *Heterocycles* **2001**, *55*, 1467–1474.

(30) On the basis of our previous report, trifluorotoluene seems to be an effective promoter if used in higher concentration (30 mol % trifluorotoluene and 1 mol % catalyst).

(31) Schueler, P. E.; Rhodes, Y. E. *J. Org. Chem.* **1974**, *39*, 2063–2069.

(32) Qualitative observations suggest bpy is the generally preferred ligand for succinic anhydrides and pyphos is the preferred ligand for glutaric anhydrides.

Table 3. Succinic Anhydride Substrate Scope

							
Entry <sup>a</sup>	Anhydride	Product	Yield (%)	Entry <sup>a</sup>	Anhydride	Product	Yield (%)
1			95 <sup>b,c</sup>	11			91
2			87	12			84
3			95 <sup>b,c</sup>	13			68 <sup>b,d</sup>
4			90	14			71 <sup>d</sup>
5			90 <sup>d</sup>	15			61 <sup>b,c</sup>
6			61 <sup>d</sup>	16			74
7			79 <sup>b,c,d</sup>	17			88 <sup>b,c</sup>
8			91 <sup>b,c</sup>	18			93 <sup>b,c</sup>
9			88 <sup>b,c</sup>	19			75
10			96 <sup>b,c</sup>				

<sup>a</sup> Reactions conducted in the presence of Ni(COD)<sub>2</sub> (5 mol %), bpy (6 mol %), 4-F-sty (10 mol %), and 1.2 equiv of Et<sub>2</sub>Zn at 0 °C in THF unless otherwise stated. <sup>b</sup> Reaction conducted using Ni(COD)<sub>2</sub> (10 mol %), bpy (12 mol %), and 4-F-sty (20 mol %). <sup>c</sup> 4-CF<sub>3</sub>-sty used as promoter. <sup>d</sup> Isolated as the corresponding methyl ester.

respectively as single diastereomers (entries 7 and 8). Alkylation of polyoxygenated bicyclic anhydride **58** proceeds uneventfully to provide the pentasubstituted cyclopentane **59**, containing several labile elements, in 88% yield (entry 9).

**Nucleophile Scope.** The reaction is not limited to the use of diethyl zinc as the nucleophilic coupling partner (Table 5). Subjection of anhydride **1** to the reaction conditions using Me<sub>2</sub>Zn and Ph<sub>2</sub>Zn provides the corresponding methyl and phenyl ketones in excellent yields (entries 1 and 2). The secondary diorganozinc reagent, diisopropyl zinc, smoothly provides the isopropyl ketone with no signs of *iso*-propyl to *n*-propyl isomerization (entry 3). Alkylzinc halides are also competent

coupling partners. Although the bpy derived catalyst system is less efficient, providing the cross-coupled product in 66% yield using 20 mol % catalyst loading, we found that changing the ligand to the bidentate phosphine DPPE resulted in a more effective catalyst for alkylzinc halide coupling (entries 4 and 5). Functionalized zinc reagents were also found to be compatible with this reaction manifold, allowing for incorporation of reactive functionality in both coupling partners (entry 6). Diaryl and dialkyl zinc reagents<sup>33</sup> formed in situ from the corresponding

(33) Currently, alkenyl and alkynyl zinc reagents are beyond the scope of this transformation.

**Table 4.** Glutaric Anhydride Substrate Scope

Entry <sup>a</sup>	Anhydride	Product	Yield (%)
			(5)
1			81 <sup>c</sup>
2			77
3			52
4			57 <sup>b</sup>
5			75
6			85
7			90 <sup>b</sup>
8			88 <sup>b</sup>
9			88

<sup>a</sup> Reactions conducted in the presence of Ni(COD)<sub>2</sub> (10 mol %), pyphos (12 mol %), and Et<sub>2</sub>Zn (1.2 eq.) at 0 °C in THF unless otherwise stated.

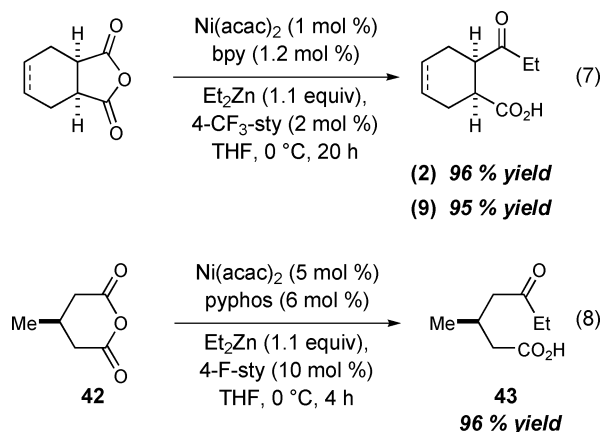
<sup>b</sup> Reaction conducted using Ni(COD)<sub>2</sub> (5 mol %), pyphos (6 mol %), and 4-F-sty (10 mol %).

lithium or Grignard reagents also participate in the reaction demonstrating that byproduct lithium and magnesium salts are benign (entries 7–12). It is noteworthy that the aryllithium reagents (entries 10–12) were generated from the aryl bromide by treatment with *n*-butyllithium, producing butyl bromide as a byproduct which does not seem to affect the outcome of the reaction.<sup>34</sup>

**Application of an Air-Stable Precatalyst.** The nickel (0) pre-catalyst, Ni(COD)<sub>2</sub>, although commercially available, is extremely air-sensitive requiring the use of an inert atmosphere glovebox. In the interest of making the reaction protocol more amenable in a practical sense, we sought the development of an air-stable catalyst precursor thereby obviating the need for glovebox manipulation.<sup>35</sup> Anhydrous nickel (II) acetylacetonate

(34) It should be noted that generation of aryllithium reagents from aryl iodides by treatment with *n*-butyllithium leads to no observed product.

(35) Although all of our observations suggest that Ni(acac)<sub>2</sub> and Ni(COD)<sub>2</sub> are completely interchangeable in this reaction, Ni(COD)<sub>2</sub> was used for consistency in our studies regarding the substrate scope.

**Scheme 1.** Use of an Air Stable Precatalyst

(Ni(acac)<sub>2</sub>) was used as a catalyst precursor affording an active nickel (0) catalyst upon in situ reduction by diethyl zinc. Taking advantage of the most active reductive elimination promoter, 4-trifluoromethyl styrene, catalyst loading was reduced to 1 mol % in the case of cyclohexylsuccinic anhydrides **1** and **8** providing the desired keto acid products **2** and **9** in excellent yield with a longer reaction time (Scheme 1, eq 7). Each reaction was executed on multigram scale (15 mmol) and upon completion, simple acid–base workup provided analytically pure material circumventing the need for chromatographic separation. The nickel (II) pre-catalyst can also be applied to glutaric anhydrides. Methylglutaric anhydride **42** undergoes smooth alkylation in the presence of 5 mol % pyphos derived catalyst providing the desired  $\delta$ -keto acid **43** in excellent yield (Scheme 1, eq 8).

**Mechanistic Considerations.** Two potential mechanistic pathways for this reaction are depicted in Scheme 2. Pathway A involves oxidative addition of the low-valent nickel complex to the electron-deficient C–O bond of the cyclic anhydride to yield the cyclic acyl-nickel carboxylate **I**. Transmetalation of **I** provides acyl–alkyl nickel species **III** which could then undergo reductive elimination to provide the desired product along with regeneration of the active catalyst. Another potential route, depicted as pathway B, involves the initial formation of an alkyl nickel intermediate **II** from direct alkyl group transfer from the zinc reagent to the catalyst.<sup>36</sup> Intermediate **II** can then react with the starting anhydride through addition of the alkyl group to the anhydride directly providing tetrahedral intermediate **IV** which upon collapse would provide product. In our previous work on the decarbonylative cross-coupling of cyclic anhydrides,<sup>37</sup> we observed the corresponding direct addition product in minor amounts in some reactions, suggesting that the alkylation product in the present reaction manifold may arise from a similar mechanistic pathway, namely a discrete oxidative addition of the low-valent nickel catalyst (Pathway A). Furthermore, a wealth of precedent exists for the stoichiometric interaction of electron-rich nickel complexes and cyclic anhy-

(36) Alkyl-transition metal intermediates arising from alkyl or aryl group transfer from a main-group organometallic have been invoked in related reaction manifolds; see: (a) Bogdanovic, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610–4612. (b) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609–612. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.

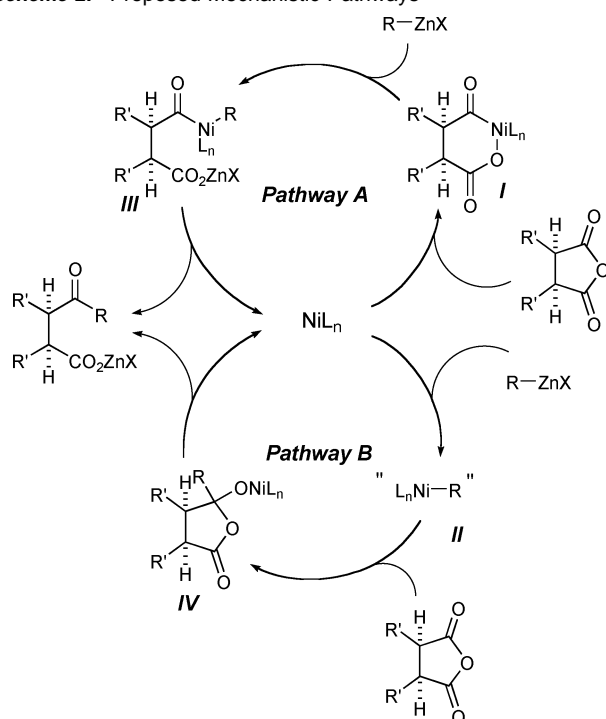
(37) O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498–10499.

Table 5. Nucleophile Scope

Entry <sup>a</sup>	Anhydride	NuZnX	Ligand	Yield (%)	Entry <sup>a</sup>	Anhydride	NuZnX	Ligand	Yield (%)
1		Me <sub>2</sub> Zn	bpy	86 <sup>d</sup>	9		F-C <sub>6</sub> H <sub>4</sub> -MgBr /ZnBr <sub>2</sub> (2 : 1)	bpy	68 <sup>b,e</sup>
2		Ph <sub>2</sub> Zn	bpy	88 <sup>d</sup>	10		Me-C <sub>6</sub> H <sub>4</sub> -Li /ZnBr <sub>2</sub> (2 : 1)	bpy	63 <sup>b,e</sup>
3		<i>i</i> -Pr <sub>2</sub> Zn	bpy	77 <sup>b</sup>	11		MeO-C <sub>6</sub> H <sub>3</sub> (OMe)-Li /ZnCl <sub>2</sub> (2 : 1)	bpy	90 <sup>b</sup>
4		BuZnBr	bpy	66 <sup>c,d,e</sup>	12		MeO-C <sub>6</sub> H <sub>3</sub> (OMe)-Li /ZnCl <sub>2</sub> (2 : 1)	bpy	96 <sup>b</sup>
5		BuZnBr	dppe	67 <sup>d,e</sup>					
6		BrZnCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Et	dppe	53 <sup>d,e</sup>					
7		2-furyl-Li/ZnCl <sub>2</sub> (2 : 1)	bpy	65 <sup>b,e</sup>					
8		<i>n</i> -propyl-MgCl/ZnCl <sub>2</sub> (2 : 1)	bpy	61 <sup>b,e</sup>					

<sup>a</sup> All reactions conducted in the presence of Ni(COD)<sub>2</sub> (10 mol %), indicated ligand (12 mol %), and RZnX (1.2 eq.) at 0 °C in THF unless otherwise stated. <sup>b</sup> Reaction conducted using Ni(COD)<sub>2</sub> (5 mol %), bpy (6 mol %), and 4-F-sty (10 mol %). <sup>c</sup> Reaction conducted using Ni(COD)<sub>2</sub> (20 mol %), bpy (22 mol %), and 4-F-sty (40 mol %). <sup>d</sup> sCF<sub>3</sub>-sty used as promoter. <sup>e</sup> Isolated as the corresponding methyl ester.

## Scheme 2. Proposed Mechanistic Pathways



drives indicating that oxidative addition clearly occurs when the two are admixed.<sup>38</sup> In one instance, this intermediate has

(38) (a) Trost, B. M.; Chen, F. *Tetrahedron Lett.* **1971**, *12*, 2603–2607. (b) Uhlig, V. E.; Fehske, G.; Nestler, B. *Z. Z. Anorg. Allg. Chem.* **1980**, *465*, 141–146. (c) Komiya, S.; Yamamoto, A.; Yamamoto, T. *Chem. Lett.* **1981**, 193–196. (d) Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräunlich, G.; Eibisch, H.; Droscher, P. *Tetrahedron Lett.* **1990**, *31*, 1257–1260.

been characterized by crystallography.<sup>39</sup> Nevertheless, the slight difference in our optimized reaction conditions compounded with the caveat that stoichiometrically generated species are not always intermediates in catalytic cycles spurred us to investigate the mechanism of this reaction in some detail.

We reasoned the use of an unsymmetrical anhydride may provide information regarding the active mechanistic pathway based on the regioisomer obtained. The regioselective alkylation<sup>40</sup> and reduction<sup>41</sup> of unsymmetrical succinic anhydrides is well-known. Reaction principally takes place at the carbonyl group adjacent to the more highly substituted carbon atom. This observation has been attributed to a more favored nucleophilic attack trajectory<sup>42</sup> that proceeds over the least sterically hindered  $\alpha$ -carbon thereby delivering the nucleophile to the carbonyl neighboring the more substituted  $\alpha$ -carbon (Figure 1).<sup>43</sup> In the event, subsection of 2,2-dimethylsuccinic anhydride **60** to the standard reaction conditions provides a > 9:1 regioisomeric mixture of acids **61** and **62** favoring addition at the carbonyl adjacent to the least substituted  $\alpha$ -carbon (Scheme 3). This observation suggests that the anhydride is activated by the oxidative addition of the low-valent nickel catalyst as depicted

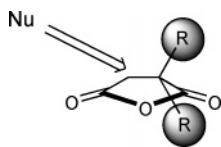
(39) Fischer, R.; Walther, D.; Kempe, R.; Sieler, J.; Schönecker, B. *J. Organomet. Chem.* **1993**, *447*, 131–136.

(40) (a) For the addition of Grignard reagents; see: Canonne, P.; Kassou, M.; Akssira, M. *Tetrahedron Lett.* **1986**, *27*, 2001–2004; Berrier, C.; Bonnaud, B.; Patoiseau, J. F.; Bigg, D. *Tetrahedron* **1991**, *47*, 9629–9640. (b) For the addition of enolates; see: Murray, W. V.; Wachter, M. P. *J. Org. Chem.* **1990**, *55*, 3424–3426. (c) For Friedel–Crafts acylation; see: Hagishita, S.; Kuriyama, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3216–3224.

(41) (a) Bloomfield, J. J.; Lee, S. L. *J. Org. Chem.* **1967**, *32*, 3919–3924. (b) Cross, B. E.; Stewart, J. C. *Tetrahedron Lett.* **1968**, 3589–3590. (c) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574–3576.

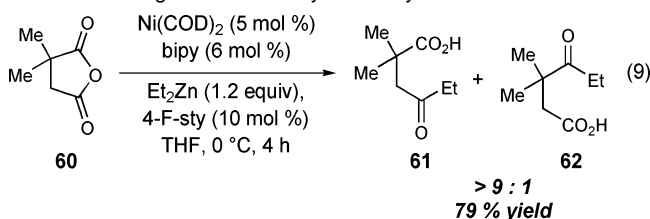
(42) (a) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956–1957. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572.

(43) Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, 695–698.



**Figure 1.** Nucleophilic trajectory.

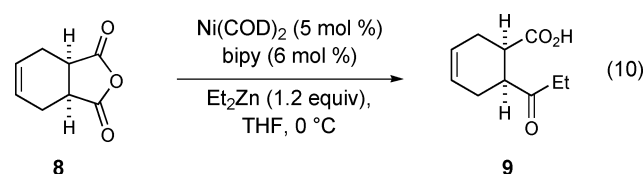
**Scheme 3.** Regioselective Anhydride Alkylation



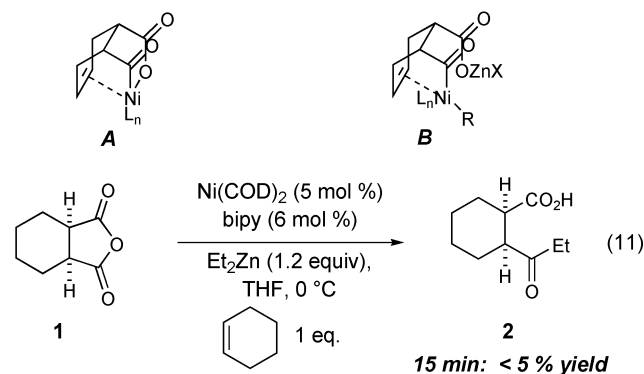
in pathway A. The regiochemical outcome can be rationalized by the steric encumbrance imparted by the geminal dimethyl substituents effectively shielding the adjacent carbonyl thus favoring precoordination and subsequent oxidative addition of the catalyst to the more accessible C–O bond.

During the course of our olefinic promoter studies we noted that subjecting of anhydride **8** to standard reaction conditions using 4-fluorostyrene as the promoter provided the desired product **9** in less than 5 min. To our surprise, when the same reaction was carried out in the absence of styrenic additive, the product keto acid **9** was isolated in excellent yield in 15 min constituting a striking rate enhancement when compared to the corresponding saturated anhydride derivative (Scheme 4, eq 10).

**Scheme 4.** Backbone of Olefin Effects



**No Promoter, 15 min: 80 % yield**  
**4-F-sty (10 mol %), < 5 min: 78 % yield**

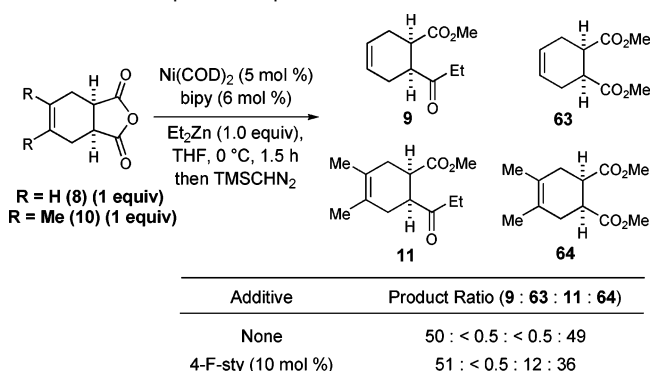


We attributed the observed acceleration of reaction rate to the ability of the olefinic backbone to stabilize the oxidative addition intermediate by an intramolecular coordination event (A) or facilitate the subsequent reductive elimination of the proposed acyl–alkyl nickel intermediate (B).<sup>44</sup> However, we could not rule out the possibility of an intermolecular promotion of the reaction by interaction of the olefinic backbone of the starting

material or product with reaction intermediates. To establish whether the proposed interaction was intra- or intermolecular in nature, cyclohexanedicarboxylic anhydride **1** was subjected to standard reaction conditions in the presence of 1 equiv of cyclohexene (Scheme 4, eq 11). After a 15 min reaction time, less than 5% of the desired alkylation product was observed, suggesting that the rate enhancement is a consequence of an intramolecular coordination event.

With evidence of olefinic backbone acceleration arising from an intramolecular coordination event we still could not rule out the possibility that the cyclohexenyl anhydride was more reactive due to geometric rigidity imparted by unsaturation in the backbone. We reasoned that if the rate difference is a consequence of geometric constraint, then substitution of the olefin should not affect the reaction rate; similarly, if the rate enhancement is a product of an intramolecular coordination event, then differences in olefin structure should have a sizable impact on the course of the reaction. To probe this question, a competition experiment was performed in which a 1:1 mixture of cyclohexenyl anhydride **8** and dimethylcyclohexenyl anhydride **10** was subjected to standard reaction conditions in the presence of 1 equiv of nucleophile (Scheme 5). After 1.5 h, the

**Scheme 5.** Competition Experiment



reaction was quenched and the unpurified reaction mixture was esterified and analyzed by gas chromatography to obtain ratios of all four possible reaction components. In the absence of styrenic promoter, virtually complete consumption of anhydride **8** in preference to anhydride **10** is observed. Even in the presence of 4-fluorostyrene anhydride **8** is preferentially consumed, although keto ester **11** is observed in minor amounts compared to ester **9**. These observations suggest that intramolecular coordination is the contributing factor to the increase in reaction rate when unsaturation is present in the anhydride backbone. The efficiency of coordination is influenced by the nature of the olefin with tetrasubstituted derivatives being far less effective than their disubstituted counterparts.

In light of our mechanistic investigations and based on previously described literature precedent, we propose that the present reaction proceeds through a manifold which involves discrete oxidative addition of the low-valent nickel catalyst followed by alkyl-group transfer and catalyst turnover as illustrated in pathway A (Scheme 2). The intermediacy of an alkyl-nickel intermediate that directly adds to the anhydride coupling partner is unlikely based on our observations involving the cross-coupling of a geminally disubstituted succinic anhydride derivative. Furthermore, the rate acceleration imparted by unsaturation in the anhydride backbone is easiest to rationalize

(44) A similar effect has been observed by Knochel in the context of nickel-catalyzed  $Csp^3$ – $Csp^3$  cross-coupling reactions, see: Refs 23 and 26.



by invoking an intramolecular coordination event, with the presence of the olefin stabilizing intermediates and/or transition states in the catalytic cycle.

**Conclusion.** A nickel-catalyzed alkylation of cyclic anhydrides with alkylzinc reagents has been developed. The reaction proceeds rapidly under mild conditions providing the product keto acids containing up to six contiguous stereocenters in good yields. A dramatic rate enhancement has been observed by the addition of styrenic olefins. The substrate scope has been extended to succinic and glutaric anhydride derivatives bearing a range of functionality as well as a variety of zinc nucleophiles including functionalized zinc reagents. An air-stable nickel precatalyst has also been developed obviating the need for air-sensitive nickel (0) and allowing for the reduction of catalyst loading to 1 mol %. Insight into the possible mechanism has also been gained by the examination of the regioselective

alkylation of unsymmetrical anhydrides as well as examination of the unexpected impact of unsaturation present in the anhydride backbone.

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

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