

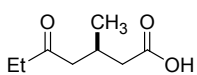
Ligand Dependent Catalytic Cycle and Role of Styrene in Nickel-Catalyzed Anhydride Cross-Coupling: Evidence for Turnover Limiting Reductive Elimination

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Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was purged with argon and passed through two columns of neutral alumina. Anhydrides **4** and **8** and Et₂Zn were obtained from Aldrich Chemical Co. and utilized without further purification. Anhydride **6** was prepared by cyclization of the corresponding commercially available diacid,¹ and anhydride **10** was prepared according to literature procedure.² Carbonyl labeled ¹³C anhydride **5** was prepared according to literature procedure.³ Ni(COD)₂ and Ph₂Zn were purchased from Strem Chemical, Inc. and used without further purification. *i*PrPHOX was prepared according to literature procedure.⁴ Alkylated compounds **5**, **7**, **9**, and **11** have been previously prepared and characterized.¹ ¹H, ¹³C, and ³¹P NMR spectra were obtained on a Varian 300 MHz spectrometer at ambient temperature unless otherwise noted. *In situ* infrared spectra were acquired on a Bruker Tensor 27 IR spectrometer equipped with an Axion Analytical DPR-207 ATM immersion probe. Analytic high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC using Chiracel chiral columns.



3-methyl-5-oxo-heptanoic acid (9). Procedure will be illustrated with a specific example. A dry round bottom flask was charged with Ni(COD)₂ (10.6 mg, 0.039 mmol, 10 mol%) and *i*PrPHOX (16 mg, 0.043 mmol, 11 mol%) in an inert atmosphere glove box. Upon removal from the box, 2 mL of THF was added via

syringe, followed by addition of styrene (10 μ L, 0.083 mmol, 21 mol%) and Et₂Zn (51 μ L, 0.50 mmol, 1.2 equiv). The solution was then cooled to 0 °C in an ice bath and 4-methyl glutaric anhydride **8** (50 mg, 0.39 mmol, 1 equiv) in 1 mL THF was added. Acid-base workup provided an oily solid which was purified by column chromatography (9:1 hexanes:EtOAc), yielding a white crystalline solid. The product was converted to benzyl ester for analysis. HPLC analysis (Chiracel OD-H, 97:3 hex/*i*PrOH, 0.5 mL, 254 nm; tr (minor) 17.8 min, tr (major) 18.6 min gave the isomeric composition of this compound.

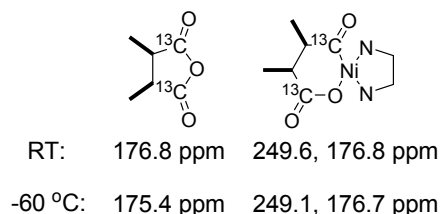
Kinetic Method. The general kinetic method will be illustrated with a specific example. A 2 mL THF solution (“Solution A”) 0.028 M in Ni(COD)₂ (15.3 mg, 0.056 mmol) and 0.032 M in *i*PrPHOX (24.2 mg, 0.064 mmol) was prepared in an argon purged 10 mL round bottom flask. To this solution styrene (10 μ L, 0.087 mmol) and Et₂Zn (100 μ L, 0.975 mmol) were added. A second 2 mL THF solution (“Solution B”) containing 0.297 M 4-methylglutaric anhydride (76mg, 0.593 mmol) was prepared in an argon purged 5 mL round bottom flask.

The dipping probe of the in situ IR was placed into a 50 mL pear shaped flask equipped with two septum covered sidearms. This flask was purged with argon for 15 minutes prior to addition of 0.5 mL of catalyst-containing solution A. A background IR spectrum was acquired, and subsequent spectra were acquired every 5 seconds. The anhydride containing solution was then added, and the concentration of the substrate was monitored by the CO stretching frequency at 1770 and 1812 cm⁻¹ (1791 cm⁻¹ for *cis*-1,2-cyclohexanedicarboxylic anhydride). The reactions were generally followed to at least 50% completion, and the reaction rates were determined from the first ~20% of anhydride consumption.

Examination of Oxidative Addition Reversibility will be illustrated with a specific example. A 2 mL THF solution containing Ni(COD)₂ (50 mg, 0.182 mmol), bipy (32 mg, 0.205 mmol) and styrene (40 μ L, 0.349 mmol) was prepared in a 15 mL argon purged round bottom flask. To this deep purple catalyst solution was added a 1 mL THF solution of *cis*-1,2-cyclohexanedicarboxylic anhydride (34 mg, 0.221 mmol), resulting in a deep red solution. Approximately 10 min later a 1 mL THF solution of 2,3-

dimethylsuccinic anhydride was added. After approximately 2 addition min, a 1 mL THF solution of Et₂Zn (19 μ L, 0.185 mmol) was added. The reaction mixture was stirred for 2 h prior to acid/base workup. Upon workup, the ratio of ketoacids from *cis*-1,2-cyclohexanedicarboxylic anhydride and 2,3-dimethylsuccinic anhydride were determined by ¹H NMR spectroscopy.

Spectroscopic Characterization of Oxidative Addition A 0.5 mL THF-*d*₈ solution of Ni(COD)₂ (3.7 mg, 0.013 mmol), bipy (2.3 mg, 0.015 mmol) and styrene (3 μ L, 0.026 mmol) was added a 0.25 mL solution of carbonyl-¹³C-labeled 2,3-dimethylsuccinic anhydride (¹³C-**6**) (8 mg, 0.068 mmol) in a resealable NMR tube with a Teflon screw cap. ¹³C NMR spectra were obtained at both ambient temperature and at -60 °C. The carbonyl resonances are included below:

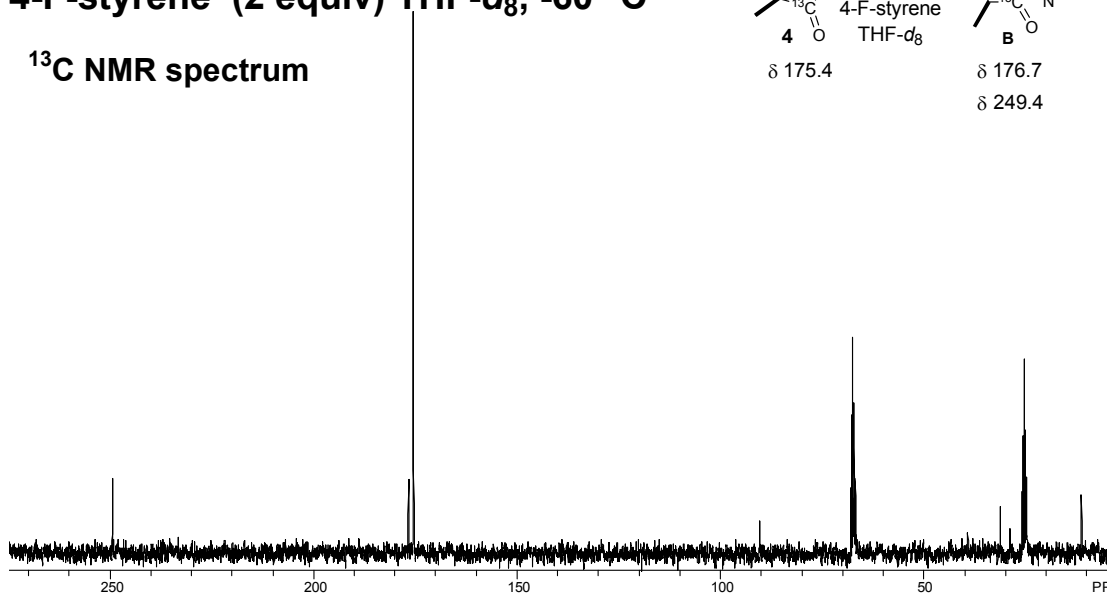
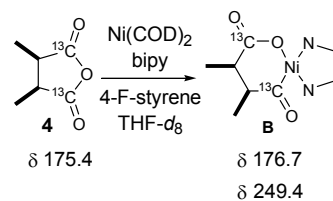


At -78 °C, Et₂Zn (35 μ L, 0.35 mmol) was added to the NMR tube containing the catalyst and anhydride. The tube was quickly inserted into an NMR spectrometer precooled to -60 °C. Resonances corresponding to ¹³C-**6** (δ 175.4) and product ¹³C-**7** (δ 212.4 and 182.0) were observed, in addition to two transient peaks (δ 174.2 and 213.5) which were observed until all starting material was consumed. These peaks are tentatively assigned to intermediate **C**.

The above procedure was repeated with Ni(COD)₂ (3.7 mg, 0.014 mmol) and *i*PrPHOX (5.1 mg, 0.014 mmol) in the presence of styrene (3 μ L, 0.026 mmol). ³¹P NMR spectroscopy on this complex displays a single resonance at δ 32.6, presumably intermediate **E**. Upon addition of 4-methylglutaric anhydride **8** (7 mg, 0.054 mmol), new resonances were observed in the ³¹P NMR spectrum at δ 39.6 (*J* = 21 Hz) and 22.5 (br). These resonances have been tentatively assigned to the diastereomers resulting from oxidative addition to the Ni/*i*PrPHOX complex.

Ni/bipy w/ ^{13}C labeled **4** (5 equiv)
 4-F-styrene (2 equiv) THF- d_8 , -60 °C

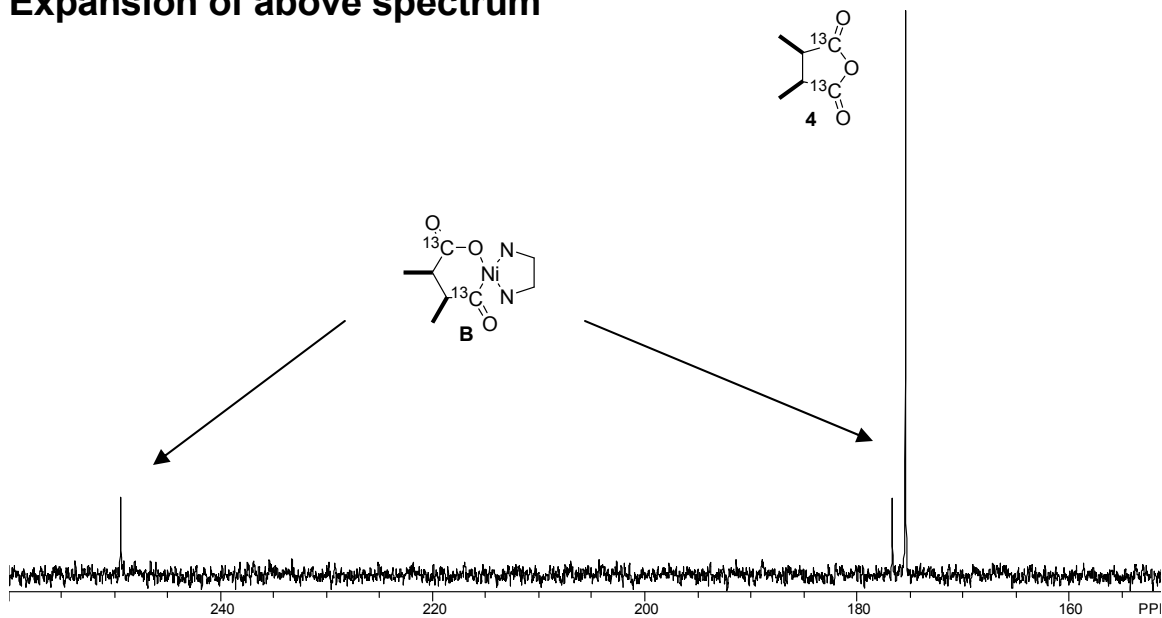
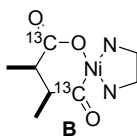
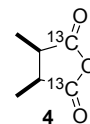
^{13}C NMR spectrum



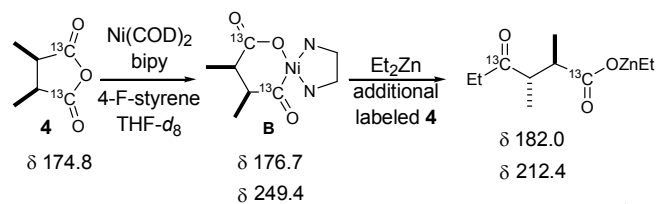
249.411

176.669
175.418

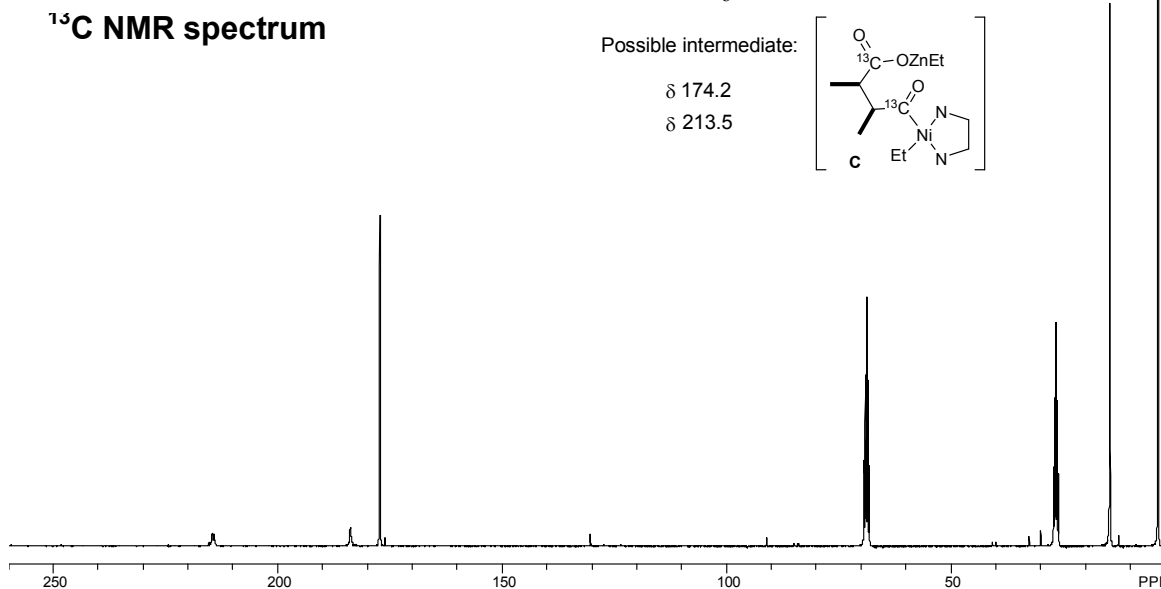
Expansion of above spectrum



Ni/bipy w/ ^{13}C -4 (5 eq)
after add'n of 25 eq Et_2Zn
 THF-d_8 , -60°C

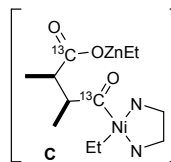


^{13}C NMR spectrum

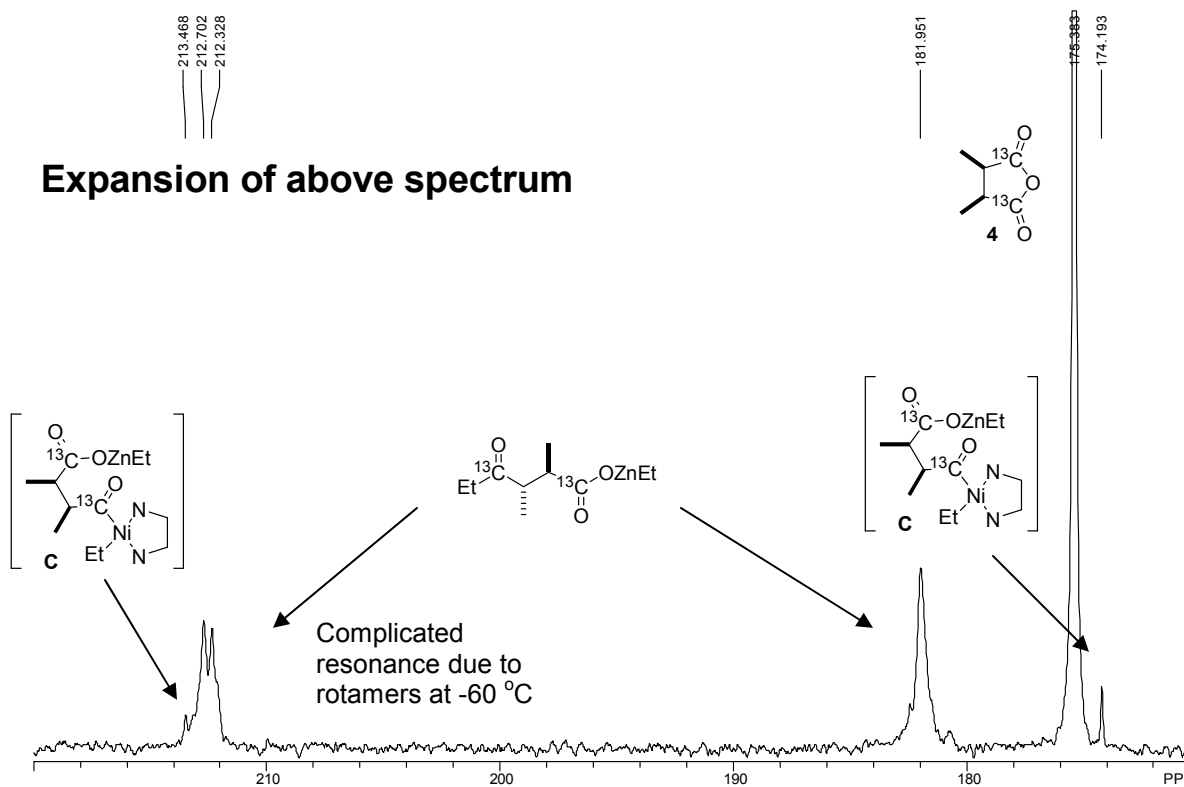


Possible intermediate:

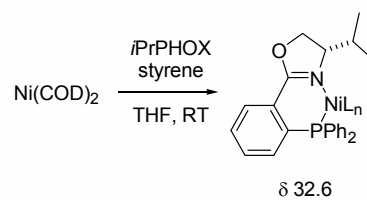
δ 174.2
 δ 213.5



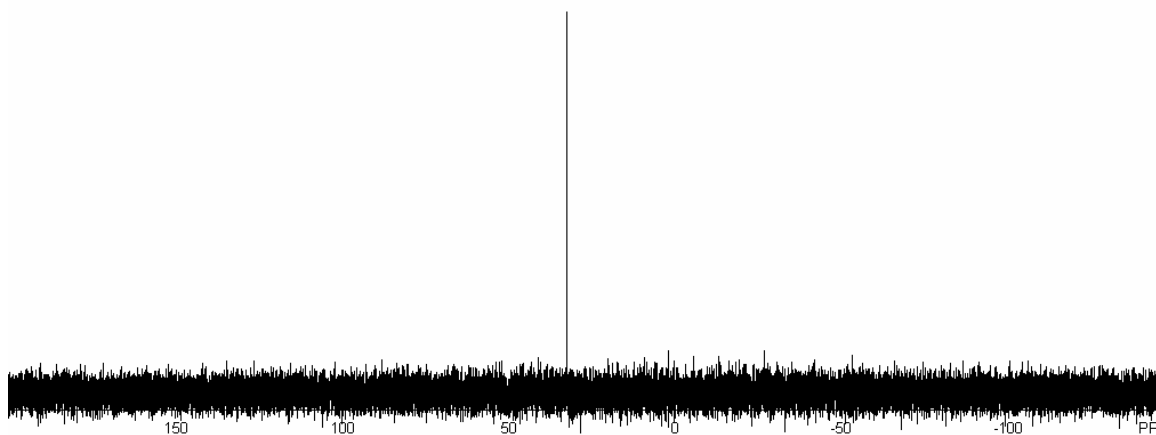
Expansion of above spectrum



Ni(COD)₂/*i*PrPHOX
Styrene (2 equiv) THF-*d*₈, RT

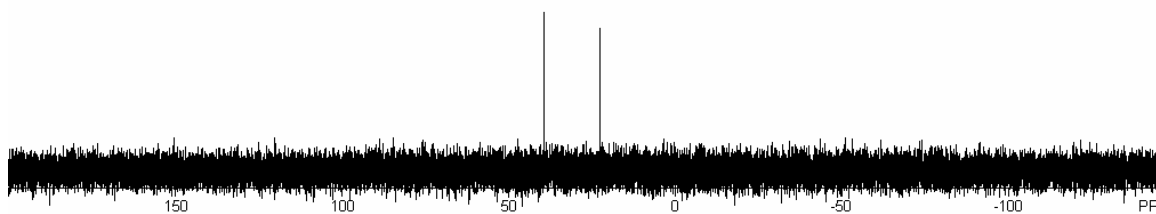
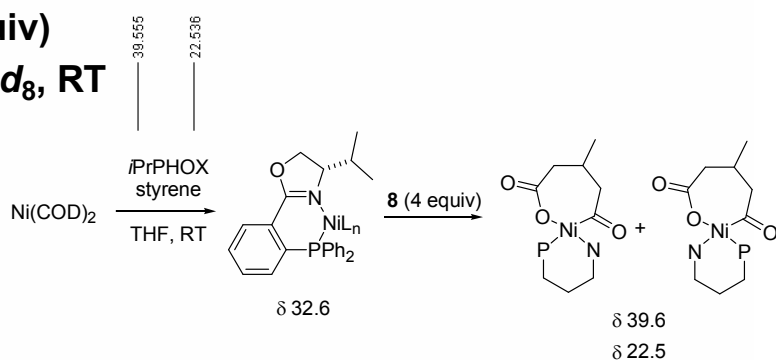


³¹P NMR Spectrum



Ni/*i*PrPHOX w/ **8 (4 equiv)**
Styrene (2 equiv) THF-*d*₈, RT

³¹P NMR Spectrum



Kinetic Data for Desymmetrization of *cis*-1,2-cyclohexanedicarboxylic anhydride (4**) with Ni(COD)₂, bipy and 4-F-styrene.**

Table S1. Initial rate versus Ni(COD)₂-bipy concentration, with [**4**] = 0.10 M, [Et₂Zn] = 0.15 M, [4-F-styrene] = 0.016 M, 23 ± 0.5 °C

Ni(COD) ₂ /bipy (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)	Ni(COD) ₂ /bipy (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)
0.00259	5.1	0.00635	10.9
0.00259	5.3	0.00745	12.2
0.00259	5.0	0.00745	11.8
0.00423	7.4	0.00745	13.3
0.00423	6.9	0.0104	17.5
0.00635	9.9	0.0104	16.6
0.00635	10.6	0.0104	16.5
0.00635	10.0		

Table S2. Initial rate versus *cis*-1,2-cyclohexanedicarboxylic anhydride (**4**) concentration, with [Et₂Zn] = 0.15 M, [4-F-styrene] = 0.016 M, [Ni(COD)₂] = 7.7 mM, [bipy] = 8.2 mM, 23 ± 0.5 °C.

Anhydride (4) (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)	Anhydride (4) (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)
0.098	11.3	0.15	10.9
0.098	12.6	0.15	12.2
0.098	10.6	0.15	12.8
0.10	11.8	0.054	12.2
0.10	11.2	0.054	11.2
0.10	10.8	0.054	11.5
0.19	12.3	0.20	11.1
0.19	12.1	0.20	12.1
0.19	11.6	0.20	10.5

Table S3. Initial rate versus Et₂Zn concentration, with [4] = 0.10 M, [Ni(COD)₂] = 7.7 mM, [bipy] = 8.2 mM, [4-F-styrene] = 0.016 M, 23 ± 0.5 °C

Et ₂ Zn (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)	Et ₂ Zn (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)
0.146	10.6	0.0976	9.9
0.146	10.8	0.0976	9.7
0.146	10.4	0.0976	10.0
0.146	11.5	0.0732	8.7
0.146	11.7	0.0732	8.3
0.146	11.9	0.0732	9.2
0.293	12.3	0.195	12.6
0.293	12.5	0.195	12.2
0.293	11.9	0.195	11.5
0.195	11.1	0.244	10.5
0.195	10.8	0.244	11.1
0.195	11.4	0.244	10.0
0.183	11.4	0.122	11.3
0.183	11.2	0.122	11.5
0.183	10.6	0.122	11.4
0.222	11.3	0.0732	9.3
0.222	11.0	0.0732	8.7
0.222	11.6	0.0732	9.2
0.256	12.5	0.0366	5.5
0.256	12.1	0.0366	5.8
0.256	11.7	0.0366	5.1
0.305	12.2	0.122	10.5
0.305	12.9	0.122	10.2
0.305	12.7	0.122	10.8
0.488	13.2	0.0523	7.3
0.488	13.2	0.0523	7.6
0.488	13.3	0.0523	7.7
0.0976	10.0		
0.0976	10.4		
0.0976	9.8		

Table S4. Initial rate versus 4-F-styrene concentration, with [4] = 0.10 M, [Et₂Zn] = 0.15 M, [Ni(COD)₂] = 7.7 mM, [bipy] = 8.2 mM, 23 ± 0.5 °C.

4-F-styrene (M)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)	4-F-styrene (M)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)
0.016	12.6	0.008	11.9
0.016	11.3	0.008	12.4
0.016	12.0	0.008	11.4
0.016	11.8	0.003	11.6
0.016	11.6	0.003	11.7
0.016	12.6	0.003	11.8
0.005	12.3	0	13.0
0.005	14.3	0	12.8
0.005	13.1	0	13.7
0.005	12.2	0.003	11.9
0.005	12.5	0.003	11.5
0.005	12.9	0.003	12.4
0.011	12.0	0	12.6
0.011	12.1	0	12.0
0.011	12.5	0	11.7

Table S5. Initial rate versus Ph₂Zn concentration, with [4] = 0.10 M, [Ni(COD)₂] = 7.7 mM, [bipy] = 8.2 mM, [4-F-styrene] = 0.016 M, 23 ± 0.5 °C.

Ph ₂ Zn (M)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)	Ph ₂ Zn (M)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)
0.15	6.7	0.09	4.2
0.15	6.0	0.09	4.8
0.15	6.9	0.09	5.2
0.21	10.2	0.11	18.3
0.21	9.1	0.11	17.6
0.21	10.8	0.11	19.2
0.27	14.2		
0.27	12.8		
0.27	12.1		

Table S6. Initial rates at variable temperatures, with [4] = 0.10 M, [Et₂Zn] = 0.15 M, [Ni(COD)₂] = 7.7 mM, [bipy] = 8.0 mM, [4-F-styrene] = 15.7 mM.

Temperature (°C)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)	Temperature (°C)	Initial Rate ($\times 10^{-5}$ M s ⁻¹)
23	11.6	35	22.0
23	11.4	35	19.9
23	10.8	35	20.9
0	0.86	31	16.7
0	0.83	31	13.3
0	0.91	31	14.8
41	38.3	15	4.0
41	34.3	15	3.8
39	29.6	15	3.9
39	28.8		

Kinetic Data for Desymmetrization of 4-methylglutaric anhydride (8**) with Ni(COD)₂, *i*PrPHOX and styrene.**

Table S7. Initial rate versus Ni(COD)₂-*i*PrPHOX concentration, with [**8**] = 0.11 M, [Et₂Zn] = 0.16 M, [styrene] = 0.032 M, 0 ± 0.5 °C

Ni(COD) ₂ / <i>i</i> PrPHOX (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)	Ni(COD) ₂ / <i>i</i> PrPHOX (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)
0.0095	8.12	0.012	9.70
0.0093	6.93	0.012	8.60
0.0093	7.36	0.012	9.30
0.0093	7.23	0.0050	4.37
0.0181	12.7	0.0050	4.16
0.0181	13.8	0.0042	3.77
0.0057	4.62	0.0075	6.22
0.0057	5.29	0.0075	6.12
0.0057	4.53	0.0075	5.86
0.0098	6.81		
0.0098	6.61		
0.0098	7.35		

Table S8. Initial rate versus Et₂Zn concentration, with [**8**] = 0.11 M, [Ni(COD)₂] = 6.5 mM, [*i*PrPHOX] = 7.2 mM, [styrene] = 0.032 M, 0 ± 0.5 °C

Et ₂ Zn (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)	Et ₂ Zn (M)	Initial Rate (× 10 ⁻⁵ M s ⁻¹)
0.08	6.14	0.325	6.89
0.08	6.81	0.325	6.49
0.08	6.56	0.325	6.78
0.244	5.96	0.162	6.41
0.244	5.97	0.162	6.72
0.244	6.48	0.162	6.31

Table S9. Initial rate versus anhydride **8** concentration, with $[\text{Ni}(\text{COD})_2] = 6.5 \text{ mM}$, $[\text{iPrPHOX}] = 7.2 \text{ mM}$, $[\text{Et}_2\text{Zn}] = 0.16 \text{ M}$, $[\text{styrene}] = 0.032 \text{ M}$, $0 \pm 0.5 \text{ }^\circ\text{C}$

Anhydride (8) (M)	Initial Rate ($\times 10^{-5} \text{ M s}^{-1}$)	Anhydride (8) (M)	Initial Rate ($\times 10^{-5} \text{ M s}^{-1}$)
0.10	5.27	0.07	3.56
0.10	6.03	0.07	3.66
0.10	5.17	0.07	4.20
0.18	9.53	0.14	7.02
0.18	9.30	0.14	6.58
0.18	8.43	0.14	

Table S10. Initial rate versus styrene concentration, with $[\textbf{8}] = 0.11 \text{ M}$, $[\text{Et}_2\text{Zn}] = 0.16 \text{ M}$, $[\text{Ni}(\text{COD})_2] = 6.5 \text{ mM}$, $[\text{iPrPHOX}] = 7.2 \text{ mM}$, $0 \pm 0.5 \text{ }^\circ\text{C}$.

Styrene (M)	Initial Rate ($\times 10^{-5} \text{ M s}^{-1}$)	Styrene (M)	Initial Rate ($\times 10^{-5} \text{ M s}^{-1}$)
0.11	7.22	0.02	6.52
0.11	7.59	0.02	6.50
0.11	7.20	0.02	6.60
0	2.16	0.05	6.87
0	2.60	0.05	7.00
0	2.40	0.05	7.13
0.01	5.14		
0.01	5.12		
0.01	4.96		

References

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‡ Cornell University

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