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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 297–307

Intramolecular asymmetric C–H insertion of *N*-arylalkyl, *N*-bis(trimethylsilyl)methyldiazoamides mediated by chiral rhodium(II) catalysts. Synthesis of (*R*)-β-benzyl-γ-aminobutyric acid

Andrew G. H. Wee,* Sammy C. Duncan and Gao-jun Fan

Department of Chemistry and Biochemistry, University of Regina, Regina, Saskatchewan, Canada S4S 0A2

Received 25 November 2005; accepted 13 December 2005

Abstract—The enantio- and site-selectivity of the intramolecular C–H insertion reactions of acyclic *N*-arylalkyl, *N*-bis(trimethylsilyl)methyl α-diazoacetamides, and α-carboalkoxy-α-diazoacetamides **1a–g**, catalyzed by chiral Rh(II) carboxamidates and Rh(II) carboxylates were studied. In general, the reaction showed good to excellent chemoselectivity. Regioselectivity for most of the reactions was high, but was also found to be influenced by the structure of the diazo substrate and the chiral Rh(II) catalyst employed. The highest enantioselectivity for the reactions catalyzed by chiral Rh(II) carboxamidates was 69% and Rh_2(4*R*-MEOX)$_4$ was found to be the most effective. For the chiral Rh(II) carboxylate catalyzed reactions, the highest ee obtained was 75% and Rh_2(*S*-PTTL)$_4$ is the optimal catalyst. The method was applied toward the synthesis of a GABA analogue, (*R*)-β-benzyl-γ-aminobutyric acid.

1. Introduction

The γ-lactam moiety is found in many natural and non-natural, biologically active molecules,[1] as well as in many useful synthetic intermediates. Its widespread occurrence and use has spurred the interest of synthetic chemists to develop methods for the synthesis of γ-lactam derivatives.[2]

The Rh(II)-catalyzed intramolecular C–H insertion reaction of diazoamides for the preparation of chiral, non-racemic γ-lactams has not been as extensively investigated compared to the Rh(II)-catalyzed asymmetric C–H insertion of diazoacetates to form γ-lactones. However, it has been shown that chiral non-racemic γ-lactams were accessible via Rh(II)-catalyzed intramolecular C–H insertion reaction of tertiary diazoamides. For example, an ee of γ-lactams as high as 98% was realized in the Rh(II)-catalyzed C–H insertion of chiral ester diazoanilides.[3a] Further, the chiral Rh(II)-catalyzed reaction of ester diazoanilides[4a,b] and diazoamides[4c,d] yielded γ-lactams with ee up to 81% and 91%, respectively.

Furthermore, it is also clear that the efficiency for γ-lactam formation is often undermined by the poor regio- and chemoselectivity of the reaction of the diazoamides and, consequently, much effort has been directed at carefully designing diazoamides wherein one of the *N*-substituents of the tertiary diazoamide unit is unreactive toward the Rh(II)-carbenoid intermediate, with the aim of promoting C–H insertion at the desired *N*-substituent. Several *N*-protecting groups [e.g., *N*-(2,4,6-trimethylbenzyl),[2b] *N*-(*p*-methoxyphenyl),[3] *N*-(*p*-nitrophenyl),[4a,b] *N*-*tert*-butyl[4c,d]] have been explored and some have been evaluated in asymmetric C–H insertion reaction of diazoamides.[5]

We recently reported the intramolecular C–H insertion of *N*-[bis(trimethylsilyl)methyl]diazoamides and demonstrated that the *N*-[bis(trimethylsilyl)methyl] (*N*-BTMSM) group is a practical conformational control element,[6a,b] which promoted good to excellent site-selectivity in the reaction of *N*-(BTMSM)diazoamides. Moreover, we have shown[7] that the C–H insertion reaction in 5-*N*-(BTMSM)diazoamide derivatives of

* Corresponding author. Tel.: +1 306 585 4767; fax: +1 306 337 2409; e-mail: andrew.wee@uregina.ca

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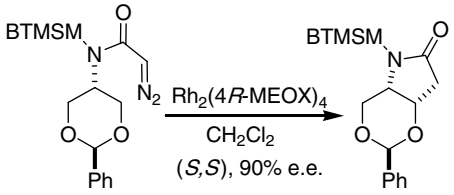
doi:10.1016/j.tetasy.2005.12.020

1,3-dioxanes, catalyzed by homochiral Rh(II)-carboxamidates, gave bicyclic-γ-lactams in high yield and high enantioselectivity (Eq. 1).



(1)

The influence of the *N*-BTMSM group on the enantioselectivity of the C–H insertion reaction in conformationally flexible *N*-arylalkyl, *N*-BTMSM diazoamides has not yet been reported. Here, we describe the results of our studies on the reaction of *N*-BTMSM diazoacetamides and α-carboalkoxy diazoacetamides catalyzed by chiral Rh(II) carboxamidates and Rh(II) carboxylates. It was found that the chemoselectivity of the reaction, in general, ranges from good to excellent. Regioselectivity, however, was found to be catalyst dependent and $Rh_2(4R\text{-MEOX})_4$ and $Rh_2(S\text{-PTTL})_4$ were identified as optimal catalysts herein.

2. Results and discussion

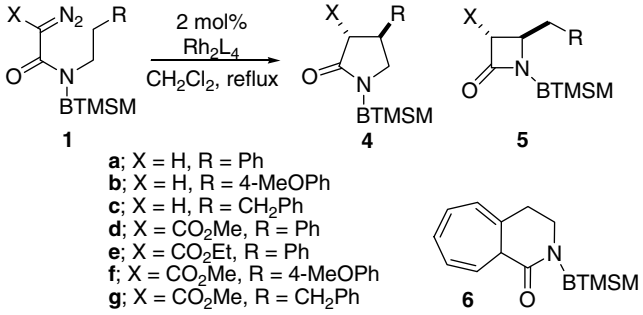
2.1. Preparation of diazo compounds 1b,e,f

The *N*-arylalkyl-*N*-(BTMSM)diazoamides **1a**–**g** were used in this study. Diazoamides **1a**,**c**,**d**,**g** have previously been described[6a,b] with the exception of the diazoamides **1b**,**e**,**f**. The latter diazoamides were prepared (Scheme 1 and Fig. 1), using our established procedures,[6a,b] in good overall yields (74–85%).

Thus, acylation of the amine **2** (R = 4-MeOPh$(CH_2)_2$) with diketene followed by diazotization (MsN_3, DBU) of the crude keto amide gave the diazoamide **3** in 74% yield. Subsequent deacylation (aq THF, LiOH·H_2O) of **3** furnished **1b** (74%). Acylation of **2** (R = Ph$(CH_2)_2$) with ethyl diazomalonyl chloride gave **1e** (80%) and treatment of **2** (R = 4-MeOPh$(CH_2)_2$) with methyl diazomalonyl chloride afforded **1f** (85%).

2.2. Chiral Rhodium(II)-catalyzed reaction of compounds 1 and determination of the enantioselectivity and assignment of C-4 absolute configuration of γ-lactams

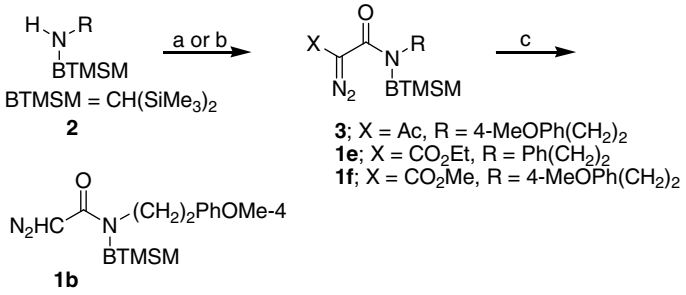
The intramolecular C–H insertion reaction of diazoamides **1a**–**g** was catalyzed by 2 mol % of chiral Rh(II) carboxamidates and Rh(II) carboxylates in dry dichloromethane (Eq. 2).



(2)

All products were readily separated by flash chromatography. The *N*-(BTMSM)-γ-lactams **4** were quite nonpolar and were not amenable to HPLC analysis using various Chiralcel® columns (e.g., OB and OD). Therefore, the γ-lactams **4** were chemically transformed to the more polar γ-lactams **7a**–**c** (Scheme 2).

Thus, for the γ-lactams **4a** and **c**[6a,b] the *N*-(BTMSM) group was oxidatively (CAN)[8] converted to the corresponding *N*-formyl derivative, which was then hydro-



Scheme 1. Preparation of *N*-BTMSM diazoamides **1b**,**e**,**f**. Reagents and conditions: (a) for **3**: (i) diketene, cat. DMAP, THF, rt; (ii) MsN_3, DBU, MeCN, rt; 74%, (b) $EtO_2CC(=N_2)COCl$ (**1e**, 80%) or $MeO_2CC(=N_2)COCl$ (**1f**, 85%), 2,6-lutidine, CH_2Cl_2, 0 °C, (c) LiOH·H_2O, THF–H_2O (1:1 v/v), rt; 74%.

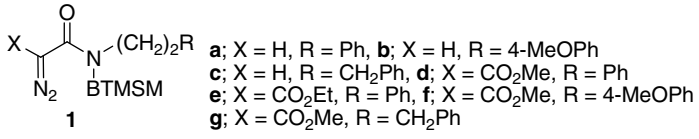
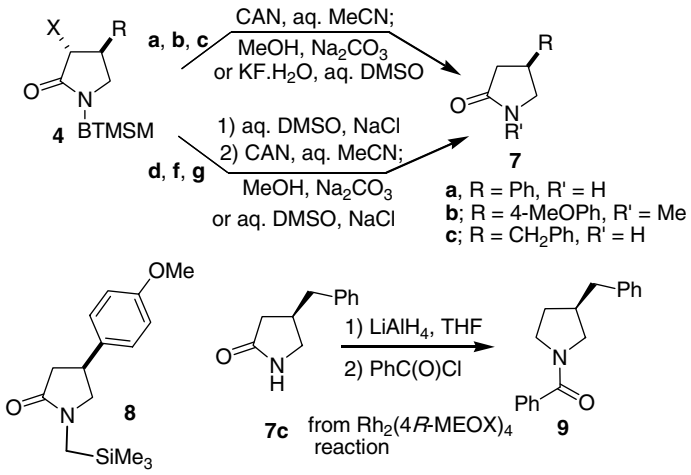


Figure 1. *N*-BTMSM diazoamides **1a**–**g**.



Scheme 2. Conversion of γ-lactams **4** to **7** and **9**.

lyzed under basic conditions (Na_2CO_3) to give **7a**[3a,9] and **7c**, respectively. With **4b**, double desilylation was achieved using potassium fluoride in hot, aqueous DMSO to furnish a 73% yield of **7b**. The ester lactams **4d** and **g** were subjected to Krapcho decarboxylation[10] followed by removal of the *N*-(BTMSM) group (CAN; Na_2CO_3) to afford γ-lactams **7a** (from **4d**[6a]) and **7c** (from **4g**[6a]), respectively. In the case of **4f**, decarboxylation (aq DMSO, NaCl) gave the desired **7b** and the mono-desilylated product **8**, and in a ratio of 1:4.3.

The sense of induction at the newly formed C-4 in γ-lactam **7a** was determined by comparison of the specific rotation of **7a** with that of the known[3a,9] (*S*)-4-phenyl-2-pyrrolidinone ($[\alpha]_D = +37.5$) and (*R*)-4-phenyl-2-pyrrolidinone ($[\alpha]_D = -37.5$). The sense of induction for compound **7b** was inferred from that of compound **7a**. For compound **7c**, the sense of induction at C-4 was determined via a chemical correlation approach. Thus γ-lactam **7c**, derived from the $Rh_2(4R\text{-MEOX})_4$-catalyzed reaction of **1c**, was reduced with lithium aluminium hydride to obtain the corresponding 4-benzylpyrrolidine, which was immediately treated with benzoyl chloride under Schotten–Bauman[11] conditions to obtain the known[12] benzamide **9** (Scheme 2). The sign of the specific rotation of synthetic **9**, $[\alpha]_D^{23} = -28.6$ (*c* 0.35, CH_2Cl_2), was the same as that reported in the literature for (*R*)-**9** ($[\alpha]_D = -57.4$ (*c* 0.76, CH_2Cl_2)). This indicated that the C-3 absolute configuration in synthetic **9** was *R*, which in turn, indicated that the C-4 absolute configuration was *R* in **7c** as well as in **4c**.

The enantioselectivity of the C–H insertion reaction for the formation of γ-lactams **4** was determined via HPLC analysis of compounds **7** using either a Chiralcel OB® (γ-lactams **7a** and **7c**) or AD® (γ-lactam **7b**) column. No attempts were made at determining the enantiomeric excesses of the β-lactam products **5** or the cycloheptatriene derivative **6**. The combined results are summarized in Table 1.

2.3. Regio- and chemoselectivity

The reaction of **1a**, catalyzed by the chiral Rh(II) carboxamidate catalysts, proceeded efficiently to give primarily **4a** with varying amounts of the cycloheptatriene **6**.[6a,b] The corresponding β-lactam **5a** was not detected. The ratio of **4a**:**6** was found to be dependent on the chiral Rh(II) carboxamidate catalyst employed. With $Rh_2(5R\text{-MEPY})_4$, $Rh_2(4R\text{-MEOX})_4$, and $Rh_2(4R\text{-MEAZ})_4$, **1a** reacted with excellent regio- and high chemoselectivity to afford the γ-lactam **4a** (entries 1–3). Only a small amount (3–6%) of the cycloaddition product **6** was formed. It is useful to note that achiral Rh(II) carboxamidate catalysts, such as $Rh_2(Cap)_4$, gave a 3.3:1[6b] ratio of **4a**:**6**, whereas the chiral Rh(II) carboxamidates exhibited a high degree of chemoselectivity (13–24:1 of **4a**:**6**). However, with $Rh_2(4S\text{-MACIM})_4$ and $Rh_2(4S\text{-MPPIM})_4$ (entries 4 and 5), **1a** yielded a significant amount of the cycloaddition product **6** along with the desired γ-lactam **4a**. The ratio of **4a**:**6** was 2–3.5:1, which was similar to that obtained with the achiral Rh(II) catalysts.[6b] The poor chemoselectivity observed with $Rh_2(MPPIM)_4$ and $Rh_2(MACIM)_4$ when compared to $Rh_2(5R\text{-MEPY})_4$, $Rh_2(4R\text{-MEOX})_4$, and $Rh_2(4R\text{-MEAZ})_4$ may be attributed to the steric size of the catalysts; both $Rh_2(MPPIM)_4$ and $Rh_2(MACIM)_4$ are bulkier catalysts. It is plausible that the steric bulk of these catalysts and the steric size of the *N*-BTMSM protecting group of the diazoamide result in an increase in steric congestion within the environment surrounding the metallocarbenoid centre. Therefore, it is reasonable to suggest that before the key C–H insertion reaction step, the bulky catalyst could have dissociated from the carbenoid carbon centre, which would result in the generation of a very reactive, achiral free carbene. The free carbene is expected to undergo C–H insertion and aromatic cycloaddition to form **4a** and **6**, respectively.

Compound **1b** (entry 6) was also investigated to determine whether the presence of an electron-donating methoxy group on the phenyl ring would promote the formation of the corresponding cycloheptatriene derivative over the γ-lactam **4b**. When **1b** was treated with $Rh_2(4R\text{-MEOX})_4$ only the γ-lactam **4b** was formed in high yield (83%); neither the β-lactam **5b** nor a cycloheptatriene derivative was detected. Compared to the phenylethyl system **1a** (entry 2) the reaction of **1b**

Table 1. Reaction of diazoamide **1a**–**g** catalyzed by homochiral Rh(II) catalysts

Entry	Diazoamide	$Rh_2L_4^*$[a]	Yield (%)[d]	Rel. yield (%)	C_4 config. of **7**
				4[e]:**5**:[e]**6**	ee (%)
1	**1a**	Rh_2(5*R*-MEPY)$_4$	87	93:0:7	**7a**, *R*, 38
2	**1a**	Rh_2(4*R*-MEOX)$_4$[b]	89	95:0:5	**7a**, *R*, 43
3	**1a**	Rh_2(4*R*-MEAZ)$_4$	82	96:0:4	**7a**, *R*, 34
4	**1a**	Rh_2(4*S*-MACIM)$_4$	86	67:0:33	**7a**, *S*,[i] 8
5	**1a**	Rh_2(4*S*-MPPIM)$_4$	93	78:0:22	**7a**, —, 0
6	**1b**	Rh_2(4*R*-MEOX)$_4$	83	100:0:0	**7b**, *R*, 69
7	**1c**	Rh_2(5*R*-MEPY)$_4$	90	100:0	**7c**, *R*,[j] 32
8	**1c**	Rh_2(4*R*-MEOX)$_4$	92	100:0	**7c**, *R*,[k] 43
9	**1d**	Rh_2(*S*-PTPA)$_4$	92	100:0:0	**7a**, *R*, 5
10	**1d**	Rh_2(*S*-PTV)$_4$	87	100:0:0	**7a**, *R*, 7
11	**1d**	Rh_2(*S*-PTTL)$_4$	80	71:29[f,g]:0	**7a**, *R*, 65
12	**1d**	Rh_2(*S*-PTTL)$_4$[c]	80	50:50:[g]0	**7a**, *R*, 75
13	**1d**	Rh_2(*S*-DOSP)$_4$	77	100:0:0	**7a**, nd, 9
14	**1d**	Rh_2(4*R*-MEAZ)$_4$	89	100:0:0	**7a**, *S*, 35
15	**1e**	Rh_2(*S*-PTPA)$_4$	92	100:0:0	nd
16	**1e**	Rh_2(*S*-PTV)$_4$	87	100:0:0	nd
17	**1e**	Rh_2(*S*-PTTL)$_4$	80	55:45:[h]0	nd
18	**1f**	Rh_2(*S*-PTTL)$_4$	82	90:10:0	**7b**, *R*, 51
19	**1g**	Rh_2(*S*-PTPA)$_4$	73	100:0	**7c**, *S*,[l] 24
20	**1g**	Rh_2(*S*-PTV)$_4$	90	85:15	**7c**, *S*,[l] 44
21	**1g**	Rh_2(*S*-PTTL)$_4$	75	56:44	**7c**, *S*,[m] 64

nd, Not determined.

[a] All the reactions were conducted in refluxing dry dichloromethane, under argon, using 2 mol % of the chiral Rh(II) catalysts.

[b] The Rh_2(4*S*-MEOX)$_4$-catalyzed reaction gave the 43% ee of **7a**.

[c] Reaction was conducted in dry toluene at 50 °C (oil bath).

[d] Isolated yield.

[e] The C2–C3 trans stereochemistry in compounds **4d**–**g** was assigned based on the H-3 doublet, $J_{3,4} = 9$ Hz. The C2–C3 *trans* stereochemistry in β-lactam product **5d**,**e** was assigned based on the vicinal coupling constant, $J_{3,4}$, of 3 Hz.[6b]

[f] Compounds **4d** and **5d** are run very close together during TLC. Careful separation by column chromatography afforded an analytical sample of **5d** for characterization purposes.

[g] ^{1}H NMR analysis of the crude reaction mixture after prefiltration over a short pad of silica gel to remove the Rh(II) catalyst. Ratio of **4e**:**5e** was based on the integration of the double doublet centred at δ 2.68 due to one of the benzylic protons of **5d** and the double doublet at δ 3.42 due to H-5 in **4d**.

[h] ^{1}H NMR analysis of the crude reaction mixture after prefiltration over a short pad of silica gel to remove Rh(II) catalyst. Ratio of **4e**:**5e** was based on the integration of the double doublet centred at δ 2.76 due to one of the benzylic protons of **5e** and the double doublet at δ 3.40 due to H-5 in **4e**.

[i] Absolute configuration assigned based on comparison of sign of specific rotation to **7a**.

[j] Absolute configuration was inferred from data obtained for **7c** derived from **4c** (entry 8) via comparison of $[\alpha]_D$.

[k] **7c** derived from **4c** (entry 8) $[\alpha]_D^{23} = +4.4$ (*c* 1.30, CH_2Cl_2).

[l] Absolute configuration was inferred from data obtained for **7c** derived from **4c**,**g** via comparison of $[\alpha]_D$ of **7c**.

[m] **7c** derived from **4g**, $[\alpha]_D^{23} = -3.1$ (*c* 0.80, CH_2Cl_2).

showed excellent regio- and chemoselectivity. The presence of an electron-donating *p*-methoxy group in the phenyl ring appears to be especially conducive for C–H insertion at the benzylic position even though cycloaddition of the metallocarbenoid to the electron-rich phenyl moiety is also feasible.

Diazoacetamide **1c** is the homologue of **1a**; however, the Rh_2(5*R*-MEPY)$_4$- and Rh_2(4*R*-MEOX)$_4$-catalyzed C–H insertion reaction of **1c** proceeded with high regioselectivity and excellent chemoselectivity to give only **4c** (compare entries 7 and 8–1 and 2). This outcome was also in accord with the results obtained when achiral Rh(II) catalysts were used.

The reaction of the α-carbalkoxy substituted diazoacetamides **1d**–**g** catalyzed by Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-PTV)$_4$, Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-DOSP)$_4$, and Rh_2(4*R*-MEAZ)$_4$ was studied next. Although Rh_2(4*R*-MEAZ)$_4$ is classified as a Rh(II) carboxamidate, it has been shown to possess higher reactivity compared to its relatives,[13] such as Rh_2(5*R*-MEPY)$_4$ and Rh_2(4*R*-MEOX)$_4$, and is effective for the decomposition of the ester diazoamides. We tested Rh_2(4*R*-MEAZ)$_4$ on **1d** to examine its efficiency in catalyzing the C–H insertion reaction and to ascertain the level of asymmetric induction that can be achieved with this catalyst.

With **1d**, all the catalysts with the exception of Rh_2(*S*-PTTL)$_4$ were found to provide excellent regioselectivity to give only the γ-lactam **4d** (entries 9, 10, 13, and 14). Further, in the case of Rh_2(4*R*-MEAZ)$_4$, the presence of an α-substituent on the metallocarbenoid carbon suppressed the aromatic cycloaddition pathway, which would have led to the formation of the corresponding cycloheptatriene compound (compare entries 3 and

14). With Rh_2(*S*-PTTL)$_4$, the closely moving γ-lactam **4d** and the β-lactam **5d** were formed[14] in an overall yield of 80%, and in a ratio of 2.4:1 (entry 11). More surprisingly, when the Rh_2(*S*-PTTL)$_4$-catalyzed reaction of **1d** was repeated in toluene[15] (50 °C), the metallocarbenoid reaction showed no regioselectivity in the C–H insertion reaction. Although a high overall yield of **4d** and **5d** was obtained, the ratio of **4d**:**5d** was 1:1 (entry 12). The results from **1d** prompted us to study the reaction of **1e** catalyzed by Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-PTV)$_4$, and Rh_2(*S*-PTTL)$_4$ in refluxing dichloromethane to assess whether a slight change from an *O*-methyl to an *O*-ethyl group in the diazomalonyl unit would affect the regioselectivity of the reaction.

We found that with Rh_2(*S*-PTPA)$_4$ and Rh_2(*S*-PTV)$_4$ (entries 15 and 16), the reaction of **1e** proceeded very efficiently and with excellent regioselectivity to afford only the γ-lactam **4e**. Again, Rh_2(*S*-PTTL)$_4$ behaved anomalously in this trio of catalysts; a 1.2:1 ratio of an inseparable mixture of **4e**:**5e** was obtained in high overall yield. Compared to the results of **1d** (entry 11), it is clear that with Rh_2(*S*-PTTL)$_4$ a small structural change in the ester *O*-alkyl group (OMe→OEt) of the diazomalonyl unit had a detrimental effect on the regioselectivity of the reaction (compare entries 11 and 17). It is also interesting to note that the regioselectivity obtained in this case is comparable to the result from the Rh_2(*S*-PTTL)$_4$-catalyzed reaction of **1d** in toluene (compare entries 12 and 17). The reactions of **1f**,**g** proved to be interesting. As was observed in the reaction of **1b** (entry 6), a *p*-methoxy substituent on the phenyl moiety promoted metallocarbenoid insertion exclusively at the benzylic position. It was surmised that the regioselectivity of the C–H insertion reaction in **1d** could be improved upon through the incorporation of a methoxy group on the phenyl ring. This notion was confirmed through the Rh_2(*S*-PTTL)$_4$-catalyzed reaction of **1f**, which afforded a 9:1 ratio of **4f**:**5f** (compare entries 11 and 18).

The reaction of **1g** (homologue of **1d**) catalyzed by chiral Rh(II) carboxylates was also interesting in light of the results obtained for **1d** (compare entries 9, 10, and 11 with 19, 20, and 21). With Rh_2(*S*-PTPA)$_4$, **1g** gave only the γ-lactam **4g** and this outcome was identical to the result obtained for **1d** (compare entries 9 and 19). The Rh_2(*S*-PTTL)$_4$-catalyzed reaction of **1g** afforded a mixture of **4g** and **5g** as was in the case of **1d** (compare entries 11 and 21). However, the regioselectivity of the reaction was poor; the ratio of **4g**:**5g** was 1.2:1. Unlike **1d**, the Rh_2(*S*-PTV)$_4$-catalyzed reaction of **1g** gave a 5.5:1 ratio of **4g**:**5g** (compare entries 10 and 20). The reasons for the decrease in regioselectivity for Rh_2(*S*-PTTL)$_4$ and especially Rh_2(*S*-PTV)$_4$ accompanying a very small change in chain length is not well understood at this time, but may be related to the overall steric interplay of the N-substituent in **1d** with the chiral carboxylate ligands in the transition states for C–H insertion. The data showed that as the size of steric crowding in the carboxylate ligand (Bn < *i*-Pr < *t*-Bu) of the Rh(II) catalysts increases, there is an increasing tendency for β-lactam formation.

2.4. Enantiomeric excess and absolute configuration of γ-lactams 4a–d,f,g

The highest enantioselectivity observed for the reaction of **1a** was with Rh_2(4*R*-MEOX)$_4$ where a 43% level of asymmetric induction was realized (entry 2). Both Rh_2(5*R*-MEPY)$_4$ and Rh_2(4*R*-MEAZ)$_4$ were provided nearly the same degree of asymmetric induction (entries 1 and 3), but were obviously inferior to Rh_2(4*R*-MEOX)$_4$. The poorest enantioselectivity was observed for Rh_2(MPPIM)$_4$ and Rh_2(MACIM)$_4$ (entries 4 and 5), in which the former catalyst provided a racemic mixture of **7a**. However, the reaction of **1b** with the optimal catalyst, Rh_2(4*R*-MEOX)$_4$, gave the best result wherein a respectable 69% level of asymmetric induction was realized (entry 6). The lack of asymmetric induction observed for the Rh_2(4*S*-MACIM)$_4$ and Rh_2(4*S*-MPPIM)$_4$ (entries 4 and 5) lends further support to the notion that the bulky, chiral Rh(II) catalysts and the carbenoid carbon were not closely associated with each other during the key C–H insertion reaction step leading to the formation of γ-lactam **4a**.

Modest enantioselectivity was obtained for the reaction of **1c** (entries 7 and 8); the ees were comparable to the enantioselectivity obtained for the Rh_2(5*R*-MEPY)$_4$ and Rh_2(4*R*-MEOX)$_4$-catalyzed reaction of **1a** (entries 1 and 2). It has also been documented[3a,4d,16] that the type of solvent has an effect on the stereoselectivity of Rh(II)-carbenoid mediated reactions. Ether-type solvents were found to be useful in enhancing the enantioselectivity of the C–H insertion reaction without adversely affecting the catalytic efficiency of the Rh(II) catalyst. Further, a recent study[4d] showed that ether type solvents were especially conducive for achieving high enantioselectivity in the Rh_2(4*R*-MEOX)$_4$-catalyzed reaction of *N*-(benzyloxyethyl),*N*-(*tert*-butyl)-α-diazoacetamide.

Encouraged by these results, we studied the Rh_2(4*R*-MEOX)$_4$-catalyzed reaction of **1c** in refluxing dry diethyl ether, tetrahydrofuran (THF), dimethoxyethane (DME), and 1,4-dioxane to determine whether any improvement in enantioselectivity of the reaction could be realized. In general, a high yield (96–99%) of the product **4c** was obtained, but the ees of the reactions were disappointingly lower than that obtained in dichloromethane (entry 8). Interestingly, the ee for **7c** (**4c**) fell into two groups; the lower boiling ether and THF gave lower but very similar ee (ether, 15%; THF, 17%) and the higher boiling solvents DME and 1,4-dioxane gave slightly higher ees (DME, 24%; 1,4-dioxane, 23%).[17]

The sense of induction at the C-4 stereocentre in the γ-lactams **7a**,**b**,**c** was found to be *R* when an *R*-configurated catalyst was used and *S* when an *S*-configurated catalyst was utilized.

In the C–H insertion reaction of **1d** catalyzed by chiral Rh(II) carboxylates and conducted in dichloromethane, Rh_2(*S*-PTTL)$_4$ exhibited the highest enantioselectivity of 65% (entry 11). The ee of the reaction was higher (75%) when toluene was used as the solvent (entry 12).

Enantiocontrol was, however, very poor for Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-PTV)$_4$, and Rh_2(*S*-DOSP)$_4$ (entries 9, 10, and 13). The enantioselectivity of the reaction of **1f** with Rh_2(*S*-PTTL)$_4$ depreciated significantly when compared to **1d** (entry 11), which indicated that the presence of the electron-donating methoxy group was disadvantageous for enantiocontrol. The sense of induction at C-4 in compounds **7a**,**b** for the reactions catalyzed by the *S*-configurated Rh(II) carboxylates was *R*.

The Rh_2(4*R*-MEAZ)$_4$-catalyzed reaction of **1d** provided a 35% ee of **7a** (entry 14). It is useful to note that the level of induction at C-4 is almost identical to the result obtained for the Rh_2(4*R*-MEAZ)$_4$-catalyzed reaction of **1a** (entry 3). Interestingly, the sense of induction at C-4 for the Rh_2(4*R*-MEAZ)$_4$-catalyzed reaction was opposite to that realized with Rh_2(*S*-PTTL)$_4$ (compare entries 11 and 14) as well as that obtained for **1a** (compare entries 3 and 14).

Among the three Rh(II) carboxylate catalysts tested against **1g**, Rh_2(*S*-PTTL)$_4$ provided the highest enantioselection at C-4 (64% ee) in the formation of **4g** (entry 21). The enantioselectivity achieved in the Rh_2(*S*-PTPA)$_4$- and Rh_2(*S*-PTV)$_4$-catalyzed reaction were also substantially higher than that obtained with **1d** (compare entries 19 and 20 to entries 9 and 10). The sense of induction at C-4 in **7c** was determined as *S* for the *S*-configurated Rh(II) carboxylate catalysts.

2.5. Synthesis of β-benzyl-γ-aminobutyric acid 10

The *N*-BTMSM-γ-lactams are useful starting materials that can be readily transformed into biologically active compounds. To demonstrate this concept, we synthesized β-benzyl-γ-aminobutyric acid **10** from the γ-lactam **4c** (Scheme 3). It is well documented that β-aryl-γ-aminobutyric acid, typified by (*R*)-(−)-γ-amino-β-(4-chlorophenyl)butyric acid **11a** [(*R*)-Balcofen] and (*R*)-(−)-γ-amino-β-(phenyl)butyric acid **11b**, are clinically important agonists that act on $GABA_B$-receptors;[18] (*R*)-balcofen being the most potent and selective agonist. These types of compounds have been shown to possess a range of physiologically important properties such as antispasticity, anti-epileptic, anti-hypertensive, anti-asthmatic, and analgesic activities and, therefore, have potential use in therapeutic applications. As a result, there is much interest directed at the synthesis of β-aryl-γ-aminobutyric acid.[19] In contrast, less attention has been paid to the synthesis of β-arylmethyl-γ-aminobutyric acid, exemplified by **10**, which can be considered as the β-side chain homologue of **11**. The synthesis of compounds of type **10** has been described in four patents,[20] and compounds **10** were claimed to possess similar biological activities to those of **11**.

The preparation of **10** was readily achieved starting from **4c** (43% ee). N-Deprotection of **4c** (CAN; Na_2CO_3, MeOH) yielded **7c** as a solid; recrystallization of **7c** from petroleum ether/ethyl acetate slightly improved its ee to 47% (50% yield of recrystallized **7c**). Hydrolysis of **7c** using aqueous 6 M HCl at reflux furnished **10** as its hydrochloride salt. Subsequent purification of **10**·HCl on Dowex 50 × 2–400 (H^+) afforded the amino acid (*R*)-**10** {mp: 169–169.6 °C; $[\alpha]_D^{22}$ + 6.25 (*c* 1.20, MeOH)}.

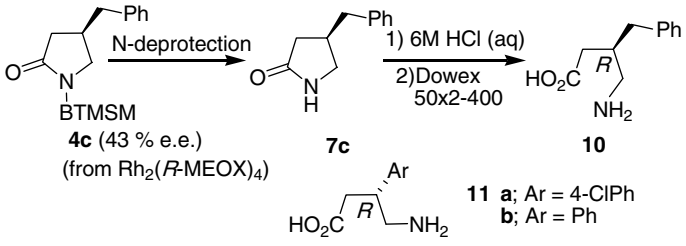
3. Summary

In summary, we have found that the intramolecular C–H insertion reaction of the diazoacetamides **1a**–**c** catalyzed by chiral Rh(II) carboxamidates proceeded with excellent regioselectivity to afford good to high yields of γ-lactams **4**. However, the chemoselectivity of the reaction was found to be catalyst dependent; the hindered Rh(II) carboxamidate catalysts Rh_2(4*R*-MACIM)$_4$ and Rh_2(4*R*-MPPIM)$_4$ showed poor chemoselectivity. The chiral Rh(II) carboxylate catalyzed reaction of the diazoamides **1d**–**g** proceeded with excellent chemoselectivity, but regioselectivity was influenced by the type of catalyst used. Rh_2(*S*-PTTL)$_4$ showed a consistent pattern for promoting β-lactam **5** formation. Enantioselectivity up to 69% was realized with the Rh(II) carboxamidates, with Rh_2(4*R*-MEOX)$_4$ as the best catalyst in the group. For the Rh(II) carboxylates, asymmetric induction up to 75% were achieved; Rh_2(*S*-PTTL)$_4$ was found be the best catalyst, but its effectiveness is tempered by the poor regioselectivity obtained for the C–H insertion reaction. The utility of the N-BTMSM-γ-lactams in synthesis was demonstrated by the facile conversion of (*R*)-**4c** to a GABA analogue, (*R*)-β-benzyl-γ-aminobutyric acid (**10**, 47% ee). Studies directed at improving the enantioselectivity of the reaction of *N*-BTMSM diazoamides and the use of the application of the method in natural product synthesis are ongoing.

4. Experimental

4.1. General

Only diagnostic absorptions in the infra-red spectrum are reported. ^1H and ^{13}C NMR spectra were



Scheme 3. Synthesis of (*R*)-**10**.

recorded in $CDCl_3$, unless stated otherwise, using either a Bruker 200 MHz QNP or Varian Mercury 300 MHz NMR spectrometer. Tetramethylsilane ($\delta_H = 0.00$) and the $CDCl_3$ resonance ($\delta_C = 77.0$) were used as internal references. Reaction progress was monitored by thin-layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminium backed sheets. Air and moisture sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Chromatographic purification implies flash chromatography, which was performed on Merck silica gel 60 (230–400 mesh). Optical rotations were measured, at the Na_D line, on an Optical Activity (AA-5) polarimeter. HPLC analysis of compounds was performed using a Waters 600 pump equipped with a Waters 2487 UV detector ($\lambda = 254$ nm) and controlled by PC workstation running the Millenium32® program; enantiomeric separation was achieved using either a Chiralcel® OB or AD column (1.5 mm × 250 mm) using hexane/2-propanol (90:10 or 95:5 v/v) as eluent, and a flow rate of 1.2 mL/min. Dichloromethane, 1,4-dioxane, dimethoxyethane, and acetonitrile were dried by distillation from calcium hydride. THF and diethyl ether were dried by distillation from sodium using sodium benzophenone ketyl as indicator. Compounds **1a**,**c**,**d**,**g** and racemic **4a**,**c**,**d**,**g** have been reported[6a] previously.

4.2. *N*-Bis(trimethylsilyl)methyl-*N*-[2-(4-methoxyphenyl)ethyl]-α-diazoacetamide, 1b

N-(4-Methoxyphenethyl)bis(trimethylsilyl)methylamine was prepared in 54% yield from the alkylation of **2** (R = H, 637 mg, 3.63 mmol) with 4-methoxyphenethyl bromide (781 mg, 3.63 mmol) in dry DMF containing Na_2CO_3 (270 mg, 2.54 mmol) and NaI (150 mg, 1 mmol). IR: ν_{max} (neat) 1613, 1583 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.0$ (s, 18H, $2 \times SiMe_3$), 0.75 (br s, 1H, NH), 1.32 (s, 1H, $(Me_3Si)_2CH$), 2.55–2.90 (m, 4H, NCH_2, CH_2Ph), 3.80 (s, 3H, OMe), 6.81 (d, 2H, $J = 8.8$ Hz, Ph), 7.12 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR (50.3 MHz) $\delta = 0.70$, 35.7, 39.7, 55.2, 55.6, 113.8, 129.6, 132.3.

Amine **2** (R = 4-MeOPh$(CH_2)_2$, 300 mg, 0.97 mmol) was treated with diketene (122 mg, 0.12 mL, 1.45 mmol) in dry THF containing DMAP (24 mg, 0.194 mmol) to give the crude acetoacetamide (381 mg), which was not purified but subjected to diazotization with methanesulfonyl azide (235 mg, 1.94 mmol) in dry acetonitrile containing DBU (295 mg, 0.29 mL, 1.94 mmol) to give **3** (330 mg, 81%). IR: ν_{max} (neat): 1721, 1658, 1626 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.14$ (s, 18H, $2 \times SiMe_3$), 2.18 (br s, 1H, $(Me_3Si)_2CH$), 2.30 (s, 3H, Me), 2.83 (t, 2H, $J = 8.4$ Hz, CH_2), 3.40 (t, 2H, $J = 8.4$ Hz, NCH_2), 3.78 (s, 3H, OMe), 6.84 (d, 2H, $J = 8.8$ Hz, Ph), 7.08 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR (50.3 MHz) $\delta = 0.60$, 26.9, 34.0, 45.4, 56.2, 65.9, 113.9, 114.1, 128.5, 129.7, 158.4; HRMS: calcd for $C_{20}H_{33}N_3O_3Si_2$ (M^+) 419.2060, found 419.2059.

Compound **3** (330 mg, 0.79 mmol) was dissolved in 1:1 v/v THF–H_2O (16 mL) and a solution of $LiOH \cdot H_2O$ (118 mg, 2.75 mmol) in H_2O (0.5 mL) was added. The mixture was stirred at rt and reaction progress was closely monitored by TLC. After 3 h, the reaction mixture was evaporated to remove THF, saturated NH_4Cl was added and the aqueous mixture was extracted thoroughly with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water, dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by chromatography to give **1b** (220 mg, 74%). IR: ν_{max} (neat): 3067, 2102, 1697, 1606 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.12$ (s, 18H, $2 \times SiMe_3$), 1.94 (br s, 1H, $(Me_3Si)_2CH$), 2.65–2.90 (m, 2H, CH_2), 3.30–3.10 (m, 2H, NCH_2), 3.80 (s, 3H, OMe), 4.95 (s, 1H, CHN_2), 6.88 (d, 2H, $J = 8.8$ Hz, Ph), 7.10 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR (50.3 MHz) $\delta = 0.70$, 34.1, 46.0, 46.9, 54.6, 55.2, 114.2, 129.9, 129.7, 158.4; HRMS: calcd for $C_{17}H_{28}N_3O_2Si_2$ (M−15) 362.1720, found 362.1718.

4.3. General procedure for the preparation of α-carboalkoxy-α-diazoacetamides 1e,f

The appropriate secondary amine **2** (R = Ph$(CH_2)_2$ or 4-MeOPh$(CH_2)_2$) (1.0 mmol) was dissolved in dry CH_2Cl_2 (3 mL) under Ar. 2,6-Lutidine (2.0 mmol) was added to the solution and the mixture was cooled to 0 °C. The appropriate diazomalonyl chloride (1.5 mmol) in dry CH_2Cl_2 (3 mL) was then transferred to the reaction mixture via cannula. The reaction was stirred at 0 °C and then at rt. After 2 h, it was washed successively with saturated $NaHCO_3$, H_2O, and then saturated NaCl. The organic layer was dried (Na_2SO_4), the filtered solution was concentrated in vacuo, and the residue was purified by flash chromatography.

4.4. *N*-Bis(trimethylsilyl)methyl-*N*-phenethyl-α-carboethoxy-α-diazoacetamide, 1e

Yield: 80%; IR: ν_{max} (neat): 3064, 3027, 2123, 1709, 1618 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.13$ (s, 18H, $2 \times SiMe_3$), 1.30 (t, 3H, $J = 8.0$ Hz, CO_2CH_2Me), 2.08–2.24 (br s, 1H, $(Me_3Si)_2CH$), 2.95 (t, 2H, $J = 8.0$ Hz, CH_2Ph), 3.48 (t, 3H, $J = 8.0$ Hz, NCH_2), 4.28 (q, 2H, $J = 8.0$ Hz, CO_2CH_2Me), 7.10–7.40 (m, 5H, Ph).; ^{13}C NMR (50.3 MHz) $\delta = 0.50$, 14.4, 35.1, 45.2, 55.2, 61.3, 126.5, 128.6, 138.1, 158.4, 162.8; HRMS: calcd for $C_{19}H_{30}N_3O_3Si_2$ (M−15) 404.1825, found 404.1820.

4.5. *N*-Bis(trimethylsilyl)methyl-*N*-[2-(4-methoxyphenyl)ethyl]-α-methoxycarbonyl-α-diazoactetanamide, 1f

Yield: 85%; IR: ν_{max} (neat): 2120, 1713, 1616 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.10$ (s, 18H, $2 \times SiMe_3$), 2.12 (br s, 1H, $(Me_3Si)_2CH$), 2.86 (t, 2H, $J = 7.9$ Hz, CH_2), 3.45 (t, 2H, $J = 7.9$ Hz, NCH_2), 3.80 (s, 6H, CO_2Me, OMe), 6.85 (d, 2H, $J = 8.8$ Hz, Ph), 7.12 (d, 2H, $J = 8.8$ Hz Ph). ^{13}C NMR (50.3 MHz) $\delta = 0.60$, 34.2, 45.1, 52.2, 55.2, 55.4, 114.0, 129.6, 130.1, 158.3, 163.3. HRMS: calcd for $C_{20}H_{33}N_3O_4Si_2$ (M−15) 420.1775, found 420.1774.

4.6. General procedure for chiral rhodium(II)-catalyzed reactions of diazoamides 1a–g

The appropriate chiral catalyst (2 mol %) in dry CH_2Cl_2 (3 mL) was refluxed at 45 °C under argon. A solution of the appropriate diazo compound in dry CH_2Cl_2 (2 mL) was added slowly, via cannula, to the refluxing solution. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was cooled to rt and concentrated in vacuo, and the residue purified by flash chromatography.

4.6.1. 1-Bis(trimethylsilyl)methyl-4-phenyl-2-pyrrolidinone, 4a. Yield: Rh_2(5*R*-MEPY)$_4$, 81%; Rh_2(4*R*-MEOX)$_4$, 85%; Rh_2(4*R*-MEAZ)$_4$, 79%; Rh_2(4*R*-MACIM)$_4$, 58%; Rh_2(4*R*-MPPIM)$_4$, 73%; Mp: 66.8–68.4 °C; IR: ν_{max} ($CDCl_3$): 3038, 1661, 1604 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.10$ (d, 18H, $2 \times SiMe_3$), 2.66 (dd, 1H, $J = 16.4$, 8.8 Hz, H-3′), 2.78 (dd, 1H, $J = 16.4$, 8.8 Hz, H-3), 3.10–3.24 (br s, 1H, $(Me_3Si)_2CH$), 3.32–3.60 (m, 1H, H-4), 3.44 (dd, 1H, $J = 15.9$, 7.8 Hz, H-5′), 3.70 (dd, 1H, $J = 15.9$, 7.8 Hz, H-5), 7.05–7.45 (m, 5H, Ph). HRMS: calcd for $C_{17}H_{29}NOSi_2$ (M^+) 319.1778, found 319.1783.

4.6.2. 1-Bis(trimethylsilyl)methyl-4-(4-methoxyphenyl)-2-pyrrolidinone, 4b. Yield: 83%; IR: ν_{max} (neat): 1677, 1613 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.01$ (s, 18H, $2 \times SiMe_3$), 2.55 (dd, 1H, $J = 16.5$, 9.5 Hz, H-3′), 2.78 (dd, 1H, $J = 16.5$, 9.5 Hz, H-3), 3.12–3.25 (br s, 1H, $(Me_3Si)_2CH$), 3.39 (dd, $J = 16.0$, 7.5 Hz, H-5′), 3.49 (ddd, 1H, $J = 15.5$, 8.7, 8.7 Hz, H-4), 3.72 (dd, 1H, $J = 16.0$, 7.6 Hz, H-5), 3.80 (s, 3H, OMe), 6.90 (d, 2H, $J = 8.8$ Hz, Ph), 7.16 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR (50.3 MHz) $\delta = 0.0$, 36.3, 36.9, 38.7, 55.3, 57.1, 114.2, 127.8, 133.3, 158.6, 172.3; HRMS: calcd for $C_{18}H_{31}NO_2Si_2$ (M^+) 349.1993, found 349.1896.

4.6.3. 1-Bis(trimethylsilyl)methyl-4-benzyl-2-pyrrolidinone, 4c. Yield: Rh_2(5*R*-MEPY)$_4$, 90%; Rh_2(4*R*-MEOX)$_4$, 92%; IR: ν_{max} (CH_2Cl_2 film): 3065, 1657 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.10$ (s, 18H, $2 \times SiMe_3$), 2.19 (dd, 1H, $J = 16.1$, 5.8 Hz, H-3′), 2.40–2.80 (m, 4H, CH_2Ph, H-4, H-3), 3.08 (br s, 1H, $(Me_3Si)_2CH$), 3.15 (dd, 1H, $J = 9.9$, 5.1 Hz, H-5′), 3.42 (dd, 1H, $J = 9.8$, 6.9 Hz, H-5), 7.05–7.40 (m, 5H, Ph). HRMS: calcd for $C_{17}H_{28}NOSi_2$ (M−15) 318.1709, found 318.1710.

4.6.4. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-phenyl-2-pyrrolidinone, 4d. Yield: Rh_2(*S*-PTPA)$_4$, 92%; Rh_2(*S*-PTV)$_4$, 87%; Rh_2(*S*-PTTL)$_4$, 44%; Rh_2(*S*-DOSP)$_4$, 77%; IR: ν_{max} (neat): 3063, 3030, 1742, 1633 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.10$ (s, 18H, $2 \times SiMe_3$), 2.90–3.12 (br s, 1H, $(Me_3Si)_2CH$), 3.42 (dd, 1H, $J = 9.8$, 7.7 Hz, H-5′), 3.50 (d, 1H, $J = 8.8$ Hz, H-3), 3.65 (s, 3H, CO_2Me), 3.64 (dd, 1H, $J = 9.8$, 8.7 Hz, H-5), 3.84 (ddd, 1H, $J = 8.8$, 8.7, 7.7 Hz, H-4), 7.10–7.45 (m, 5H, Ph). HRMS: calcd for $C_{18}H_{28}NO_3Si_2$ (M−15) 362.1607, found 362.1598.

4.6.5. 1-Bis(trimethylsilyl)methyl-3-ethoxycarbonyl-4-phenyl-2-pyrrolidinone, 4e. Yield: Rh_2(*S*-PTPA)$_4$, 92%; Rh_2(*S*-PTV)$_4$, 87%; Rh_2(*S*-PTTL)$_4$, 44%; IR: ν_{max} (neat): 3063, 3031, 1735, 1682 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.14$ (s, 18H, $2 \times SiMe_3$), 1.27 (t, 3H, $J = 8.0$ Hz, CO_2CH_2Me), 2.96–3.15 (br s, 1H, $(Me_3Si)_2CH$), 3.42 (dd, 1H, $J = 10.0$, 8.0 Hz, H-5′), 3.60 (d, 1H, $J = 10.0$ Hz, H-3), 3.78 (dd, 1H, $J = 10.0$, 8.0 Hz, H-4), 3.98 (dd, 1H, $J = 10.0$, 8.0 Hz, H-5), 4.20 (q, 2H, $J = 8.0$ Hz, CO_2 CH_2Me), 7.10–7.45 (m, 5H, Ph); ^{13}C NMR δ (50.3 MHz): 0.1, 14.1, 41.5, 41.7, 55.3, 61.5, 127.0, 127.5, 128.5, 129.0, 140.3, 167.4, 169.9; HRMS: calcd for $C_{19}H_{30}NO_3Si_2$ (M−15) 376.1764, found 376.1753.

For the Rh_2(*S*-PTTL)$_4$-catalyzed reaction, an inseparable mixture of the γ-lactam **4e** and the β-lactam **5e** was obtained. IR: ν_{max} (neat): 3063, 3031, 1755, 1734, 1685 cm^{-1}; ^{1}H NMR (β-lactam signals are within square brackets) (200 MHz) $\delta = 0.14$ (s, 18H, $2 \times SiMe_3$), [1.20 (t)] and 1.25 (t) (3H, $J = 7.2$ Hz, Me)(3H), [2.05 (br s)] and 3.00–3.10 (br s) (1H, $NCH(SiMe_3)_2$), [3.04 (dd, $J = 14.0$, 6.2 Hz, PhCH)], [3.40 (dd, $J = 14.0$, 6.2 Hz, PhCH)], 3.40 (dd, $J = 9.3$, 8.2 Hz, H-5), and 3.78 (dd, $J = 9.3$, 8.2 Hz, H-5′) (2H), [3.59 (d, $J = 2.3$ Hz)] and 3.61 (d, $J = 8.4$ Hz) (1H, H-3), 3.90–4.30 (m, 3H, H-4, OCH_2), 7.10–7.40 (m, 5H, PhH).

4.6.6. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-(4-methoxyphenyl)-2-pyrrolidinone, 4f. Yield: 74%; IR: ν_{max} (neat): 1742, 1682, 1613 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.10$ (m, 18H, $2 \times SiMe_3$), 3.13–2.94 (br s, 1H, $(Me_3Si)_2CH$), 3.41 (dd, $J = 14.6$, 8.9 Hz, H-5′), 3.58 (d, 1H, $J = 8.9$ Hz, H-3), 3.58–4.18 (m, 8H, H-4, H-5, OMe, CO_2Me), 6.89 (d, 2H, $J = 8.8$ Hz, Ph), 7.15 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR δ (50.3 MHz): 0.0, 37.5, 40.9, 51.7, 52.7, 55.3, 55.4, 113.9, 114.3, 128.1, 128.3, 159.1, 170.1; HRMS: cacld. For $C_{19}H_{30}NO_4Si_2$ (M−15) 392.1713, found 392.1704.

4.6.7. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-benzyl-2-pyrrolidinone, 4g. Yield: Rh_2(*S*-PTPA)$_4$, 73%; Rh_2(*S*-PTV)$_4$, 77%; Rh_2(*S*-PTTL)$_4$, 42%; IR: ν_{max} (neat): 3027, 1742, 1683 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.10$ (s, 18H, $2 \times SiMe_3$), 2.78 (d, 2H, $J = 7.3$ Hz, CH_2Ph), 2.94–3.17 (m, 3H, H-5′, $(Me_3Si)_2CH$, H-4), 3.21 (d, 1H, $J = 6.9$ Hz, H-3), 3.49 (dd, 1H, $J = 9.1$, 7.3 Hz, H-5), 3.63 (s, 3H, CO_2Me), 7.05–7.40 (m, 5H, Ph). HRMS: calcd for $C_{20}H_{33}NO_3Si_2$ (M−15) 376.1764, found 376.1765.

4.6.8. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-phenyl-2-azetidinone, 5d. Yield: 23%; IR: ν_{max} (neat): 3029, 1755, 1734 cm^{-1}; ^{1}H NMR (200 MHz) $\delta = 0.11$ (d, 18H, $2 \times SiMe_3$), 2.04 (s, 1H, $(Me_3Si)_2CH$), 2.76 (dd, 1H, $J = 14$, 8.2 Hz H-5′), 3.05 (dd, 1H, $J = 14$, 5.3 Hz, H-5), 3.62 (d, 1H, $J = 2.4$ Hz, H-3), 3.68 (s, 3H, CO_2Me), 4.07 (ddd, 1H, $J = 8.4$, 6.0, 2.2 Hz, H-4), 7.10–7.40 (m, 5H, Ph); ^{13}C NMR δ (50.3 MHz): −0.5, 0.1, 38.3, 38.6, 52.3, 57.8, 58.7, 127.0, 128.5, 128.6, 128.8, 135.2, 160.8, 162.1; HRMS: calcd for $C_{18}H_{28}NO_3Si_2$ (M−15) 362.1607, found 362.1577.

4.6.9. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-(4-methoxybenzyl)-2-azetidinone, 5f. Yield: 8%; IR:

ν_{max} ($CDCl_3$): 1750, 1734 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.15$ (s, 18H, $2 \times SiMe_3$), 2.10 (s, 1H, $(Me_3Si)_2CH$), 2.68 (dd, 1H, $J = 7.9$, 13.0 Hz, H-5′), 3.01 (dd, 1H, $J = 13.0$, 5.0 Hz, H-5), 3.60 (d, 1H, $J = 2.4$ Hz, H-3), 3.69 (s, 3H, OMe), 3.79 (s, 3H, CO_2Me), 3.97 (ddd, 1H, $J = 8.6$, 5.7, 2.4 Hz, H-4), 6.85 (d, 2H, $J = 8.8$ Hz, Ph), 7.10 (d, 2H, $J = 8.8$ Hz, Ph); ^{13}C NMR δ (50.3 MHz): −0.2, 0.0, 37.7, 38.3, 52.3, 55.2, 58.0, 58.7, 114.2, 128.1, 129.7, 158.6, 168.1; HRMS: calcd for $C_{19}H_{30}NO_4Si_2$ (M−15) 392.1713, found 392.1723.

4.6.10. 1-Bis(trimethylsilyl)methyl-3-methoxycarbonyl-4-(2-phenylethyl)-2-azetidinone, 5g. Yield: Rh_2(S-PTV)$_4$, 14%; Rh_2(S-PTTL)$_4$, 38%; IR: ν_{max} (neat): 3063, 1750, 1734 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.11$ (d, 18H, $2 \times SiMe_3$), 1.68–1.52 (m, 1H, H-5′), 2.15 (s, 1H, $(Me_3Si)_2CH$), 2.03–2.29 (m, 1H, H-5), 2.68 (t, 2H, $J = 8.0$ Hz, CH_2Ph), 3.41 (d, 1H, $J = 2.4$ Hz, H-3), 3.71 (s, 3H, CO_2Me), 3.82–3.58 (m, 1H, H-4), 7.0–7.40 (m, 5H, Ph); ^{13}C NMR δ (50.3 MHz): −0.2, −0.1, 31.9, 33.2, 37.8, 52.3, 57.1, 58.9, 126.4, 128.2, 128.6, 140.2, 160.8, 168.4; HRMS: calcd for $C_{19}H_{30}NO_3Si_2$ (M−15) 371.1764, found 371.1742.

4.6.11. 2-Bis(trimethylsilyl)methyl-2,3,4,9a-tetrahydro-1*H*-cyclohepta[*c*]pyridin-1-one, 6. Yield: Rh_2(5*R*-MEPY)$_4$, 6%; Rh_2(4*R*-MEOX)$_4$, 5%; Rh_2(4*R*-MEAZ)$_4$, 3%; Rh_2(4*R*-MACIM)$_4$, 28%; Rh_2(4*R*-MPPIM)$_4$, 21%; IR: ν_{max} ($CDCl_3$): 3026, 1633, 1622 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.10$ (s, 18H, $2 \times SiMe_3$), 2.40–2.72 (br s, 3H, H-4, $(Me_3Si)_2CH$), 3.20–3.62 (m, 2H, H-3), 4.10–4.30 (br s, 1H, H-10), 5.39 (dd, 1H, $J = 5.1$, 9.0 Hz, H-6), 5.99–6.04 (br s, 1H, H-5), 6.08–6.27 (m, 1H, H-7), 6.42–6.63 (m, 2H, H-8, H-9); ^{13}C NMR δ (50.3 MHz): 0.1, 30.9, 39.1, 45.5, 47.8, 118.4, 120.3, 122.4, 125.7, 129.8, 130.1, 132.8, 168.4. HRMS: calcd for $C_{17}H_{29}NOSi_2$ (M^+) 319.1788, found 319.1783.

4.7. General procedure for the preparation of 7a and 7c

To a mixture of either **4d** or **4g** (1.0 mmol) and NaCl (3.0 mmol) was added aqueous DMSO (4.0 mL, 3:1 v/v DMSO/H_2O). The mixture was heated at 150 °C (oil bath) under argon and the progress of the decarboxylation was monitored by TLC. After 28 h, the reaction mixture was cooled to rt and excess solid NaCl was added. The aqueous mixture was extracted with EtOAc (3×5 mL), washed with brine, and dried over Na_2SO_4. The residue was purified by flash chromatography to give **4a** or **4c**.

A solution of ceric(IV) ammonium nitrate (6.0 mmol) in distilled water (4 mL) was added, under argon, to a solution of the *N*-BTMSM γ-lactam **4a** or **4c** (1.0 mmol) in CH_3CN (8 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and at rt for 3 h. Sodium bisulfite was added to the mixture and the mixture was stirred at room temperature for an additional 20 min. The crude product was concentrated and the residue was extracted with EtOAc (3×5 mL). The combined organic layers were dried, filtered, and the solvent evaporated to give the crude product. Purification by flash chromatography yielded the *N*-formyl lactams. For *N-formyl-4-phenyl-2-pyrrolidinone* (85%): IR: ν_{max} (neat): 3060, 1744, 1696 cm^{-1}; ^1H NMR (200 MHz) $\delta = 2.77$ (dd, 1H, $J = 17.6$, 7.5 Hz, H-3′), 2.98 (dd, 1H, $J = 17.4$, 7.5 Hz, H-3), 3.54–3.75 (m, 2H, H-5′, H-4), 4.10–4.28 (m, 1H, H-5), 7.02–7.50 (m, 5H, Ph), 9.12 (s, 1H, CHO); ^{13}C NMR (50.3 MHz) $\delta = 36.9$, 39.6, 48.7, 126.5, 127.6, 129.0, 140.1, 159.8, 175.8. For *N-formyl-4-benzyl-2-pyrrolidinone* (85%): IR: ν_{max} (neat): 3061, 3027, 1750, 1695 cm^{-1}; ^1H NMR δ (200 MHz): 2.54–2.89 (m, 2H, H-4, H-3), 2.72 (d, 2H, $J = 8.8$ Hz, CH_2Ph), 2.73 (dd, 1H, $J = 18.5$, 7.8 Hz, H-3′), 3.38 (dd, 1H, $J = 12.6$, 5.8 Hz, H-5′), 3.78 (dd, 1H, $J = 12.6$, 5.8 Hz, H-5), 7.05–7.40 (m, 5H, Ph), 9.08 (s, 1H, CHO); ^{13}C NMR (50.3 MHz) $\delta = 33.2$, 38.2, 39.7, 46.9, 126.7, 128.6, 128.7, 138.0, 159.9, 175.8.

Sodium carbonate (1.5 mmol) was added to the *N*-formyl γ-lactams (1.0 mmol) in MeOH (3 mL). The mixture was stirred at room rt for 1 h. The mixture was concentrated and the residue was extracted with CH_2Cl_2 (3×5 mL), the combined organic layers were dried, filtered and evaporated. The residue was purified by flash chromatography to give either **7a** or **7c**.

4.7.1. 4-Phenyl-2-pyrrolidinone, 7a. Yield: 85%; IR: ν_{max} ($CDCl_3$): 3240, 3029, 1691 cm^{-1}; ^1H NMR (200 MHz) $\delta = 2.50$ (dd, 1H, $J = 16.3$, 9.5 Hz, H-3′), 2.75 (dd, 1H, $J = 16.3$, 9.5 Hz, H-3), 3.43 (dd, 1H, $J = 9.5$, 6.8 Hz, H-5′), 3.57–3.98 (m, 2H, H-4, H-5), 6.80–7.10 (br s, 1H, NH), 7.15–7.60 (m, 5H, Ph). ^{13}C NMR (50.3 MHz) $\delta = 38.0$, 40.2, 49.6, 126.7, 127.1, 128.8, 142.2, 177.9.

Compound **7a** derived from Rh_2(4*R*-MEOX)$_4$-catalyzed reaction product **4a** had $[\alpha]_D^{22} = -12.8$ (*c* 0.60, MeOH); lit.:[9] (*R*)-**7a**, $[\alpha]_D^{22} = -37.8$; (*S*)-**7a**, $[\alpha]_D^{22} = +37.5$.

Compound **7a** derived from: Rh_2(4*R*-MEPY)$_4$-catalyzed reaction product **4a** had $[\alpha]_D^{22} = -6.3$ (*c* 1.6, MeOH); Rh_2(4*R*-MEAZ)$_4$-catalyzed reaction product **4a** had $[\alpha]_D^{22} = -9.5$ (*c* 0.50, MeOH); Rh_2(4*R*-MACIM)$_4$-catalyzed reaction product **4a** had $[\alpha]_D^{22} = +2.7$ (*c* 0.90, MeOH); Rh_2(4*R*-MEAZ)$_4$-catalyzed reaction product **4d** had $[\alpha]_D^{22} = +16.0$ (*c* 0.63, MeOH); Rh_2(*S*-PTTL)$_4$-catalyzed reaction product **4d** had $[\alpha]_D^{22} = -20.0$ (*c* 0.40, MeOH).

HPLC analysis using Chiralcael OB® column eluting with hexane/2-propanol, 90:10 v/v: t_R (*R*)-**7a** = 9.20 min, t_R (*S*)-**7a** = 12.4 min.

4.7.2. 4-Benzyl-2-pyrrolidinone, 7c. Yield: 84%; Mp: 102.5–103.9 °C; IR: ν_{max} ($CDCl_3$): 3220, 3031, 1693 cm^{-1}; ^1H NMR (200 MHz) δ= 2.09 (dd, 1H, $J = 16.5$, 6.8 Hz, H-3′), 2.41 (dd, 1H, $J = 16.5$, 6.8 Hz, H-3), 2.62–2.87 (m, 1H, H-4), 2.74 (br s, 2H, CH_2Ph), 3.10 (dd, 1H, $J = 8.8$, 5.8 Hz, H-5′), 3.39 (dd, 1H, $J = 8.8$, 5.8 Hz, H-5), 6.78–6.99 (br s, 1H, NH), 7.05–7.40 (m, 5H, Ph). ^{13}C NMR (50.3 MHz) $\delta = 33.2$, 36.5, 40.3, 47.4, 126.3, 128.5, 128.6, 139.2, 178.3. HRMS: calcd for $C_{11}H_{13}NO$ 175.0997, found 175.1002.

HPLC analysis using Chiralcael OB® column eluting with hexane/2-propanol, 90:10 v/v: t_R (*R*)-**7c** = 11.5 min, t_R (*S*)-**7c** = 15.8 min.

4.7.3. 1-Methyl-4-(4-methoxyphenyl)-2-pyrrolidinone, 7b

4.7.3.1. From 4b. γ-Lactam **4b** (35 mg, 0.1 mmol) and powdered $KF{\cdot}2H_2O$ (28 mg, 0.3 mmol) were mixed in aqueous DMSO (4.0 mL, 10:1 v/v DMSO/H_2O). The mixture was refluxed at 170 °C (oil bath) under argon and the progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was cooled to rt, excess solid NaCl was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by flash chromatography. Yield of **7b**: 73%.

4.7.3.2. From 4f. γ-Lactam **4f** (105 mg, 0.41 mmol) and powdered NaCl (142 mg, 2.43 mmol) were mixed in aqueous DMSO (4.0 mL, 10:1 v/v DMSO/H_2O). The mixture was refluxed at 170 °C (oil bath) under argon and the progress of the reaction was monitored by TLC. After 19 h, the reaction mixture was cooled to rt, excess solid NaCl was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solution was filtered, concentrated, and purified by flash chromatography to give the desired **7b** (12 mg, 23%) and the mono-desilylated γ-lactam **8** (51 mg, 72%).

4.7.3.3. Compound 7b. IR: ν_{max} (neat): 1688, 1612 cm^{-1}; ^1H NMR (200 MHz) $\delta = 2.48$ (dd, 1H, $J = 16.8$, 8.4 Hz, H-3′), 2.88 (dd, 1H, $J = 16.8$, 8.4 Hz, H-3), 2.98 (s, 3H, NMe), 3.35 (dd, 1H, $J = 9.0$, 2.5 Hz, H-5′), 3.42–3.61 (m, 1H, H-4), 3.72 (dd, 1H, $J = 7.0$, 2.6 Hz, H-5), 3.78 (s, 3H, OMe), 6.87 (d, 2H, $J = 8.8$ Hz, Ph), 7.14 (d, 2H, $J = 8.8$ Hz, Ph). ^{13}C NMR (50.3 MHz) $\delta = 29.5$, 35.4, 38.9, 55.3, 56.9, 114.1, 127.7, 137.4, 158.5; HRMS: calcd for $C_{12}H_{15}NO_2$ (M^+) 205.1103, found 205.1102.

HPLC analysis using Chiralcael AD® column eluting with hexane/2-propanol, 95:5 v/v: t_R (*S*)-**7b** = 20.9 min, t_R (*R*)-**7b** = 23.1 min.

4.7.4. 4-(4-Methoxyphenyl)-1-(trimethylsilyl)methyl-2-pyrrolidinone, 8.

IR: ν_{max} (neat): 3062, 1684, 1603 cm^{-1}; ^1H NMR (200 MHz) $\delta = 0.10$ (s, 9H, $SiMe_3$), 2.53 (dd, 1H, $J = 15.6$, 8.5 Hz, H-3′), 2.79 (dd, 1H, $J = 15.6$, 8.5 Hz, H-3), 2.85 (s, 2H, Me_3SiCH_2), 3.37 (dd, 1H, $J = 9.6$, 6.0 Hz, H-5′), 3.43–3.62 (m, 1H, H-4), 3.70 (dd, 1H, $J = 9.6$, 6.0 Hz, H-5), 7.10–7.40 (m, 5H, Ph); ^{13}C NMR (50.3 MHz) $\delta = -1.7$, 34.1, 37.1, 38.2, 57.0, 126.7, 126.8, 128.7, 142.5, 172.7; HRMS: calcd for $C_{14}H_{20}NO_2Si$ (M−1) 246.1314, found 246.1317.

4.8. (*R*)-1-Benzoyl-3-benzylpyrrolidine, 9

$LiAlH_4$ (0.49 mmol) was suspended in dry THF (2 mL) and cooled to 0 °C under argon. To this was added 4-benzyl-2-oxopyrrolidine **7c** (from the Rh_2(4*R*-MEOX)$_4$ catalyzed reaction product **4c**) 34.0 mg, 0.19 mmol in dry THF (3 mL) via cannula. The mixture was stirred at rt for 15 min and refluxed for 24 h. The reaction mixture was cooled to 0 °C and 10% aqueous NaOH was added until all the solid component was dissolved. To this was added benzoyl chloride (3.0 mol equiv). The reaction mixture was stirred at rt for about 20 h. THF was evaporated and solid NaCl was added to the aqueous layer. It was then extracted with Et_2O (3 × 5 mL) and dried over Na_2SO_4. The residue was purified by flash chromatography (4:1 CH_2Cl_2/acetone). Yield: 67%; $[\alpha]_D^{22} = -28.6$ (*c* 0.35, CH_2Cl_2); lit.[12] $[\alpha]_D^{22} = -57.4$ (*c* 0.76, CH_2Cl_2); IR: ν_{max} (neat): 3059, 3026, 1628, 1575 cm^{-1}; ^1H NMR (200 MHz) $\delta = 1.50$–1.80 (m, 1H, H-4′), 2.19–1.88 (m, 1H, H-4), 2.35–2.89 (m, 3H, H-3, CH_2Ph), 3.22 (dd, 1H, $J = 18.0$, 8.4 Hz, H-5′), 3.30–3.70 (m, 2H, H-2′, H-5), 3.70–3.90 (m, IH, H-2), 6.95–7.60 (m, 10H, Ph). ^{13}C NMR (mixture of amide rotamers) (50.3 MHz) $\delta =$ [29.9] 32.0, [38.7] 39.2, [39.5] 41.2, [45.6] 49.1, [51.3] 54.5, 126.2, 127.0, 128.2, 128.4, 128.5, 128.6, 129.7, 136.8, 139.9, 169.7.

Compound **7c**, derived from Rh_2(4*R*-MEOX)$_4$-catalyzed reaction product **4c** had $[\alpha]_D^{22} = +2.3$ (*c* 1.10, CH_2Cl_2), gave (*R*)-**9**. Compound **7c** derived from the Rh_2(4*R*-MEPY)$_4$-catalyzed reaction product **4a** had $[\alpha]_D^{22} = +2.3$ (*c* 1.10, CH_2Cl_2), and from Rh_2(*S*-PTTL)$_4$-catalyzed reaction product **4g** had $[\alpha]_D^{22} = -3.1$ (*c* 0.8, CH_2Cl_2).

4.9. (*R*)-3-Benzyl-4-aminobutanoic acid, 10

A solution of γ-lactam (**7c**, 25 mg, 0.14 mmol) in 6 M aqueous HCl solution (3 mL) was heated at reflux for 2.5 h. Upon cooling, the green solution was washed once with EtOAc (3 mL). The aqueous layer was then concentrated under reduced pressure. The resulting residue was applied to ion exchange chromatography (Dowex 50 × 2–400 ion exchange resin, 200–400 mesh) eluted with water and then 5% ammonium hydroxide solution. Evaporation of water gave **10** as a white solid (25 mg, 91%). Mp: 169–169.6 °C; $[\alpha]_D^{22} = +6.25$ (*c* 1.2, MeOH); IR 3416 (br), 1636 cm^{-1}; ^1H NMR (D_2O, 300 MHz) $\delta = 2.19$ (dd, 2H, $J = 7.4$, 1.5 Hz, 2H-2), 2.230–2.38 (m, 1H, H-3), 2.60 (d, 2H, $J = 7.2$ Hz, $PhCH_2$), 2.84 (dd, 1H, $J = 13.0$, 5.4 Hz, H-4), 2.92 (dd, 1H, $J = 13.0$, 5.4 Hz, H-4′), 7.15–7.25 (m, 3H, Ph), 7.25–7.35 (m, 2H, Ph); ^{13}C NMR (D_2O, 75 MHz) $\delta =$ 36.0, 37.9, 40.1, 43.2, 126.9, 128.9, 129.5, 139.2, 180.6. HRMS: calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1104.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council, Canada and the University of Regina for financial support. We thank Marcela Valenzuela and Professor Michael P. Doyle for initial chiral HPLC analysis of compound **7b**.

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