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Facially Selective Cu-Catalyzed Carbozincation of Cyclopropenes Using Arylzinc Reagents Formed by Sequential I/Mg/Zn Exchange

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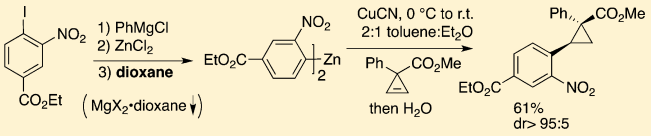
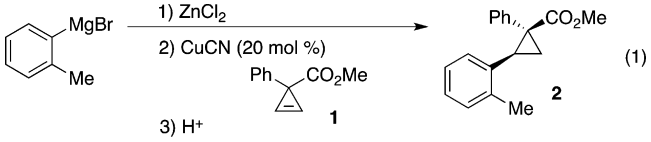
Supporting Information

ABSTRACT: Described is a Cu-catalyzed directed carbozincation of cyclopropenes with organozinc reagents prepared by I/Mg/Zn exchange. This protocol broadens the scope with respect to functional group tolerance and enables use of aryl iodide precursors, rather than purified diorganozinc precursors. Critical to diastereoselectivity of the carbozincation step is the removal of magnesium halide salts after transmetalation with $ZnCl_2$.



The directed carbometalation of cyclopropenes is a powerful method for the construction of functionalized cyclopropanes.[1−3] In recent years, a number of facially selective methods[2,3] for carbomagnesation of cyclopropenes have been described.[4,5] While carbomagnesation reactions are effective with a diverse range of nucleophiles, these protocols are not currently compatible with cyclopropene carboxylic esters which can be directly prepared by transition metal catalyzed reactions of alkynes with α-diazoesters.[4e] Organozinc reagents tolerate a much broader range of functional groups, including esters, nitriles, and nitro groups.[6] In pioneering work, Negishi[7] and Nakamura[1f,8] established that allylzinc reagents combine with cyclopropenes. Nakamura has described the enantioselective Fe-catalyzed addition of diorganozinc reagents to cyclopropenone ketals,[9] and Richey has described addition reactions of Et_2Zn to spiro[2.5]oct-1-enes.[10] More recently, Lautens has described an enantioselective Pd-catalyzed carbozincation of cyclopropenes.[11]

Recently, we described a facially selective method for carbozincation of cyclopropenes.[12] The stereoselectivity of this reaction can be directed by ester or acyloxazolidinone substituents. As only a limited number of diorganozinc reagents are commercially available, we also investigated the *in situ* formation of organozinc reagents from Grignard reagents.[12] For example, *o*-tolylMgBr was combined with $ZnCl_2$, and the resulting solution of $(o\text{-tolyl})_2Zn$ was combined with methyl 3-phenylcyclopropene carboxylate to give **2** after aqueous quenching (eq 1). While this protocol broadened the scope



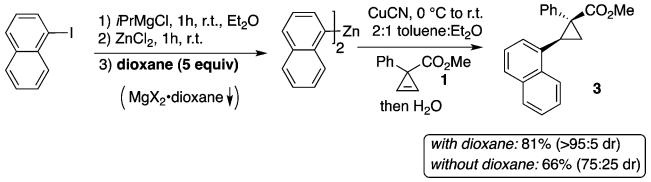
(1)

of nucleophilic zinc reagents that could combine with cyclopropenes, our protocol was still limited by the use of preformed Grignard reagents, which excluded functional group substitution on the nucleophile.

Knochel and co-workers have elegantly demonstrated that functionalized organomagnesium reagents can be made by I/Mg exchange.[13] The procedure involves combining reactive Grignard reagents with aryl iodides that bear functional groups including esters, halides, nitro, nitrile, alkoxy, and acetoxy groups.[13] Berman and Johnson showed that such functionalized Grignard reagents can be treated with $ZnCl_2$ to give rise to functionalized diorganozinc reagents.[14] Described herein is a method for the Cu-catalyzed directed carbozincation of cyclopropenes with functionalized organozinc reagents prepared by I/Mg/Zn exchange.

Initial studies were carried out with 1-iodonaphthalene and *i*-PrMgCl in diethyl ether at room temperature; I/Mg exchange took place to form 1-naphthylmagnesium chloride. Without isolation, this Grignard reagent was treated with $ZnCl_2$ at room temperature to provide $(1\text{-naphthyl})_2Zn$. After the transmetalation with zinc, it was found beneficial both in terms of yield and diastereoselectivity to include toluene as a cosolvent. Only complex mixtures were obtained when THF was the sole solvent. A better result was obtained when cyclopropene derivative **1**[2f] was treated with $(1\text{-naphthyl})_2Zn$ in the presence of CuCN in 1:2 diethyl ether/toluene; the desired product **3** was obtained in 66% yield but only 75:25 diastereoselectivity (Scheme 1). It was considered that the poor diastereoselectivity may be attributable to the presence of Mg-salts formed during

Scheme 1. Effect of Removing Mg-Salts on Diastereoselectivity



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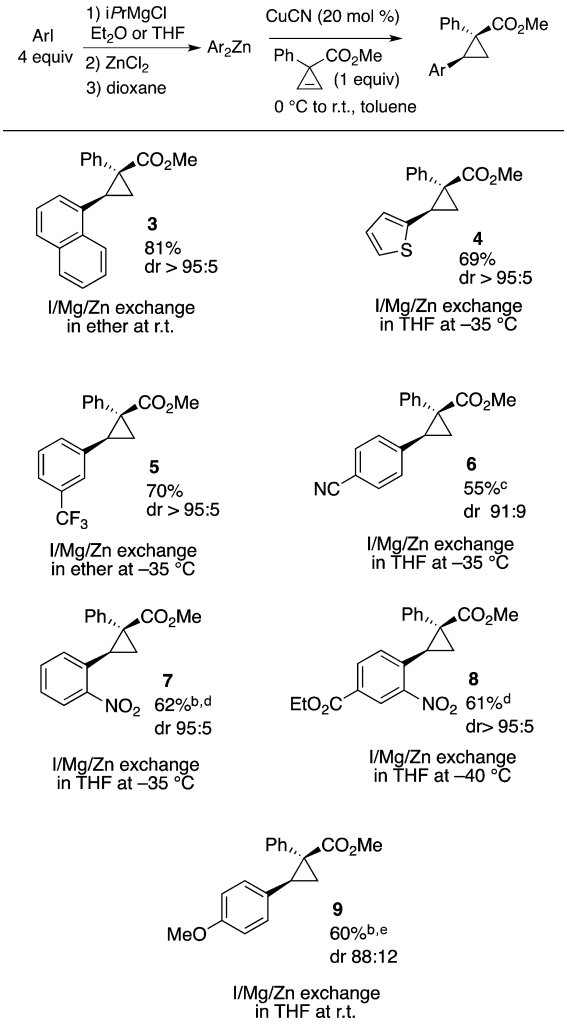
the dinaphthylzinc preparation. Magnesium salt byproducts have been reported to affect the efficiency and selectivity of reactions such as catalytic enantioselective additions of organozinc reagents to imines.[15] We speculated that the Mg-salts reduce selectivity in the present reaction by coordinating to the ester and impeding the ability of the ester to direct carbozincation. Consistent with this hypothesis, it was found that the diastereoselectivity increased to >95:5 when a slight excess of 1,4-dioxane was added to the dinaphthyl zinc reagent and the insoluble dioxane•MgX_2 complex was removed by centrifugation (Scheme 1).

The optimized conditions from Scheme 1 were applied to a range of aryliodides in reactions with methyl 1-phenylcycloprop-2-ene carboxylate. As shown in Table 1, phenyl,

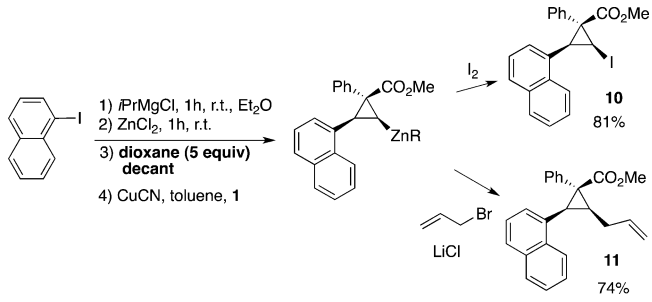
Table 1. Sequential I/Mg/Zn Exchange and Cyclopropene Carbozincation[a]



[a]All yields are the average of two runs. [b]Diastereomers were inseparable. [c]Yield of the major diastereomer. [d]PhMgBr was used instead of *i*-PrMgCl. [e]*i*-PrMgBr was used instead of *i*-PrMgCl.

naphthyl, and 2-thienyl iodides with a range of functionality (nitrile, ester, nitro, alkoxy, CF_3) participated in the I/Mg/Zn exchange with subsequent carbozincation. Upon aqueous quenching, good yields (55−81%) and high diastereoselectivities (84:16 to >95:5) were obtained in the preparations of compounds **3**−**9**. The carbometalation product of the di-1-naphthylzinc addition was combined with iodide and allyl bromide to provide substituted cyclopropane derivatives **10** and **11** in 81% and 74% yield respectively (Scheme 2).

Scheme 2



The stereochemistry of compounds **3**−**11** were assigned by analogy to *rel*-(1*R*, 2*R*)-methyl 1,2-diphenylcyclopropane carboxylate, which is formed upon addition of Ph_2Zn with **1**.[12] As expected, the methyl esters of **3**−**11** resonated at high field (3.14 to 3.44 ppm) in the ^1H NMR spectrum due to shielding by the *syn* aryl group. For compound **6**, two separable diastereomers are formed. For the minor diastereomer of **6**, in which the aryl and methyl ester are *anti*, the methyl group resonates at 3.66 ppm, considerably downfield relative to the methyl ester for the major isomer of **6** (3.31 ppm).

In conclusion, functionalized diarylmagnesium halide reagents were prepared from the corresponding iodoarenes following the Knochel protocol. These functionalized Grignard reagents were converted to the corresponding diarylzinc reagents by treatment with $ZnCl_2$ and subsequently combined with methyl 1-phenylcycloprop-1-ene carboxylate to provide products of carbozincation. The removal of magnesium halide salts by complexation with dioxane was critical for realizing high diastereoselectivity in the carbozincation step. Carbozincation adducts were quenched by water, iodine, or allyl bromide to provide highly functionalized cyclopropanes.

■ EXPERIMENTAL SECTION

General Considerations. High grade $ZnCl_2$ (anhydrous, beads, −10 mesh, 99.999% or 99.99%) was used. LiCl was flame-dried under vacuum and cooled under nitrogen. Ethyl 4-iodo-3-nitrobenzoate,[16] *i*-PrMgBr,[17] and **1**[2f] were prepared using the reported literature procedure.[16] For ^{13}C NMR, multiplicities were distinguished using an APT pulse sequence, typical methylene and quaternary carbons appear 'up' (u), and methine and methyl carbons appear 'down' (dn). HRMS was performed using a triple-sector mass spectrometer. The yields in Table 1 are reported as the average of two or more runs.

General Procedure for Addition of Diaryl Reagents to 1. Diarylzinc reagents were prepared by I/Mg/Zn exchange, as described for each individual preparation. After the point at which dioxane (or dioxane/toluene) had been used to precipitate the Mg salts, the mixture was centrifuged to separate the magnesium salts from the reagent. The clear supernatant solution was carefully transferred via a syringe to a 10 mL round-bottomed flask equipped with a stir bar and CuCN (3.6 mg, 0.040 mmol). Care was taken not to take up the precipitate into the syringe. The flask was cooled by an ice bath, and a solution of **1**[2f] (35 mg, 0.20 mmol) in toluene (1 mL) was added dropwise via syringe. After 5 min, the ice bath was removed, and the resulting mixture was allowed to stir for 3−19 h while warming to rt. The mixture was again cooled by an ice bath, and the reaction was quenched by the addition of aq HCl (0.1 M). The mixture was extracted with CH_2Cl_2 (25 mL × 3), and the combined organics were

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dried ($MgSO_4$), filtered, concentrated, and purified by chromatography.

***rel*-(1*R*, 2*R*)-Methyl 2-(Naphthalen-1-yl)-1-phenylcyclopropane Carboxylate (3).** A dry glass tube (16 mm × 150 mm disposable culture tube, Borosilicate glass) was fitted with a septum cap (Screw Thread, Black Phenolic, with open top, Kimble Glass Inc., Art. No. 73804-15425 and National Scientific, B7995-13) and a stir bar. It was evacuated through a needle and refilled with N_2 three times. 1-Iodonaphthalene (0.118 mL, 0.804 mmol) was added via syringe followed by diethyl ether (0.5 mL). To this solution was added isopropylmagnesium chloride (0.41 mL of 1.97 M solution in THF, 0.80 mmol) via syringe at rt. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 1 h, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in diethyl ether (0.5 mL) was added via syringe and the mixture was allowed to stir for 1 h. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. Stirring was continued for 1 h. Toluene (1 mL) was added, and the mixture was allowed to stir for 2 min. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 3 h of stirring after addition of **1**. Analysis of the crude product by ^{1}H NMR showed >95% diastereomeric purity. Flash chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 48 mg (0.16 mmol, 79%) of the title compound as an oil. The purity by ^{1}H NMR was measured to be >95%. An identical experiment gave 50 mg (0.17 mmol, 82%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.40 (app d, J = 8.8 Hz, 1H), 7.89 (app d, J = 8.8 Hz, 1H), 7.80 (app d, J = 7.6 Hz, 1H), 7.71−7.68 (m, 2H), 7.60−7.56 (m, 1H), 7.53−7.45 (m, 5H), 7.40−7.36 (m, 1H), 3.33 (app t, J = 8.2 Hz, 1H), 3.14 (s, 3H), 2.54 (dd, J = 7.6, 4.8 Hz, 1H), 1.82 (dd, J = 9.2, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.4 (u), 140.2 (u), 133.7 (u), 133.3 (u), 133.1 (u), 129.7 (dn), 128.8 (dn), 128.7 (dn), 127.8 (dn), 127.8 (dn), 127.5 (dn), 126.9 (dn), 126.1 (dn), 126.1 (dn), 125.7 (dn), 125.4 (dn), 124.3 (dn), 52.0 (dn), 37.6 (u), 31.0 (dn), 19.8 (u); IR (CH_2Cl_2, cm^{-1}): 3030, 2953, 2872, 1723, 1599, 1498, 1436, 1317, 1237, 1199, 1175, 1113, 912; HRMS (CI) m/z calcd for $C_{21}H_{18}O_2$ 302.1307, found 302.1313.

***rel*-(1*R*, 2*R*)-Methyl 1-Phenyl-2-(thiophen-2-yl)cyclopropane Carboxylate (4).** A dry glass tube was fitted with a septum cap and a stir bar. It was evacuated through a needle and refilled with N_2 three times. 1-Iodothiophene (0.082 mL, 0.80 mmol) was added via syringe followed by THF (0.5 mL), and the mixture was cooled to −35 °C. To this solution was added isopropylmagnesium chloride (0.40 mL of 2.0 M solution in THF, 0.80 mmol) via syringe. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 1 h at −35 °C, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in THF (0.5 mL) was added via syringe. Stirring was continued for 45 min at −35 °C. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. The mixture was then warmed to rt and allowed to stir for 2 h. Toluene (1 mL) was added, and the mixture was allowed to stir for 2 min. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 16 h of stirring after addition of **1**. Flash chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 36 mg (0.14 mmol, 69%) of the title compound as an oil. The purity by ^{1}H NMR was measured to be 94%. An identical experiment gave 36 mg (0.14 mmol, 69%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.50−7.48 (m, 2H), 7.40−7.30 (m, 3H), 7.20−7.18 (m, 1H), 6.97−6.96 (m, 2H), 3.43 (s, 3H), 2.89 (dd, J = 9.2, 7.2 Hz, 1H), 2.35 (dd, J = 7.2, 5.2 Hz, 1H), 1.73 (dd, J = 8.8, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 170.7 (u), 140.5 (u), 139.7 (u), 130.3 (dn), 128.6 (dn), 127.7 (dn), 126.9 (dn), 126.4 (dn), 124.6 (dn), 52.4 (dn), 39.1 (u), 27.5 (dn), 20.4 (u); IR (CH_2Cl_2, cm^{-1}): 3030, 2955, 2873, 1723, 1496, 1437, 1383, 1311, 1237, 1202, 1173, 1111, 1079, 1041, 1026; HRMS (CI) m/z [M^+] calcd for $C_{15}H_{14}O_2S$ 258.0715, found 258.0717.

***rel*-(1*R*,2*R*)-Methyl 1-Phenyl-2-(3-(trifluoromethyl)phenyl)-cyclopropane Carboxylate (5).** A dry glass tube was fitted with a septum cap and a stir bar. It was evacuated through a needle and refilled with N_2 three times. 3-Iodobenzotrifluoride (0.116 mL, 0.804 mmol) was added via syringe followed by diethyl ether (0.5 mL), and the mixture was cooled to −35 °C. To this solution was added isopropylmagnesium chloride (0.408 mL of 1.97 M solution in THF, 0.804 mmol) via syringe. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 1 h at −35 °C, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in diethyl ether (0.5 mL) was added via syringe. Stirring was continued for 1 h at −35 °C. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. The mixture was then warmed to rt and allowed to stir for 1 h. Toluene (1 mL) was added, and the mixture was allowed to stir for 2 min. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 16 h of stirring after addition of **1**. In the GC analysis of the crude product, two peaks were detected in a ratio of >99:1. Flash chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 44 mg (0.14 mmol, 68%) of the title compound as an oil. The purity by ^{1}H NMR was measured to be >95%. An identical experiment gave 46 mg (0.14 mmol, 71%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.61 (s, 1H), 7.56−7.50 (m, 4H), 7.46−7.37 (m, 3H), 7.35−7.30 (m, 1H), 3.33 (s, 3H), 2.89 (t, J = 8.0 Hz, 1H), 2.36 (dd, J = 7.6, 5.2 Hz, 1H), 1.69 (dd, J = 8.8, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 170.9 (u), 139.9 (u), 138.0 (u), 132.7 (dn), 130.7 (q, J_{CF} = 32 Hz), 130.3 (dn), 128.7 (dn), 128.6 (dn), 127.8 (dn), 126.1−126.0 (q, dn), 124.4 (q, J_{CF} = 273 Hz), 123.9−123.8 (q, dn), 52.2 (dn), 38.5 (u), 32.8 (dn), 18.7 (u); IR ($CDCl_3$, cm^{-1}): 3031, 2954, 1722, 1495, 1437, 1330, 1272, 1213, 1168, 1130, 1076, 807; HRMS (CI) m/z [M^+] calcd for $C_{18}H_{15}F_3O_2$ 320.1024, found 320.1015.

***rel*-(1*R*, 2*R*)-Methyl 2-(4-cyanophenyl)-1-phenylcyclopropane Carboxylate (6).** A dry glass tube was fitted with a septum cap and a stir bar. It was evacuated through a needle and refilled with N_2 three times. 4-Iodobenzonitrile (184 mg, 0.804 mmol) was added via syringe followed by THF (0.5 mL), and the mixture was cooled to −35 °C. To this solution was added isopropylmagnesium chloride (0.40 mL of 2.0 M solution in THF, 0.80 mmol) via syringe. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 1.5 h at −35 °C, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in THF (0.5 mL) was added via syringe. Stirring was continued at −35 °C for 1 h. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. The mixture was then warmed to rt and allowed to stir for 2 h. Toluene (1 mL) was added, and the mixture was allowed to stir for 2 min. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 16 h of stirring after addition of **1**. In the GC analysis of the crude product, two peaks were detected in a ratio of >91:9. Gravity chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 30 mg (0.11 mmol, 54%) of the major diastereomer as a white solid, mp 120−123 °C, and 5 mg (0.02 mmol, 9%) of the minor diastereomer as a viscous oil. The purity by ^{1}H NMR was measured to be >95%. An identical experiment gave 31 mg (0.11 mmol, 56%) of the major diastereomer.

Spectral Properties of Major Diastereomer (6). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.60−7.57 (m, 2H), 7.46−7.43 (m, 4H), 7.38−7.27 (m, 3H), 3.31 (s, 3H), 2.84 (app t, J = 8.4 Hz, 1H), 2.33 (dd, J = 7.6, 5.2 Hz, 1H), 1.69 (dd, J = 9.2, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 170.7 (u), 142.5 (u), 139.6 (u), 132.0 (dn), 130.2 (dn), 130.0 (dn), 128.6 (dn), 127.8 (dn), 119.1 (u), 110.8 (u), 52.4 (dn), 39.0 (u), 33.2 (dn), 18.9 (u); IR ($CDCl_3$, cm^{-1}): 3030, 2954, 2929, 2872, 2230, 1724, 1609, 1497, 1448, 1382, 1318, 1214, 1165, 1115, 1078, 1064, 1027, 910, 845; HRMS (CI) m/z [M^+] calcd for $C_{18}H_{15}NO_2$ 277.1103, found 277.1104.

Spectral Properties of Minor Diastereomer (6a). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.34−7.32 (m, 2H), 7.18−7.13 (m, 3H), 7.00−6.98 (m, 2H), 6.84−6.82 (m, 2H), 3.67 (s, 3H), 3.14 (dd, J = 9.3, 7.4 Hz, 1H), 2.21 (dd, J = 9.2, 5.2 Hz, 1H), 1.91 (dd, J = 7.2, 5.2 Hz, 1H). Impurity peaks at 1.55, 1.26, and 0.90−0.84 were also observed. ^{13}C

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NMR ($CDCl_3$, 100 MHz, δ): 173.9 (u), 142.7 (u), 134.0 (u), 131.9 (dn), 131.6 (dn), 128.8 (dn), 128.2 (dn), 127.7 (dn), 119.0 (u), 110.2 (u), 53.1 (dn), 38.5 (u), 32.8 (dn), 21.1 (u). An impurity peak was observed at 29.9 ppm.

***rel*-(1*R*,2*R*)-Methyl 2-(2-nitrophenyl)-1-phenylcyclopropane Carboxylate (7).** A dry glass tube was fitted with a septum cap and a stir bar. It was evacuated through a needle and refilled with N_2 three times. 1-Iodo-2-nitrobenzene (200 mg, 0.804 mmol) was added via syringe followed by THF (0.5 mL), and the mixture was cooled to −35 °C. To this solution was added phenylmagnesium bromide (0.81 mL of 1.0 M solution in THF, 0.80 mmol) via syringe. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 25 min at −35 °C, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in diethyl ether (0.5 mL) was added via syringe. Stirring was continued at −35 °C for 30 min. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. The mixture was then warmed to rt and allowed to stir for 1.5 h. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 3 h of stirring after addition of **1**. In the GC analysis of the crude product, two peaks were detected in a ratio of 95:5. Gravity chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 35 mg (0.12 mmol, 59%) of the title compound as an oil. The purity by ^{1}H NMR was measured to be 93% (a mixture of two diastereomers in the ratio of 93:7). An identical experiment gave 38 mg (0.13 mmol, 64%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.86 (dd, J = 8.0, 1.2 Hz, 1H), 7.60−7.52 (m, 4H), 7.44−7.36 (m, 3H), 7.33−7.29 (m, 1H), 3.36 (s, 3H), 3.31 (app t, J = 8.0 Hz, 1H), 2.24 (dd, J = 7.6, 5.2 Hz, 1H), 1.73 (dd, J = 8.8, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.4 (u), 151.1 (u), 139.0 (u), 132.7 (dn), 132.5 (dn), 132.2 (u), 130.3 (dn), 128.6 (dn), 128.2 (dn), 127.7 (dn), 124.3 (dn), 52.6 (dn), 38.1 (u), 30.2 (dn), 20.0 (u); IR ($CDCl_3$, cm^{-1}): 3064, 3031, 2953, 2854, 1722, 1606, 1527, 1498, 1437, 1356, 1310, 1275, 1210, 1170, 1145, 783, 700; HRMS (CI) m/z [M + H] calcd for $C_{17}H_{16}NO_4$ 298.1079, found 298.1089. Peaks attributed to the minor diastereomer were observed in the ^{1}H NMR spectrum: at 7.23−7.19 (m), 7.11−7.06 (m), 6.76−6.72 (m), 3.53 (t, J = 7.4 Hz), 2.18−2.11 (m), and in the ^{13}C NMR spectrum: 131.1 (dn), 129.1 (dn), 128.8 (dn), 128.0 (dn), 52.4 (dn), 30.3 (dn), 18.8 (u).

***rel*-(1*R*,2*R*)-Ethyl 4-(2-(methoxycarbonyl)-2-phenylcyclopropyl)-3-nitrobenzoate (8).** A dry glass tube was fitted with a septum cap and a stir bar. It was evacuated through a needle and refilled with N_2 three times. The tube was then charged with ethyl 4-iodo-3-nitrobenzoate[16] (258 mg, 0.804 mmol) in THF (0.5 mL), and the mixture was cooled to −40 °C. To this solution was added phenyl magnesium chloride (0.40 mL of 2.0 M solution in THF, 0.80 mmol) via syringe. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. After 25 min at −40 °C, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in THF (0.5 mL) was added via syringe. Stirring was continued at −40 °C for 30 min. 1,4-Dioxane (89 mg, 0.090 mL, 1.0 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. The mixture was then warmed to rt and allowed to stir for 2 h. Toluene (1 mL) was added, and the mixture was allowed to stir for 2 min. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 19 h of stirring after addition of **1**. Analysis of the crude product by ^{1}H NMR showed >95% diastereomeric purity. Gravity chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 45 mg (0.12 mmol, 61%) of the title compound as a light yellow solid, mp 118−120 °C. The purity by ^{1}H NMR was measured to be >95%. An identical experiment gave 45 mg (0.12 mmol, 61%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.50 (d, J = 2.0 Hz, 1H), 8.22 (dd, J = 8.0, 1.6 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.54−7.51 (m, 2H), 7.40−7.35 (m, 2H), 7.33−7.29 (m, 1H), 4.42 (q, J = 6.8 Hz, 2H), 3.37 (s, 3H), 3.29 (app t, J = 8.0 Hz, 1H), 2.26 (dd, J = 7.6, 5.2 Hz, 1H), 1.78 (dd, J = 8.8, 5.2 Hz, 1H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.2 (u), 164.5 (u), 151.1 (u), 138.6 (u), 136.8 (u), 133.1 (dn), 132.7 (dn), 130.8 (u), 130.2 (dn), 128.6 (dn), 127.9 (dn), 125.2 (dn), 62.0 (u), 52.7 (dn), 38.4 (u), 30.2 (dn), 20.3 (u), 14.5 (dn); IR ($CDCl_3$, cm^{-1}): 2986, 2955, 1722, 1535, 1358, 1307, 1288, 1258, 914, 739, 651; HRMS (CI) m/z [M$^+$] calcd for $C_{20}H_{19}NO_6$ 369.1212, found 369.1205.

***rel*-(1*R*,2*R*)-Methyl 2-(4-Methoxyphenyl)-1-phenylcyclopropane Carboxylate (9).** A dry glass tube, fitted with a septum cap and a stir bar, was charged with 4-iodoanisole (188 mg, 0.804 mmol). It was evacuated through a needle and refilled with N_2. This process was repeated three times. Toluene (1 mL) was added via syringe. To this solution was added isopropyl magnesium bromide (0.86 mL of 0.94 M solution in THF, 0.80 mmol) via syringe at rt. Care was taken to ensure that the Grignard reagent did not touch the side of the tube during the addition. The mixture was allowed to stir vigorously for 1 h. After 1 h, a solution of $ZnCl_2$ (55 mg, 0.40 mmol) in THF (0.5 mL) was added via syringe and the mixture was allowed to stir for 1 h. 1,4-Dioxane (177 mg, 0.172 mL, 2.01 mmol) was added dropwise via syringe. Care was taken to ensure that the dioxane did not touch the side of the tube during the addition. Stirring was continued for 2 h. The general procedure for addition of diarylzinc reagents to **1** was then followed, with 3 h of stirring after addition of **1**. Analysis of the crude product by GC showed a ratio of 88:12 for two diastereomers. Gravity chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 35 mg (0.12 mmol, 61%) of the title compound as an oil. The dr by ^{1}H NMR was measured to be 92:8. The purity by ^{1}H NMR was >95%. An identical experiment gave 34 mg (0.11 mmol, 60%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 7.51 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.29 (m, 3H), 6.87 (d, J = 8.4 Hz, 2H), 3.81 (s, 3H), 3.34 (s, 3H), 2.83 (app t, J = 8.4 Hz, 1H), 2.31 (dd, J = 7.6, 5.2 Hz, 1H), 1.60 (dd, J = 9.2, 5.2 Hz, 1H); Peaks in the ^{1}H NMR attributable to the minor diastereomer were observed at 7.15, 7.03, 6.70, 6.61, 3.70 (s), 3.67 (s), 3.07, 2.13, 1.85−1.78 ppm; ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.3 (u), 158.6 (u), 140.6 (u), 130.4 (dn), 130.2 (dn), 128.7 (u), 128.5 (dn), 127.5 (dn), 113.7 (dn), 55.4 (dn), 52.2 (dn), 38.2 (u), 32.8 (dn), 18.6 (u); Peaks in the ^{13}C NMR attributable to the minor diastereomer were observed at 132.2, 129.2, 128.5, 127.9, 127.1, 113.4, 55.3, 52.7, 20.7 ppm; IR (CH_2Cl_2, cm^{-1}): 3005, 2954, 2839, 1720, 1612, 1515, 1497, 1438, 1306, 1247, 1214, 1197, 1179, 1164, 1119, 1063, 1036, 836; HRMS-CI (NH_3) m/z: [M + Na] calcd for $C_{18}H_{18}O_3Na$ 305.1154; found 305.1139.

***rel*-(1*R*,2*S*,3*S*)-Methyl 2-Iodo-3-(naphthalen-1-yl)-1-phenylcyclopropane Carboxylate (10).** The carbozincation procedure was identical to that used to prepare **3**, except that I_2 was used instead of aq. HCl to quench the cyclopropylzinc. Thus, after the cyclopropylzinc reagent was stirred for 3 h at rt, solid I_2 (254 mg, 1.00 mmol) was added in one portion and stirring was continued for another 16 h. The mixture was again cooled by an ice bath, and the reaction was quenched by the addition of aq HCl (0.1 M). A saturated solution of sodium thiosulfate (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (25 mL × 3). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 68 mg (0.16 mmol, 79%) of the title compound as an oil. An identical experiment gave 70 mg (0.16 mmol, 81%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.19−8.16 (m, 1H), 7.91−7.89 (m, 1H), 7.85−7.83 (m, 1H), 7.72−7.69 (m, 1H), 7.63−7.60 (m, 2H), 7.53−7.40 (m, 6H), 3.86 (d, J = 8.8 Hz, 1H), 3.44 (s, 3H), 3.26 (d, J = 8.8 Hz, 1H). Peaks attributable to impurities were observed at 1.30, 1.00, and 0.91 ppm in ^{1}H NMR; ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 168.7 (u), 140.5 (u), 134.0 (u), 132.7 (u), 131.3 (u), 129.1 (2 carbons, dn), 129.0 (dn), 128.3 (dn), 128.1 (dn), 127.5 (dn), 126.0 (dn), 125.8 (dn), 125.1 (dn), 124.3 (dn), 52.4 (dn), 38.5 (u), 32.8 (dn), 3.1 (dn); Impurity peaks were observed at 34.9, 31.8, 25.5, 22.9, 20.9, 14.3 ppm. IR (CH_2Cl_2, cm^{-1}): 3053, 2986, 2954, 1734, 1447, 1436, 1306, 1264, 1197, 1176, 1156, 1046, 911, 804, 786, 721, 650; HRMS (CI) m/z [M + Na] calcd for $C_{21}H_{17}IO_2Na$ 451.0171, found 451.0171.

***rel*-(1*R*,2*S*,3*S*)-Methyl 2-Allyl-3-(naphthalen-1-yl)-1-phenylcyclopropane Carboxylate (11).** The carbozincation procedure was identical to that used to prepare **3**, except that allyl bromide was

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used instead of aq. HCl to quench the cyclopropylzinc. Thus, after the cyclopropylzinc reagent was stirred for 3 h at rt, a solution of LiCl (3.4 mg, 0.08 mmol) in THF (1 mL) was added dropwise via syringe. After 5 min, allyl bromide (0.17 mL, 2.0 mmol) was added and the mixture was allowed to stir for 16 h. The mixture was again cooled by an ice bath, and the reaction was quenched by the addition of aq HCl (0.1 M). The mixture was extracted with CH_2Cl_2 (25 mL × 3). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography with a gradient of hexanes to 5% diethyl ether in hexanes furnished 50 mg (0.15 mmol, 73%) of the title compound as an oil. The purity of ^{1}H NMR was measured to be >95%. An identical experiment gave 52 mg (0.15 mmol, 76%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.27−8.23 (m, 1H), 7.90−7.86 (m, 1H), 7.81−7.78 (m, 1H), 7.62−7.59 (m, 2H), 7.52−7.41 (m, 6H), 7.35 (m, 1H), 6.06−5.96 (m, 1H), 5.17−5.08 (m, 2H), 3.39 (d, J = 9.6 Hz, 1H), 3.37 (s, 3H), 2.74−2.59 (m, 2H), 2.19 (dt, J = 5.9, 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 171.4 (u), 142.8 (u), 137.9 (dn), 134.0 (u), 133.4 (u), 132.0 (u), 129.9 (dn), 129.0 (dn), 128.7 (dn), 127.9 (dn), 127.7 (dn), 127.3 (dn), 125.9 (dn), 125.7 (dn), 125.4 (dn), 124.5 (dn), 115.9 (u), 51.9 (dn), 37.7 (u), 34.5 (dn), 34.4 (dn), 29.8 (u); IR ($CDCl_3$, cm^{-1}): 3063, 3030, 3002, 2951, 1725, 1640, 1600, 1509, 1496, 1509, 1496, 1435, 1317, 1261, 1235, 1198, 1181, 1143, 1107, 922, 897, 804, 783, 753, 700, 650; HRMS (CI) m/z [M + Na] calcd for $C_{24}H_{22}O_2Na$ 365.1518, found 365.1503.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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