Selective Substituent Transfer from Mixed Zinc Reagents in Ni-Catalyzed Anhydride Alkylation

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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 **3**, **4** and **5**, Et₂Zn, *i*Pr₂Zn, and [(1-ethoxycyclopropyl)oxy]trimethylsilane were obtained from Aldrich Chemical Co. and utilized without further purification. Anhydride **6** was prepared by cyclization of the corresponding commercially available diacid.¹ Ni(COD)₂, diphenylphosphinoethane (dppe), bipyridine (bipy), and Ph₂Zn were purchased from Strem Chemical, Inc. and used without further purification. *i*PrPHOX and pyphos were prepared according to literature procedure.^{2,3} Zn(CH₂CH₂CO₂Et)₂ and Zn(CH₂TMS)₂ were also prepared according to literature procedure.^{4,5} All products generated in this study have been previously described,^{1,6} with the exception of 6-(4-Methoxybenzoyl)-cyclohex-3-enecarboxylic acid (see below). ¹H and ¹³C NMR spectra were obtained on a Varian 300 MHz spectrometer at ambient temperature unless otherwise noted. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1100 series HPLC using Chiracel chiral columns.

Preparation of diorganozinc nucleophile *in situ* will be illustrated with a specific example. A solution of 3,4,5-trimethoxy-1-bromobenzene (632 mg, 2.56 mmol in 2.4 mL THF) was cooled to -78 °C. To this solution was added a solution of *n*BuLi in hexanes (1.56 M solution, 1.64 mL, 2.56 mmol). After this mixture was stirred for 30 minutes, a solution of ZnCl₂ (174.5 mg, 1.28 mmol in 1.5 mL THF) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 90 minutes prior to further use. This procedure provides 5.5 mL of a 0.23 M solution of the diarylzinc reagent.

General procedure for alkylation using mixed zinc reagents will be illustrated with a specific example. In a 10 mL round bottom flask, 1 mL of a solution of diphenyl zinc (prepared according to above procedure, 0.23 M in THF) was combined with an equimolar amount of Et₂Zn (24 μ L, 0.23 mmol). After stirring for 30 minutes, this solution was added to a 1 mL catalyst solution [Ni(COD)₂ (3.0 mg, 0.011 mmol), bipy (2.1 mg, 0.013 mmol) and styrene (3 μ L, 0.026 mmol)] in THF in a second 10 mL round bottom flask. After cooling to 0 °C, a solution of 2,3-dimethylsuccinic anhydride (29.5 mg, 0.32 mmol in 0.5 mL of THF) was added.

6-(4-Methoxybenzoyl)-cyclohex-3-enecarboxylic acid According to the general procedure, the diorganozinc reagent was prepared from 4-bromoanisole (68 μ L, 0.54 mmol), *n*BuLi, (340 μ L of 1.6 M solution, 0.54 mmol) and ZnCl₂ (37 mg, 0.27 mmol). To this solution was added Et₂Zn (28 μ L, 0.27 mmol). This combined solution was added to a catalyst solution of Ni(COD)₂ (5.5 mg, 0.02 mmol), bipy (3.6 mg, 0.023 mmol) and styrene (4.5 μ L, 0.039 mmol). The solution was cooled to 0 °C and *cis*-1,2,3,6-tetrahydrophtahlic anhydride **3** (60 mg, 0.39 mmol) was added and stirred for 16 h. ¹H NMR (300 MHz, CDCl₃) δ 2.35-2.59 (m, 3H), 2.75-2.88 (m, 1H), 2.94-3.07 (ddd, *J* = 6.3, 3.9, 3.3, 1H), 3.86 (s, 3H), 3.94 (ddd, *J* = 6.0, 3.6, 3.3, 1H), 5.57-5.70 (m, 1H), 5.71-5.80, 6.93 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 200.6, 179.1, 163.5, 130.9, 129.0, 126.0, 124.1, 114.0, 55.8, 41.6, 39.9, 27.5, 26.5. HRMS [C₁₅H₁₇O₄]⁺ calc 261.1136. Found 261.1127.

6-(4-Methoxybenzoyl)-cyclohex-3-enecarboxylic acid

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- ¹ Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247.
- ² Allen, J. V. ; Dawson, G. J. ; Frost, C. G.; Williams, J. M. J. *Tetrahedron*, **1994**, *50*, 799.
- ³ Toto, S. D.; Doi, J. T. *J. Org. Chem.* **1987**, *32*, 4999.
- ⁴ Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964.
- ⁵ Westerhausen, M.; Rademacher, B.; Poll, W. *J. Organomet. Chem.* **1991**, *427*, 175.
- ⁶ Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174.