Simple Strategy for the Immobilization of Dirhodium Tetraproline Catalysts Using a Pyridine-Linked Solid Support

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Supporting Information Available.

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. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) using (*R,R*)-Whelk or (*S,S*)-Whelk chiral analytical columns with 2-propanol in hexane as the eluent (2% 2-propanol). IR spectra were obtained using a Nicolet Impact series 420 IR and are reported as frequency of absorption (cm⁻¹). Inductively coupled plasma emission spectroscopy (ICP-AES) on the solid supported catalysts was performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Analytical TLC was performed on 250μm Whatman silica gel (Aluminum backing, UV 254 nm) plates using UV light and

phosphomolybdic acid dip as visualizing agents. Column chromatography was carried out using ICN 60 32-63 according to the method of Still.¹

All reactions were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Reactions were performed either on Quest 210 Parallel Synthesizer or Bohdan MiniBlock™ unless specified. Reactions on the Quest 210 Parallel Synthesizer using the Argopore resins were agitated at: agitation conditions: Mix every = 0.7 sec, Upstroke = 0.3 sec, % upward = 50 %, and the 1% and 2% polystyrene resins were agitated at: agitation conditions: Mix every = 1.4 sec, Upstroke = 0.7 sec, % upward = 50 %, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Toluene and dichloromethane (DCM) were distilled from calcium hydride. 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. Solid phase resins were purchased from Argonaut technologies or Aldrich Chemical Company. Reactions conducted using catalyst **8a**-Rh₂(S-TBSP)₄ and **8b**-Rh₂(S-biTISP)₂ have been reported earlier with full experimental procedures.² Homogeneous control experiments using 4-alkyl-pyridine **23** have been reported earlier.²

Preparation of benzyloxymethyl-pyridine linker **8**.

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

¹ Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923

² Nagashima, T.; Davies, H. M. L. *Org. Lett.* **2002**, *4*, 1989.

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 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 **7** (0.95 g).

In a 50mL 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 **7** (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 (x5). The resin was transferred into a vial and dried under vacuum to give Argopore Wang-pyridine **9** (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).

Preparation of benzyloxymethyl-phenyl linker **11**.

In a 50mL round bottom flask with a stir bar at 0°C, was added sodium hydride (0.083 g, 2.10 mmol) and a solution of 4-benzyl alcohol (0.46 g, 4.25 mmol) in 2 mL THF. The mixture was allowed to stir for 30 min and added to a shaking mixture of tetrabutylammonium iodide (0.038 g, 0.103 mmol), Argopore Wang-Br **7** (0.504 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 (x5). The resin was transferred into a vial and dried under vacuum to give Argopore Wang-**11** (0.480 g). The loading was determined to be (0.3 mmol/g) by cleavage of the 4-benzyl alcohol using TFA/DCM (1:1).

Preparation of linker 15

Argopore-Cl **14** (4.93 g, 4.44 mmol, 1.05 mmol/g) was slowly shaken in a 125 mL Erlenmeyer flask with a solution of tetrabutylammonium iodide (0.82 g, 2.20 mmol) in DMF (25 mL). In a separate 50 mL round bottom flask 4-pyridyl propanol (2.43 g, 17.7 mmol) was added to a mixture of sodium hydride (0.28g, 11.6 mmol) in THF (5 mL). A further 10mL of DMF was added to round bottom flask and allowed to stir for 1 hr. The mixture in the round bottom flask was then added to the shaking mixture of **14**. This mixture was then shaken overnight. The resin was then drained and washed with THF (3x), THF:DMF (1:1, 3x), DMF (3x), DMF:H₂O (1:1, 3x), DMF (2x), THF:DMF (1:1, 3x), THF (3x), THF:DCM (1:1, 3x), DCM (x5). The resin was transferred into a vial and dried under vacuum to give **15** (0.92 g, 0.3 mmol/g). Loading was determined by elemental analysis for nitrogen 1.41%N, 0.5 mmol/g.

Preparation of linker 16

Argopore-Cl **14** (0.81 g, 0.851 mmol, 1.05 mmol/g) was slowly shaken in a 125 mL Erlenmeyer flask with a solution of tetrabutylammonium iodide (0.192 g, 0.52 mmol) in DMF (25 mL). In a separate 50 mL round bottom flask 3-phenyl propanol (0.345 g, 3.19 mmol) was added to a mixture of sodium hydride (0.085 g, 2.10 mmol) in THF (5 mL). A further 10mL of DMF was added to round bottom flask and allowed to stir for 1 hr. The mixture in the round bottom flask was then added to the shaking mixture of **14**. This mixture was then shaken overnight. The resin was then drained and washed with THF (3x),

THF:DMF (1:1, 3x), DMF (3x), DMF:H₂O (1:1, 3x), DMF (2x), THF:DMF (1:1, 3x), THF (3x), THF:DCM (1:1, 3x), DCM (x5). The resin was transferred into a vial and dried under vacuum to give **16** (0.78 g). Loading was estimated to be 0.50 mmol/g based on the loading obtained for resin **15**.

Preparation of linker 17

1% PS-Wang pyridine resin **17** was prepared using a similar procedure to linker **8**. The loading was determined to be (0.45 mmol/g) by cleavage of the 4-pyridyl carbinol using TFA/DCM (1:1).

Preparation of linker 18

1% PS-Wang phenyl resin **18** was prepared using a similar procedure to linker **11**. The loading was determined to be (0.40 mmol/g) by cleavage of the 4-benzyl alcohol using TFA/DCM (1:1).

Preparation of linker 24

JandaJel^{TM}-Wang pyridine resin **24** was prepared using a similar procedure to linker **8**. The loading was determined to be (0.33 mmol/g) by cleavage of the 4-pyridyl carbinol using TFA/DCM (1:1).

General Method for the immobilization of rhodium(II) catalysts.

General procedure using Quest-210 parallel synthesizer: (procedure for homogeneous catalyst as limiting agent)

To a 5 mL reaction vessel with stir bar was added resin (0.020 mmol, 1.2 equiv.) and toluene (3.5 mL). The resin was agitated for 10 min, before the addition of rhodium(II) catalyst (0.017 mmol, 1 equiv.). Extra toluene (1 mL) was used to wash down the sides of the reaction vessel. The mixture was agitated for 2-4 h, after which the solution was drained and the purple/green colored beads were washed with toluene (5x). Air was used to dry the beads before transferring to a vial and dried under vacuum to give the solid supported catalyst which was analyzed by inductively coupled plasma emission spectroscopy (ICP-AES).

Standard asymmetric cyclopropanation of styrene using solid supported catalysts and methyl phenyldiazoacetate.

To a 5 mL Quest 210 reaction vessel was added solid supported catalyst (0.0005 mmol, 0.5 mol%) and magnetic stirrer bar. The reaction vessel was inserted into the Quest 210 and purged with argon for 10 mins. Toluene (3 mL), followed by styrene (0.2 mmol) was added to the reaction mixture and agitated for 10 mins. A 1 mL toluene solution of methyl phenyldiazoacetate (0.1 mmol) was prepared and added

dropwise via a syringe over 10min to the agitating mixture. Endpoint of the reaction mixture was determined by cessation of nitrogen gas evolution and by disappearance of the yellow color from the diazo compound. The reaction mixture was agitated for 10mins after reaching the end-point and drained. The resin was washed with toluene 3-4 times with toluene 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. Excess styrene from drained reaction mixture was removed by evaporation under vacuum, and product yield was determined by ^1H NMR using DMAP as internal standard, or by passing the crude reaction mixture through a short plug of silica gel (5:1 pentane:ether). (HPLC, Welch 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); ^1H NMR (500 MHz, CDCl_3) δ 7.12 (m, 3 H), 7.04 (m, 5 H), 6.76 (m, 2 H), 3.65 (s, 3 H), 3.12 - 3.09 (dd, J = 4.0, 9.0 Hz, 1 H), 2.14 - 2.11 (dd, J = 5.0, 9.5 Hz, 1 H), 1.88 - 1.86 (dd, J = 5.0, 7.5 Hz, 1 H). The spectroscopic data are consistent with previously reported data.³

Preparation of phenyldiazoacetate **26** on solid support.

To a 20 mL MiniBlock^{TM} reaction vessel was added 1% PS-Wang resin **24** (1.0 g, 0.98 mmol, 0.98 mmol/g), followed by 10 mL DMF. The resin was allowed to swell for 20 min, then a DMF (3 mL) solution of phenyl acetic acid (0.67 g, 4.92 mmol) and DMAP (0.012g, 0.098 mmol) was added. Diisopropylcarbodiimide (0.618 g, 4.90 mmol) was added and the reaction mixture was shaken overnight. The reaction mixture was then drained and washed with DMF (5x), DMF:THF (1:1, 5x), THF (5x), THF:MeOH (1:1, 5x), MeOH (2x), MeOH: H₂O (1:1, 2x), MeOH (5x), THF:MeOH (1:1, 5x), THF (5x), THF:DCM (1:1, 10x), DCM (10x). Resin **25** was then transferred to a vial and dried under high vacuum (0.91g). IR (KBr) 3024, 2921, 1733, 1677 cm^{-1} .

³ Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, 37, 4133

To a 20 mL MiniBlock™ reaction vessel was added 1% PS-Wang resin **25** (0.91 g), followed by 10 mL toluene. The resin was allowed to swell for 20 min, then tosylazide (0.58 g, 2.94 mmol) dissolved in 3 mL of toluene was added. The mixture was shaken for 15 min then DBU (0.509 g, 0.5 mL, 3.34 mmol) was added and the reaction mixture was shaken overnight. The reaction mixture was then drained and washed with toluene (2x), toluene:DCM (1:1, 5x), DCM (5x), DCM:THF (1:1, 5x), THF (5x), THF:MeOH (1:1, 5x), MeOH (2x), MeOH: H₂O (1:3, 2x), MeOH (5x), THF:MeOH (1:1, 5x), THF (5x), THF:DCM (1:1, 10x), DCM (10x). Resin **26** was then dried under high vacuum (0.90g, loading 0.95 mmol/g by elemental analysis for N). IR (KBr) 3024, 2922, 2086, 1699, 1681 cm⁻¹.

General procedure for conducting the three-phase test

To a 5 mL Quest 210 reaction vessel was added the immobilized diazo compound **26** (0.053 g, 0.05 mmol, loading 0.95 mmol/g), and a 5 mL solution of styrene (0.5 mL, excess) in toluene. The resin was allowed to swell for 10-15 mins, then the catalyst on solid support (9.4 mg, 1.51 μmol, 3 mol%) was added and the reaction mixture was agitated for 3 hr-overnight. The reaction mixture was then poured into a fritted funnel (fine) and washed with toluene (10x) air dried and analyzed by IR (KBr).

To a 25mL round bottom flask with a small magnetic stirrer bar was added the diazo compound **25** (0.050 g, 0.05 mmol, loading 0.95 mmol/g), and a 5mL solution of styrene (0.5 mL, excess) in toluene. The resin was allowed to swell for 10-15 mins, then a 1 mL toluene solution of methyl phenyldiazoacetate **9** (0.053 g, 0.301 mmol) was added followed by the catalyst on solid support (9.0 mg, 1.44 μmol , 3 mol% with respect to **26**) placed in a permeable membrane IRORI MicroKan reactor. The reaction mixture was allowed to stir overnight. The reaction mixture was then poured into a fritted funnel (fine) and washed with toluene (10x) air dried and analyzed by IR (KBr).

1. $\text{Rh}_2(\text{S-TBSP})_4$
 toluene, rt, 2h.

8d-16d– $\text{Rh}_2(\text{S-TBSP})_4$

2. Toluene wash (5x)

entry	Linker	Polymer (mmol)	$\text{Rh}_2(\text{S-TBSP})_4$ (mmol)	Loading (mmol/g) ^a	Immobilization (%)	Catalyst
1	 8	0.018	0.014	0.16	93	8d – $\text{Rh}_2(\text{S-TBSP})_4$
2	 11	0.017	0.014	0.13	75	11d – $\text{Rh}_2(\text{S-TBSP})_4$
3	 12	0.040	0.014	0.12	71	12d – $\text{Rh}_2(\text{S-TBSP})_4$
4	 13	0.039	0.014	0.12	70	13d – $\text{Rh}_2(\text{S-TBSP})_4$
5	 14	0.065	0.014	0.02	12	14d – $\text{Rh}_2(\text{S-TBSP})_4$
6	 15	0.030	0.014	0.16	92	15d – $\text{Rh}_2(\text{S-TBSP})_4$
7	 16	0.030	0.014	0.05	29	16d – $\text{Rh}_2(\text{S-TBSP})_4$

a: Loading determined by ICP analysis for Rh (mmol/g)

cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	88	87
3	10	90	83
5	15	81	81

a: Yields determined using DMAP as internal standard

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

cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	90	86
3	10	84	84
5	15	88	82

a: Yields determined using DMAP as internal standard

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

cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	89	86
3	10	70	83
5	15	78	81

a: Yields determined using DMAP as internal standard

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

cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	88	84
3	10	86	78
5	10	87	71

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{C}(\text{CO}_2\text{Me})$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{12d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	77	80
3	10	80	77
5	14	77	68

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{C}(\text{CO}_2\text{Me})$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{13d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	79	82
3	17	93	77
5	14	85	68

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{C}(\text{CO}_2\text{Me})$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{14d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	74	83
2	20	83	53
3 ^c	overnight	incomplete	incomplete

a: Yields determined using DMAP as internal standard

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

c: After overnight agitation reaction does not go to completion

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{15d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	80	85
3	20	89	79
5	20	89	77

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{16d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	89	82
3	22	73	72
5	30	79	67

a: Yields determined using DMAP as internal standard

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

entry	Linker	Polymer (mmol)	$\text{Rh}_2(\text{S-TBSP})_4$ (mmol)	Loading (mmol/g) ^a	Immobilization (%)	Catalyst
1	 17 1% crosslinked PS	0.017	0.014	0.14	78	17d $\text{Rh}_2(\text{S-TBSP})_4$
2	 18 1% crosslinked PS	0.017	0.014	0.08	46	18d $\text{Rh}_2(\text{S-TBSP})_4$
3	 19 functionalized silica gel	0.077	0.014	0.01	8	19d $\text{Rh}_2(\text{S-TBSP})_4$
4	 20 1% PS-DMAP	0.084	0.014	0.0005	<1	20d $\text{Rh}_2(\text{S-TBSP})_4$
5	 21 Polypyridine JandaJel ^{TM}	0.475	0.014	<i>b</i>	<1	21d $\text{Rh}_2(\text{S-TBSP})_4$
6	 22 JandaJel ^{TM} -Wang	0.02	0.014	0.17	97	22d $\text{Rh}_2(\text{S-TBSP})_4$

a: Loading determined by ICP analysis for Rh (mmol/g)

b: ICP-AES analysis of the resin beads gave 1.04ppm Rh which corresponds to less than 1% immobilization

0.5 mol%
17d $\text{Rh}_2(\text{S-TBSP})_4$

cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	20	85	82
3	20	87	81
5	35	83	74

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{18d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	25	84	87
2	45	82	77
3	overnight	85	76

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{19d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	10	85	78
3	120	77	66
4	overnight	80	54

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{22d}-\text{Rh}_2(\text{S-TBSP})_4}$ 10			
cyde	time, (min)	yield, (%) ^a	ee, (%) ^b
1	15	80	85
3	15	82	79
5	20	78	77

a: isolated yields. Flash chromatography 5:1 pentane:ether (silica gel)

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{8d}-\text{Rh}_2(R\text{-DOSP})_4}$ ent-10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	15	87	84
3	20	82	85
5	45	86	86

a: Yields determined using DMAP as internal standard

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

$\text{Ph}-\text{C}(\text{N}_2)=\text{CO}_2\text{Me}$ 9 + $\text{Ph}-\text{CH}=\text{CH}_2$ $\xrightarrow[\text{toluene, rt}]{0.5 \text{ mol\% } \mathbf{8d}-\text{Rh}_2(S\text{-biTISP})_2}$ ent-10			
cycle	time, (min)	yield, (%) ^a	ee, (%) ^b
1	40	86	86
3	75	88	86
5	140	79	86

a: Yields determined using DMAP as internal standard

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