Universal Strategy for the Immobilization of Chiral Dirhodium Catalysts

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Supporting Information

General Information. ¹H NMR spectra were run at either 300, 400, or 500 MHz, and ¹³C NMR at either 75 or 125 MHz in CDCl₃. Inductively coupled plasma emission spectroscopy (ICP-AES) on the solid supported catalyst was performed by Robertson Microlit Laboratories, Inc., Madison, NJ. All reactions were performed on Quest® Parallel Synthesizer.¹ Tetrahydrofuran (THF), hexanes, dichloromethane (DCM), acetonitrile and toluene were used either directly from the solvent purification system (solvent was passed through columns with activated alumina) purchased from MBRAUN. All other solvents were of reagent grade. Reagents were purchased from Aldrich Chemical Company and Acros Organics at the highest commercial quality and used without further purification unless otherwise stated. The solid phase resins were purchased from Argonaut technologies

¹ Purchased from Argonaut Technologies (www.argotech.com)

Dirhodium catalysts **5**,² **6**,³ **7**⁴ and **8**⁵ were prepared according to the reported literature procedures.

Preparation of Polymer Support **9**.

To a 20 mL Bohdan MiniBlock™ reaction vessel was added Argopore-Wang resin (1 g, 0.65 mmol),¹ followed by 10 mL dichloromethane. The reaction vessel was shaken on the mini-shaker for 15 min then carbon tetrabromide (0.607 g, 1.83 mmol) was added and the vessel was cooled by passing cold water through the block. Triphenylphosphine (0.385 g, 1.46 mmol) dissolved in 2 mL of dichloromethane was added to the vessel and allowed to shake for 2 h. Cold water circulation was stopped and the reaction mixture was allowed to warm to room temperature overnight. The mixture was drained and the

² Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998.

³ Doyle, P. M.; Davies, B. S.; Hu, W. *Org. Lett.* **2000**, 2, 1145

⁴ Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, 34, 5109. (b) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604.

⁵ Pirrung, M. C.; Zhang, J.; *Tetrahedron Lett.* **1992**, 33, 5987.

resin was washed with dichloromethane (8 x 25 mL). The resin was transferred into a vial and dried under vacuum to give Argopore-Wang-Br (0.95 g).

In a 50 mL round bottom flask with a stir bar at 0° C, was added sodium hydride (0.069 g, 2.88 mmol) and a solution of 4-pyridyl carbinol (0.25 g, 2.29 mmol) in 2 mL THF. The mixture was allowed to stir for 30 min and added to a shaking mixture of tetrabutylammonium iodide (0.611 g, 1.65 mmol), Argopore Wang-Br (0.95 g), and 18-crown-6 (0.03 g, 0.113 mmol) in 10 mL DMF. The black-brown mixture was allowed to stir for 12 h, then drained. The resin was washed with THF (3x), THF:DMF (1:1, 3x), DMF (3x), DMF:H₂O (1:1, 5x), DMF (2x), THF:DMF (1:1, 3x), THF (3x), THF:DCM (1:1, 3x), DCM (5x). The resin was transferred into a vial and dried under vacuum to give Argopore Wang-pyridine (0.92 g, 0.3 mmol/g). The loading was determined to be (0.3 mmol/g) by cleavage of the 4-pyridyl carbinol using TFA/DCM (1:1).

General Procedure for the Immobilization of Dirhodium(II) Catalysts on Resin 9

To a 5 mL reaction vessel with stir bar was added resin **9** (0.018 mmol, 1.3 equiv.) and solvent (3.5 mL). The resin was agitated for 10 min, before the addition of rhodium(II) catalyst (0.014 mmol, 1 equiv.). Extra solvent (1 mL) was used to wash down the sides of the reaction vessel. The mixture was agitated for 2 h, after which the solution was

drained and the purple colored beads were washed with solvent (5x). Air was used to dry the beads before transferring to a vial and dried under vacuum to give the solid supported catalyst. Loading was measured by mass and confirmed by inductively coupled plasma emission spectroscopy (ICP-AES). Dichloromethane was used for catalysts **4** and **5**, toluene was used for catalysts **3**, **6** and **7**.

catalyst	loading (mmol/g) ^b	immobilization (%)	immobilized catalyst
3	0.13	87	9a-3
Rh ₂ (<i>S</i> -MEPY) ₄	0.12 ^c	60	9a-Rh₂(<i>S</i>-MEPY)₄
Rh ₂ (<i>S</i> -MEAZ) ₄	0.12	61	9a-Rh₂(<i>S</i>-MEAZ)₄
Rh ₂ (<i>S</i> -PTTL) ₄	0.14	77	9a-Rh₂(<i>S</i>-PTTL)₄
Rh ₂ (<i>R</i> -BNP) ₄	0.14	81	9a-Rh₂(<i>R</i>-BNP)₄

a: The amount (mmol) of catalyst was varied to maintain 1.3 equivalents of resin **6** to the catalyst.

b: loading determined by ICP analysis for Rh (mmol/g)

c: loading determined by change in mass resin after drying

Evaluation of Immobilized Chiral Rhodium(II) Catalysts Using Standard Asymmetric Cyclopropanation of Styrene with Methyl phenyldiazoacetate (**10**).

To a 5 mL Quest 210 reaction vessel was added **9a**-Rh₂(*S*-MEAZ)₄ (2.8 mg, 0.34 μmol, 0.5 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 min. DCM (3 mL), followed by styrene (0.1 g, 0.961 mmol) was added to the reaction mixture and the mixture was agitated for 10 min. A 1 mL DCM solution of methyl phenyldiazoacetate (**10**) (12 mg, 0.068 mmol) was prepared and added dropwise via a syringe over 10 min to the agitating mixture. The endpoint of the reaction mixture was determined by cessation of nitrogen gas evolution and by disappearance of the yellow color from the diazo compound (>3 h). The reaction mixture was agitated for 10 min after reaching the end-point and drained. The resin was washed with DCM 3-4 times and dried by pushing air through the reaction vessel. The excess styrene from drained the reaction mixture was removed by evaporation under vacuum. The product was purified using flash chromatography (10:1 pentane:ether) which gave 13.1 mg, 76% yield of **11**. (HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min,

1mg/mL, t_R = 9.05 (minor) and 10.19 (major) min, UV 254 nm) 69% ee; The spectroscopic data are consistent with the previously reported data.⁶ The corresponding reaction using homogeneous catalyst gave 69% ee for **11**.

To a 5 mL Quest 210 reaction vessel was added **9a**-Rh₂(S-PTTL)₄ (12.2 mg, 1.71 μ mol, 0.5 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 min. Toluene (3 mL), followed by styrene (0.1 g, 0.961 mmol) was added to the reaction mixture and the mixture was agitated for 10 min. A toluene solution (1 mL) of methyl phenyldiazoacetate (**10**) (60.0 mg, 0.341 mmol) was prepared and added dropwise via a syringe over 10 min to the agitating mixture. The endpoint of the reaction mixture was determined by cessation of nitrogen gas evolution and by disappearance of the yellow color from the diazo compound (12 min). The reaction mixture was agitated for 10 min after reaching the end-point and drained. The resin was washed with toluene 3-4 times and dried by pushing air through the reaction vessel. The excess styrene from the drained reaction mixture was removed by evaporation under vacuum. The product was purified using flash chromatography (10:1 pentane:ether) which gave 70.5 mg, 82% yield of **ent-11**. (HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.05 (minor) and 10.19 (major) min, UV 254 nm) 10% ee; The spectroscopic data are consistent with the previously reported data.⁶ The corresponding reaction using the homogeneous catalyst gave 13% ee for **ent-11**.

⁶ Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, 37, 4133.

cycle	9a-2		9a-Rh₂(<i>R</i>-BNP)₄	
	time, min	ee, %	time, min	ee, %
1	12	53	15	40
3	15	50	30	39
5	25	48	60	38

a: reaction yields determined by ¹H-NMR using DMAP as internal standard, or isolated yields; in all cases were greater than 70%; see experimental section

cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	12	88	53
3	15	93	50
5	25	89	48

a: Yields determined using DMAP as internal standard

b : Diastereoselectivity was >92% as determined by ¹H-NMR

To a 5 mL Quest 210 reaction vessel was added solid supported catalyst (23.2 mg, 3.02 μmol, 0.5 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 min. Toluene (3 mL), followed by styrene (80.2 mg, 0.77 mmol) was added to the reaction mixture and the mixture was agitated for 10 min. A toluene solution (1 mL) of methyl phenyldiazoacetate (**10**) (70.0 mg, 0.397 mmol) was prepared and added dropwise via a syringe over 10 min to the agitating mixture. The endpoint of the reaction mixture was determined by cessation of nitrogen gas evolution and by disappearance of the yellow color from the diazo compound (15

min). The reaction mixture was agitated for 10 min after reaching the end-point and drained. The resin was washed with toluene 3-4 times and dried by pushing air through the reaction vessel. The reaction vessel was then purged with argon and filled with toluene (3 mL) for the next cycle. The excess styrene from drained the reaction mixture was removed by evaporation under vacuum, and product yield was determined by ^1H NMR using DMAP as an internal standard. (HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_{R} = 9.05 (minor) and 10.19 (major) min, UV 254 nm); The spectroscopic data are consistent with the previously reported data.⁶ The corresponding reaction using the homogeneous catalyst gave 53% ee for **ent-11**.

a: Yields determined using DMAP as internal standard

b : Diastereoselectivity was >92% as determined by ^1H -NMR

To a 5 mL Quest 210 reaction vessel was added solid supported catalyst (8.8 mg, 1.23 μmol , 0.5 mol%) and magnetic stirrer bar. The reaction was vessel was inserted into the Quest 210 and purged with argon for 10 min. Toluene (3 mL), followed by styrene (0.1 g, 0.961 mmol) was added to the reaction mixture and the mixture was agitated for 10 min. A toluene solution (1 mL) of methyl phenyldiazoacetate (**10**) (44.0 mg, 0.250 mmol) was prepared and added dropwise via a syringe over 10 min to the agitating mixture. The endpoint of the reaction mixture was determined by cessation of nitrogen

gas evolution and by disappearance of the yellow color from the diazo compound (12 min). The reaction mixture was agitated for 10 min after reaching the end-point and drained. The resin was washed with toluene 3-4 times and dried by pushing air through the reaction vessel. The reaction vessel was then purged with argon and filled with toluene (3 mL) for the next cycle. The excess styrene from the drained reaction mixture was removed by evaporation under vacuum, and product yield was determined by ^1H NMR using DMAP as an internal standard. (HPLC, Welk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_{R} = 9.05 (minor) and 10.19 (major) min, UV 254 nm); The spectroscopic data are consistent with the previously reported data.⁶ The corresponding reaction using the homogeneous catalyst gave 42% ee for **ent-11**.

Evaluation of Immobilized $\text{Rh}_2(\text{S-MEPY})_4$ Using Standard Asymmetric Cyclopropanation of Styrene with Ethyl diazoacetate

To a 5 mL Quest 210 reaction vessel was added solid supported catalyst (20mg, 0.005 mmol, 0.5 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 min. Dichloromethane (1 mL), followed by styrene (0.2 mmol) was added to the reaction mixture and the reaction mixture was agitated for 10 min. The reaction mixture was heated to reflux and a dichloromethane solution (3 mL) of ethyldiazoacetate (0.054 g, 0.476 mmol) was prepared and added

dropwise via a syringe over 10 h to the agitating mixture. The reaction mixture was agitated for 2 h after the addition and cooled to room temperature. The solution was drained and concentrated in vacuo ((**13a:13b**) *trans:cis* 1:1, determined by crude H NMR), purified using silica gel chromatography to give a combined (0.049g, 54% yield) of two diastereomers. **13a** *trans*: (HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.05 (minor) and 10.19 (major) min, UV 254 nm) 42% ee; ^1H NMR (500 MHz, CDCl_3) δ 7.28 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 7.5 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 2.52 (m, 1H), 1.90 (m, 1H), 1.60 (m, 1H), 1.31 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H). **13b** *cis*: (HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1mg/mL, t_R = 9.05 (minor) and 10.19 (major) min, UV 254 nm) 31% ee; ^1H NMR (500 MHz, CDCl_3) δ 7.27 (m, 4H), 7.20 (m, 1H), 3.87 (q, 2H, J = 7.0 Hz), 2.58 (q, 2H, J = 8.0 Hz), 2.08 (m, 1H), 1.72 (m, 1H), 1.33 (m, 1H), 0.97 (t, 3H, J = 7.0 Hz). The spectroscopic data are consistent with the previously reported data.⁷

⁷ Muller, P.; Baud, C.; Ene, D.; Motallebi, S.; Doyle, M. P.; Brandes, B. D.; Dyatkin, A. B.; See, M. M. *Helv. Chim. Acta.* **1995**, 78, 459.

Asymmetric Intramolecular Cyclopropanation of Allyl diazoacetate **14 using Immobilized Rh₂(S-MEPY)₄.**

cycle	●-Rh ₂ (S-MEPY) ₄	
	yield, %	ee, %
1	81	95
2	75	95
3	72	95

Homogeneous reaction: 79% yield, 95% ee,
Reported reaction (ref 7): 75% yield, 95% ee

To a 5 mL Quest 210 reaction vessel was added immobilized **9a**-Rh₂(S-MEPY)₄ (66.1 mg, 0.0079 mmol, 2 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210, purged with argon for 10 min, dichloromethane (1 mL) was added and the reaction mixture was heated to reflux. A dichloromethane solution (3 mL) of allyldiazoacetate (**14**) (0.050 g, 0.396 mmol) was prepared and added dropwise via a syringe over 3 h to the agitating mixture. The reaction mixture was agitated for 2 h after the addition and cooled to room temperature. The solution was drained and the resin was washed with dichloromethane (x3). The filtered solution was concentrated in vacuo and passed through a short plug of silica gel (DCM) to give cyclopropane **15** (31.5 mg, 81% yield). The resin was air dried, purged with argon and reused for the next cycle. The enantiomeric excess was determined to be 95% ee by chiral HPLC, Whelk column, 2% 2-PrOH in hexanes, 1.0 mL/min, 1 mg/mL, *t_R* = 9.05 (minor) and 10.19 (major) min, UV 254 nm; ¹H NMR (300 MHz, CDCl₃) δ 4.36 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.20 (dd, *J* = 9.0, 1 Hz, 1H), 2.23 (ddd, *J* = 9.9, 7.5, 4.5 Hz, 1H), 2.04 (dddd, *J* = 9.5, 4.7, 3.5, 1.0 Hz, 1H),

1.27 (ddd, $J = 8.9, 7.6, 5.0$ Hz, 1H), 0.85 (dt, $J = 4.5, 3.5$ Hz, 1H). The spectroscopic data are consistent with the previously reported data.⁸

Asymmetric Intramolecular Cyclopropanation of Phenyldiazoacetate **16** using Immobilized $\text{Rh}_2(\text{S-MEAZ})_4$.

cycle	$\text{Rh}_2(\text{S-MEAZ})_4$	
	yield, %	ee, %
1	80	88
2	81	72
3	77	70

Homogeneous reaction: 80% yield, 86% ee,
Reported reaction(ref 8): 82% yield, 84% ee

To a 5 mL Quest 210 reaction vessel was added immobilized $9a\text{-Rh}_2(\text{S-MEAZ})_4$ (38.5 mg, 0.0046 mmol, 2 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210, purged with argon for 10 min, dichloromethane (1 mL) was added and the reaction mixture was heated to reflux. A dichloromethane solution (3 mL) of phenyldiazoacetate **16** (0.050 g, 0.231 mmol) was prepared and added dropwise via a syringe over 3 h to the agitating mixture. The reaction mixture was agitated for 2 h after the addition and cooled to room temperature. The solution was drained and the resin was washed with dichloromethane (x3). The filtered solution was concentrated in vacuo and passed thru a short plug of silica gel (DCM) to give cyclopropane **17** (34 mg, 80% yield). The resin was air dried, purged with argon and reused for the next cycle. The enantiomeric excess was determined to be 88% ee by GC on 30 m ChiralDEX B-DM

⁸ Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

column, 100°C for 5 min then 1°C/min to 170°C, t_R = 61.5 min (minor) and t_R = 63.5 min (major); ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.23 (comp, 5H), 4.36 (d, 1H, J = 9.0 Hz), 4.19 (d, 1H, J = 9.0 Hz), 1.60 (d, 1H, J = 4.5 Hz), 1.39 (d, 1H, J = 4.5 Hz), 1.15 (s, 3H). The spectroscopic data are consistent with the previously reported data.⁹

Asymmetric Intramolecular C–H Activation of Phenyldiazoacetate **18** using Immobilized $\text{Rh}_2(\text{S-PTTL})_4$.

cycle	$\text{Rh}_2(\text{S-PTTL})_4$	
	yield, %	ee, %
1	67	83
2	70	75
3	68	75

a: >94% de by H^1 -NMR observed for all 3 cycles
Homogeneous reaction: 72% yield, >94% de, 82% ee (toluene)
Reported reaction (ref 9): 78% yield, >99:1 dr, 70% ee (hexane)

To a 5 mL Quest 210 reaction vessel was added immobilized **9a**- $\text{Rh}_2(\text{S-PTTL})_4$ (12 mg, 0.0017 mmol, 1 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210, purged with argon for 10 min, toluene (1 mL) was added and the reaction mixture was allowed to agitate for 10 min. A toluene solution (3 mL) of phenyldiazoacetate **18** (0.047 g, 0.167 mmol) was prepared and added dropwise via a syringe over 3 h to the agitating mixture. The reaction mixture was agitated for 2 h after the addition. The solution was drained and the resin was washed with toluene (x3). The

⁹ Doyle, P. M.; Davies, B. S.; Hu, W. *Org. Lett.* **2000**, 2, 1145.

filtered solution was concentrated in vacuo (>94% de by crude ^1H NMR), passed thru a short plug of silica gel (dichloromethane) to give dihydrobenzofuran **19** (28.4 mg, 70% yield). The resin was air dried, purged with argon and reused for the next cycle. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.22 (m, 7H), 6.98-6.93 (m, 2H), 6.01 (d, 1H, J = 10.0 Hz), 4.63 (d, 1H, J = 10.0 Hz), 3.20 (s, 3H). The enantiomeric excess was determined to be 83% ee by chiral HPLC: OD-H; hexane/isopropanol (10:1); flow rate 1ml/min; t_R = 8.5 min (major), t_R = 13 min (major). The spectroscopic data are consistent with the previously reported data.¹⁰

Asymmetric Intramolecular Aryl C–H Activation of diazoacetate **20** using Immobilized $\text{Rh}_2(\text{S-PTTL})_4$

cycle	$\text{Rh}_2(\text{S-PTTL})_4$	
	yield, %	ee, %
1	80	93
2	75	93
3	75	93

a: **21** isolated as enol

Homogeneous reaction: 80% yield, 94% ee
Reported reaction (ref 11): 87% yield, 93% ee

To a 5 mL Quest 210 reaction vessel was added immobilized $\text{9a-Rh}_2(\text{S-PTTL})_4$ (11.4 mg, 0.0016 mmol, 5 mol%) and magnetic stirrer bar. The reaction was vessel was inserted

¹⁰ Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

into the Quest 210, purged with argon for 10 min, dichloromethane (1 mL) was added and the reaction mixture was allowed to agitate for 10 min. A dichloromethane solution (3 mL) of diazoacetate **20** (9.8 mg, 0.032 mmol) was prepared and added dropwise via a syringe over 2 hours to the agitating mixture. The reaction mixture was agitated overnight after the addition. The solution was drained and the resin was washed with dichloromethane (x3). The filtered solution was concentrated in vacuo and passed through a short plug of silica gel (DCM) to give the enol tautomer of **21** (7.7 mg, 85% yield). The resin was air dried, purged with argon and reused in the next cycle. ¹H NMR (400 MHz, CDCl₃) δ 11.02 (br s, 1H), 7.67 (d, *J* = 8.0 Hz 1H), 7.39-7.05 (m, 8H), 4.02 (s, 3H), 1.81 (s, 3H). The enantiomeric excess was determined to be 93% ee by chiral HPLC: AD-RH; 1% isopropanol in hexane; flow rate 0.7ml/min; *t_R* = 7.7 min (minor), *t_R* = 8.3 min (major). The spectroscopic data are consistent with the previously reported data.¹¹

¹¹ (a) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2003**, *14*, 817. (b) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85.