Enantioselective copper catalysed C–H insertion reactions of 2sulfonyl-2-diazoacetamides to form y-lactams.

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Supporting Information

Leslie-Ann Clarke^a, Aoife Ring^a, Alan Ford^a, Abhijeet S. Sinha^a, Simon E. Lawrence^a and Anita R. Maguire^b

^aDepartment of Chemistry, Analytical and Biological Chemistry Research Facility, Synthesis and Solid State Pharmaceutical Centre, University College Cork, Cork, Ireland

^bDepartment of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, Synthesis and Solid State Pharmaceutical Centre, University College Cork, Cork, Ireland

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Section 1: Transition metal catalysed C-H insertion reactions of 6

Diazo precursor	Method	М	L*	Time (h)	Crude Efficiency ^a (%)	Ratio of Products (Crude) ^a 7a:8a:9a	Total Yield ^b (%)	Ratio of Products(Pure) ^c 7a (% ee) ^d :8a:9a
6a	A	CuCl ₂	1	42	~75-85	75:9:16	57	98 (48) ^{e,g,i} : 2: 0
6a	А	CuCl ₂	2	16	~80-90	90:5:5	53	99 (44) ^{f,g,i} : <1: 0
6a	A	CuCl ₂	3	16	~75-85	79:14:7	70	93 (33) ^{e,g,i} : 6:<1
6a	A	CuCl ₂	(+)4	16	~85-95	90:5:5	70	97 (66) ^{e,g,i} : 2:>1
6a	A	CuCl ₂	5	21	~85-95	88: 8:4	66	99 (60) ^{e,h,j} : <1: 0
6a	В	Rh ₂ (OAc) ₄	-	16	>90	97:2:1	70	99 (0) ^e : <1 :0

1.1 Table 1: Transition metal catalysed C–H insertion reactions of 6a

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for PhSO₂C(3)*H*, **7a** ¹H NMR (δ) 3.58 [d, *J* = 4.0 Hz, PhSO₂C(3)*H*, 1H], **8a** ¹H NMR (δ) 3.85 [d, *J* = 8.7 Hz, PhSO₂C(3)*H*, 1H] and **9a** ¹H NMR (δ) 4.15 [d, *J* = 2.2 Hz, PhSO₂C(3)*H*, 1H].

b. Total yield of cyclized products after chromatography [ethyl acetate-hexane (0:100-100:0 gradient)].

c. Product generally isolated as an inseparable mixture of 7a, 8a and 9a. Percentage of each product calculated using ¹H NMR spectra of the purified product using signals for PhSO₂C(3)H, 7a (δ) 3.58 [d, J = 4.0 Hz, PhSO₂C(3)H, 1H], 8a ¹H NMR (δ) 3.85 [d, J = 8.7 Hz, PhSO₂C(3)H, 1H] and 9a ¹H NMR (δ) 4.15 [d, J = 2.2 Hz, PhSO₂C(3)H, 1H].

d. Compound **7a** eluted over 2-3 fractions. The enantioselectivity of each individual fraction was analyzed by chiral HPLC analysis using a Phenomenex LUX Cellulose-4 chiral column: 30:70 2-propanol:Hexane as the mobile phase. The enantioselectivity of each fraction differs slightly indicating a degree of enantiomer self –disproportionation.¹

e. The enantioselectivity recorded is based on recombination of the fractions and subsequent re-analysis of enantioselectivity by chiral HPLC analysis.

f. The enantioselectivity of 44% ee is based on a weighted average. The enantioselectivity and the relative mass of each fraction are given as follows; fraction one-44% ee, 70% mass, fraction two-35% ee, 30% mass.

g. The minor enantiomer elutes at ~23 mins, while the major enantiomer elutes at ~35 mins

h. The major enantiomer elutes at ~23 mins, while the minor enantiomer elutes at ~35 mins.

i. Stereochemistry assigned as (3S,4R)- see Section 2 for full details.

j. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details.

Diazo precursor	Method	М	L*	Time (h)	Crude Efficiency ^a (%)	Ratio of products ^a (crude) 7b:8b	Total Yield ^b (%)	Ratio of Products (pure) ^c 7b (% ee) ^f :8b
6b	А	CuCl ₂	1	21	~75-85	86:14	48	90 (48) ^{h,j,l} :10
6b	А	CuCl ₂	2	21	~80-90	88:12	59	100 (52) ^{h,j,l} :0
6b	А	CuCl ₂	3	21	~80-90	85:15	53	93 (34) ^{h,j,l} :7
6b	А	CuCl ₂	(-)4	6	~80-90	96:4	61	99 (82) ^{g,i,k,m} :1
6b	А	CuCl ₂	5	48	~70-80	92:8	45	94 (70) ^{i,k,m} :6
6b	С	Rh ₂ (S-PTTL) ₄	-	30	>90	89:11	65	89 (71) ^{i,k,m} :11
6b	С	Rh ₂ (S-PTPA) ₄	-	21	~80-90	77:23	59	83 (41) ^{i,k,m} :17
6b	D	Rh ₂ (S-DOSP) ₄	-	48 ^d	~80-90	78:22	62	76 (6) ^{i,k,m} :24
6b	D	Rh ₂ (5 <i>S</i> -MEPY) ₄	-	72 ^e	~70-80	87:13	25	93 (0):7
6b	С	Rh ₂ (S-mand) ₄	-	7	~80-90	82:18	61	91 (27) ^{h,j,l} :9
6b	В	Rh ₂ (OAc) ₄	-	18	~80-90	92:8	52	95 (0):5

Table 2: Transition metal catalysed C-H insertion reactions of 6b

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(3)*H*: **8b** ¹H NMR (δ) 3.90 [d, *J* = 8.3 Hz, C(3)*H*, 1H] and **7b** (δ) 3.63 [d, *J* = 3.9 Hz, C(3)*H*, 1H].

b. Total yield of cyclized products after chromatography [ethyl acetate-hexane (10:90-40:60 gradient)].

C. Product generally isolated as an inseparable mixture of **7b** and **8b**. Percentage of each product calculated using ¹H NMR spectra of the purified product using signals C(3)*H*: **8b** ¹H NMR (δ) 3.90 [d, J = 8.3 Hz, C(3)*H*, 1H] and **7b** (δ) 3.63 [d, J = 3.9 Hz, C(3)*H*, 1H].

d. After stirring at room temperature for 30 h, the reaction was heated to reflux, and stirred at this temperature for 18 h.

e. After stirring at room temperature for 30 h, the reaction was heated to reflux, and stirred at this temperature for 42 h. After this time, the reaction was ~90% complete.

f. The enantiomeric excess was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-4 chiral column: mobile phase = 2-propanol:hexane (10:90 or 20:80).

g. The enantiomeric excess of 70% recorded is based on a weighted average. Two fractions of material were obtained. The relative masses of each fraction are given as follows; first fraction (42% mass, contains **7b** only, 71%ee), second fraction (58% mass, 7% **8b**, 93% **7b**, 69%ee **7b**).

h. The minor enantiomer elutes at 39-44 mins, while the major enantiomer elutes at 75-80 mins; mobile phase = 2-propanol:hexane (10:90)

i. The major enantiomer elutes at 39-44 mins, while the minor enantiomer elutes at 75-80mins; mobile phase = 2-propanol:hexane (10:90)

j. The minor enantiomer elutes at ~16 mins, while the major enantiomer elutes at ~26 mins; mobile phase = 2-propanol:hexane (20:80)

k. The major enantiomer elutes at ~16 mins, while the minor enantiomer elutes at ~26 mins; mobile phase = 2-propanol:hexane (20:80)

1. Stereochemistry assigned as (3*S*,4*R*)- see Section 2 for full details.

m. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details.

Diazo precursor	Method	М	L*	Time (h)	Crude Efficiency ^a (%)	Total Yield ^⁵ (%):	ee% of 7c [°]
6с	A	CuCl ₂	1	18	~70-80	40	12 ^{d,f.,h}
6c	A	CuCl ₂	2	48	~70-80	42	49 ^{d,f,h}
6c	A	CuCl ₂	3	24	~60-70	41	0 ^{f,h,}
6c	A	CuCl ₂	(–)4	25	~70-80	40	40 ^{e,i}
6c	A	CuCl ₂	5	18	~80-90	40	51 ^{e,g,i}
6c	В	Rh ₂ (OAc) ₄	-	18	>90	54	0

Table 3: Transition metal catalysed C–H insertion reactions of 6c

a. Efficiency and relative ratios of isomers determined by visual examination of the ¹H NMR spectra of the crude product.

b. Total yield of cyclized products after chromatography [ethyl acetate-hexane (0:100-100:0 gradient)].

c. The enantiomeric excess was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-2 chiral column; mobile phase = 2-propanol-hexane (1:99- 5:95 gradient or 4:96)

d. The minor enantiomer elutes at ~208-220 mins, while the major enantiomer elutes at ~221-235 mins; mobile phase = 2-propanolhexane (1:99-5:95 gradient).

e. The major enantiomer elutes at ~208-220 mins, while the minor enantiomer elutes at ~ 221-235 mins; mobile phase = 2-propanol-hexane (1:99-5:95 gradient).

f. The minor enantiomer elutes at ~103 mins, while the minor enantiomer elutes at ~ 120 mins; mobile phase = 2-propanol-hexane (4:96). The column was kept at 25 $^{\circ}$ C using a column heater.

g. The major enantiomer elutes at ~ 103 mins, while the minor enantiomer elutes at ~ 120 mins; mobile phase = 2-propanol-hexane (4:96). The column was kept at 25 °C using a column heater.

h. Stereochemistry assigned as (3S, 4R)- see Section 2 for full details.

i. Stereochemistry assigned as (3R,4S)- see Section 2 for full details

Diazo precursor	Method	М	L*	Time (h)	Crude Efficiency ^a (%)	Ratio of products (crude) ^a 7c:8b	Total Yield (%) ^c	Ratio of Products (pure) ^d 7b (% ee) ^e :8b
6d	A	CuCl ₂	1	18	~80-90	95:5	76	97 (13) ^{f,h} :3
6d	А	CuCl ₂	2	31	_b	_b	65	99 (48) ^{f,h} :1
6d	А	CuCl ₂	3	30	>90	85:15	67	90 (4) ^{f,h} :10
6d	А	CuCl ₂	(-)4	16	>90	>90:<10	58	99 (61) ^{g,i} :1
6d	А	CuCl ₂	5	40	>90	>90:<10	66	97 (67) ^{g,i} :3
6d	В	Rh ₂ (OAc) ₄	-	2	~80-90	88:12	57	90 (0):10

Table 4: Transition metal catalysed C–H insertion reactions of 6d

a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for $CH_3CH_2CH_2N$, **8d** ¹H NMR (δ) 0.95 (t, J = 7.4 Hz, $CH_3CH_2CH_2N$, 3H) and **7d** ¹H NMR (δ) 0.92 (t, J = 7.4 Hz, $CH_3CH_2CH_2N$, 3H). Relative ratios for **8d** and **7d** are estimated due to peak overlap.

b. Crude efficiency and crude ratio of products could not be determined.

c. Total yield calculated of cyclized products obtained after chromatography [ethyl acetate-hexane (10:90)].

d. Product generally isolated as an inseparable mixture of **7d** and **8d**. Percentage of each product calculated using ¹H NMR spectra of the purified product using signals for CH₃CH₂CH₂N, **8d** ¹H NMR (δ) 0.95 (t, *J* = 7.4 Hz, CH₃CH₂CH₂N, 3H) and **7d** ¹H NMR (δ) 0.92 (t, *J* = 7.4 Hz, CH₃CH₂CH₂N, 3H).

e. The enantiomeric excess was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-2 chiral column: mobile phase = 2-propanol-hexane (10:90).

f. The minor enantiomer elutes first at 25-27 min, while the major enantiomer elutes at 41-44 mins.

g. The major enantiomer elutes first at 25-27 min, while the minor enantiomer elutes at 41-44 mins.

h. Stereochemistry assigned as (3*S*,4*R*)- see Section 2 for full details.

i. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details

Diazo precursor	Method	Μ	Ligand	Time (h)	Crude Efficiency ^a (%)	Crude ratio of products ^a 7d:8d	Total Yield ^b (%)	Ratio of products (pure) ^c 7d (% ee) ^d :8d
6e	А	CuCl ₂	1	21	>90	97:3	49	97 (12) ^{e,g} :3
6e	А	CuCl ₂	2	21	>90	95:5	51	100 (45) ^{e,g} :0
6e	A	CuCl ₂	3	21	>90	95:5	49	95 (3) ^{e,g} :5
6e	A	CuCl ₂	(–)4	21	>90	98:2	61	98 (54) ^{f,h} :2
6e	А	CuCl ₂	5	50	>90	97:3	60	97 (62) ^{f,h} :3
6e	В	Rh ₂ (OAc) ₄	-	6	>90	95:5	60	95 (0):5

Table 5: Transition metal catalysed C–H insertion reactions of 6e

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for CH₃CH₂CH₂N, **8e** ¹H NMR (δ) 0.93 (t, *J* = 7.4 Hz, CH₃CH₂CH₂N, 3H) and **7e** ¹H NMR (δ) 0.92 (t, *J* = 7.4 Hz, CH₃CH₂CH₂N, 3H). Relative ratios for **8e** and **7e** are estimated due to peak overlap.

b. Total yield of cyclized products obtained column chromatography [ethyl acetate-hexane (10:90-40:60 gradient)].

C. Product generally isolated as an inseparable mixture of 7e and 8e. Percentage of each product calculated using ¹H NMR spectra of the purified product using signals for CH₃CH₂CH₂N, 8e ¹H NMR (δ) 0.93 (t, J = 7.4 Hz, CH₃CH₂CH₂N, 3H) and 7e ¹H NMR (δ) 0.92 (t, J = 7.4 Hz, CH₃CH₂CH₂N, 3H).

d. Enantioselectivity was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-2 chiral column; mobile phase = 2-propanol-hexane (10:90).

e. The minor enantiomer elutes first at 28-30 mins, while the major enantiomer elutes at 47-52 mins.

f. The major enantiomer elutes first at 28-30 mins, while the minor enantiomer elutes at 47-52 mins.

g. Stereochemistry assigned as (3S, 4R)- see Section 2 for full details.

h. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details.

					Ratio of Products-	Crude		Ratio of products ^c
Diazo Precursor	Method	М	L*	Time (h)	(Crude) ^a	Efficiency ^a	Total Yield ^b (%)	(Pure)
					7e:8e:9e	(%)		7e(%ee) ^d :8e:9e
6f	A	CuCl ₂	1	18	88:12:0	~65-75	60	98(57%ee) ^{e,h,j} :2:0
6f	A	CuCl ₂	2	48	100:0:0	>90	65	100(52%ee) ^{e,h,j} :0:0
6f	A	CuCl ₂	3	24	92:6:2	~75-85	55	93(13%ee) ^{f,h,j} :6:<1
6f	A	CuCl ₂	(–)4	25	95:3:2	~80-90	61	94(61%ee) ^{g,i,k} :5: >1
6f	A	CuCl ₂	5	18	99:1:0	~90	70	98(70%ee) ^{e,i,k} :2%:0%
6f	В	Rh ₂ (OAc) ₄	-	16	90:9:1	~90	60	90(0%ee):10:0 ^e

Table 6: Transition metal catalysed C–H insertion reactions of 6f

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for **7f** ¹H NMR (δ) 3.14-3.24 (m, 1 H of CH₃CH₂CH₂CH₂CH₂N, 1H), **8f** ¹H NMR (δ) 3.86 [d, J 8.2, PhSO₂C(3)*H*, 3H].and **9f** ¹H NMR (δ) 4.17 [d, J 2.1, PhSO₂C(3)*H*, 1H].

b. Total yield of cyclized product after chromatography [ethyl acetate-hexane (0:100-100:0 gradient)].

C. Product generally isolated as an inseparable mixture of 7f, 8f and 9f. Percentage of each product calculated using ¹H NMR spectra of the purified product using signals for 7f ¹H NMR (δ) 3.14-3.24 (m, 1 H of CH₃CH₂CH₂CH₂CH₂N, 1H), 8f ¹H NMR (δ) 3.86 [d, J 8.2, PhSO₂C(3)H, 3H].and 9f ¹H NMR (δ) 4.17 [d, J 2.1, PhSO₂C(3)H, 1H].

d. Compound **7f** eluted over 2-3 fractions. The enantiomeric excess of each individual fraction was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-4 chiral column: mobile phase = 2-propanol:Hexane (30:70). The enantiomeric excess of each fraction differs slightly indicating a degree of self-disproportionation of enantiomers.¹

e. The enantiomeric excess recorded is based on recombination of the fractions and subsequent re-measurement of enantioselectivity by chiral HPLC analysis.

f. The enantiomeric excess of 13% ee is based on a weighted average. The enantioselectivity and the relative mass of each fraction are given as follows; fraction one-20%ee, 10% mass, fraction two-16% ee, 60% mass and fraction three- 6% ee, 30% mass.

g. The enantiomeric excess of 61% ee is based on a weighted average. The enantioselectivity and the relative mass of each fraction are given as follows; fraction one-71%ee, 30% mass, fraction two-61%ee, 60% mass and fraction three-35%, 10% mass.

h. The minor enantiomer elutes first at ~ 19 mins, while the major enantiomer elutes at ~ 28 mins.

i. The major enantiomer elutes first at ~ 19 mins, while the minor enantiomer elutes at ~ 28 mins

j. Stereochemistry assigned as (3S,4R)- see Section 2 for full details.

k. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details

Table 7: Transition metal catalysed C–H insertion reactions of 6g

Diazo precursor	Method	М	L*	Time (h)	Crude Efficiency ^a (%)	Total Yield ^b (%)	ee% of 7f ^c
6g	A	CuCl ₂	1	16	~70-80	56	5 ^{d,j,l}
6g	A	CuCl ₂	2	48	~80-90	42	52 ^{e,h,l}
6g	A	CuCl ₂	(–)4	16	~80-90	56	64 ^{f,i,m}
6g	A	CuCl ₂	5	24	~80-90	50	66 ^{g,k,m}
6g	В	Rh ₂ (OAc) ₄	-	18	~80-90	54	0

a. Efficiency and relative was determined by visual examination of the crude ¹H NMR spectra.

b. Total yield of cyclized products after chromatography [ethyl acetate-hexane (0:100-100:0 gradient)].

c. The enantiomeric excess was measured by chiral HPLC analysis using a Phenomenex LUX Cellulose-2 chiral column; mobile phase = 2-propanol:hexane (1:99-5:95 gradient) or (4:96)

d. The enantiomeric excess of 5% ee is based on a weighted average. The enantioselectivity and the relative mass of each fraction are given as follows; fraction one-5% ee, 30% mass, fraction two-5% ee, 50% mass., fraction three-3% ee, 20% mass.

- e. The enantiomeric excess of each fraction was found to differ by approx. 1-3% ee, hence the enantiomeric excess recorded is the average of the three fractions-52% ee.
- f. The enantiomeric excess recorded is based on recombination of the test-tubes and subsequent re-analysis of enantioselectivity by chiral HPLC analysis.
- g. The enantiomeric excess of 66% ee is based on a weighted average. The enantioselectivity and the relative mass of each fractions are given as follows; fraction one-74%ee, 20% mass, fraction two-66%ee, 60% mass., fraction three-57%ee, 20% mass.
- h. The minor enantiomer elutes first at \sim 140 mins, while the major enantiomer elutes at \sim 172 mins mobile phase = 2-propanol-hexane (1:99-5:95 gradient).

i. The major enantiomer elutes first at \sim 140 mins, while the minor enantiomer elutes at \sim 172 mins mobile phase = 2-propanol-hexane (1:99-5:95 gradient)

j. The minor enantiomer elutes first at ~70 mins, while the minor enantiomer elutes at ~103 mins; mobile phase = 2propanol-hexane (4:96). The column was kept at 25°C using a column heater.

- k. The major enantiomer elutes first at ~70 mins, while the minor enantiomer elutes at ~103 mins; mobile phase = 2-propanol-hexane (4:96). The column was kept at 25° C using a column heater.
- 1. Stereochemistry assigned as (3*R*,4*S*)- see Section 2 for full details.
- m. Stereochemistry assigned as (3S,4R)- see Section 2 for full details.

References:

1. V. A. Soloshonok, C. Roussel, O. Kitagawa, and A. E. Soroshinsky, *Chem. Soc. Rev.* 2012, **41**, 418.

2. Absolute Stereochemistry Assignment and X-ray Crystallography Data.

7a formed using CuCl₂, (+)-(3R,4S)-4 and NaBARF.

Crystalline material of **7a** suitable for X-ray analysis was grown as follows: In a 10 mL round bottomed flask 100 mg of **7a** was dissolved in acetonitrile (~1 mL). The solvent was allowed to slowly evaporate at room temperature over ~2 weeks, after which time a crystalline sample of **7a** suitable for X-ray analysis were obtained.

The crystalline material was found to have ee >99% by chiral HPLC.



Absolute stereochemistry: (35,4R)

For **7a**: HPLC- $t_R(3R, 4S) = \sim 23$ mins, and $t_R(3R, 4S) = \sim 35$ mins

Specific Rotation: $[\alpha]_D^{20}$ – 9.5 (*c* 0.11, CHCl₃, 66% ee)

Stereochemistry for all other cyclisations was assigned by analogy, in reference to above information.



Crystal data for **7a**: C₁₄H₁₉NO₃S, *Mr* = 281.36, orthorhombic, *P*2₁2₁2₁, *a* = 7.681(3) Å, *b* = 12.525(5) Å, *c* = 14.693(6) Å, *V* = 1413.5(9) Å³, *Z* = 4, *D_c* = 1.322 g cm⁻³, *F*₀₀₀ = 600, Mo Kα radiation, λ = 0.71073 Å, *T* = 100(2) K, 2θ_{max} = 26.44°, μ = 0.233 mm⁻¹, 21075 reflections collected, 2909 unique (*R*_{int} = 0.0400), final GooF = 1.051, *R*₁ = 0.0244, w*R*₂ = 0.0626 (2814 obs. data: *I* > 2σ(*I*)); *R*₁ = 0.0257, w*R*₂ = 0.0634 (all data)

1. HPLC traces for 7a



2. HPLC traces for 7b



3. HPLC traces for 7c



4. HPLC traces for 7d



5. HPLC traces for 7e



6. HPLC traces for 7f



7. HPLC traces for 7g

































