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# The $Rh_2(OAc)_4$ Catalysed C–H Insertion In Chiral Ester Diazoanilides

Andrew G. H. Wee* and Baosheng Liu

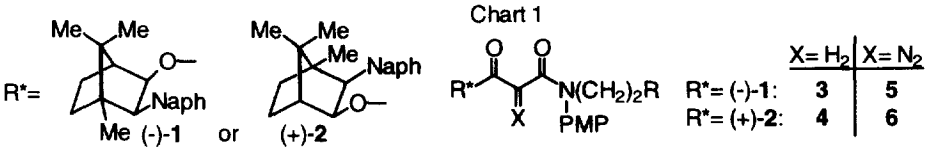
Department of Chemistry, University of Regina, Regina, Saskatchewan S4S 0A2, Canada

***Abstract:*** The $Rh_2(OAc)_4$ -catalysed C–H insertion reaction in chiral ester diazoanilides was investigated and was found to yield 4-substituted 2-pyrrolidinones with moderate to high e.e. (37-98 %) after decarbalkoxylation. Electronic effects were found to oppose steric effects in influencing the enantioselectivity of the reaction in N-arylethyl diazoanilides.

The synthetic utility of Rh(II) carbenoids, generated from the reaction of α-diazocarbonyl compounds with catalytic amounts of dirhodium(II) salts, is now well established.[1] In particular, the intramolecular Rh(II) carbenoid mediated C-H insertion reaction has emerged as a useful method for the facile construction of five membered carbocyclic and heterocyclic molecules. Recently, there has been a growing interest in the development of Rh(II) carbenoid mediated asymmetric C–H insertion for the synthesis of chiral non-racemic molecules, and two approaches have been investigated.[2] The first employs diazocarbonyl compounds possessing chiral auxiliary groups as exemplified by Taber's chiral cyclopentanone synthesis.[2a] Diastereoselectivities as high as 92% were obtained. It should be noted that removal of the chiral auxiliary from the product would result in an (net) enantioselective route to cyclic molecules. The second approach uses either chiral dirhodium(II) carboxylates[2b,c] or carboxamides[2d] to catalyse the cyclization of achiral diazocarbonyl compounds. However, the enantioselectivities of these reactions were found to vary with both the type of chiral Rh(II) catalyst and the diazocarbonyl compound. The most effective chiral catalysts developed to date are $Rh_2(5S/5R\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$[2d] and these were found to be especially useful for the cyclization of α-diazoacetates to give γ-lactones in high enantiomeric excess (91–97%).

The cyclization of diazoamides catalyzed by $Rh_2(5S/5R\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$ has been reported[3] to give 4-substituted-2-pyrrolidinones with e.e. in the range 58–78%. 2-Azetidinones (e.e. 20–80%) were also

Chart 1

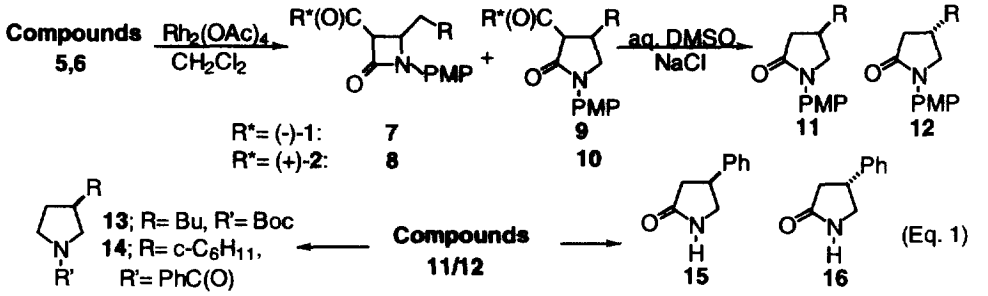



| | X= $H_2$ | X= $N_2$ |
|---|---|---|
| R*= (-)-**1**: | **3** | **5** |
| R*= (+)-**2**: | **4** | **6** |

**a**; R= n-$C_6H_{13}$, **b**; R= c-$C_6H_{11}$, **c**; R= Ph, **d**; R= 3,4-$(MeO)_2$Ph **e**; R= 2-MeOPh, **f**; R= 3-MeOPh, **g**; R= 3-$NO_2$Ph, **h**; R= 4-$NO_2$Ph. PMP= 4-MeOPh, Naph= 1-naphthyl

obtained as minor products. We report here the results of our investigation into the $Rh_2(OAc)_4$ catalyzed asymmetric C–H insertion reaction of chiral ester diazoanilides of type **5,6**, where R* is either (-)-**1** or (+)-**2** (Chart 1). This type of approach for the preparation of optically active 4-substituted 2-pyrrolidinones has not been reported before. Diazoanilides **5,6** were readily accessible from the N-substituted p-anisidines, which were

Chart 2




prepared by using established routes.[4] Coupling of the p-anisidines with malonic acid under Steglich conditions[5] gave the corresponding half acid (60–70%), which was esterified[5] with either (-)-**1**[2a] or (+)-**2** to give the ester anilides **3,4** (75–95%). Subsequent diazotization of **3,4** ($MsN_3$, KH, THF, 75–90%) gave the ester diazoanilides **5,6**. Only low yields of **5,6** were obtained when DBU was used as the base. The reaction of **6,7** with 5 mol% of $Rh_2(OAc)_4$ in dry $CH_2Cl_2$ was conducted either at RT (**5,6 a**) or at reflux (**5,6 b-h**) (Chart 2), and the results are shown in the Table.

**Table.** $Rh_2(OAc)_4$ Catalyzed Reaction of Diazoanilides **5,6**: Regioselectivity and Enatioselectivity.

| | | **7/8**[a] and **9/10**[a] | | | **11/12**[a] | | | |
|---|---|---|---|---|---|---|---|---|
| Entry | Compound | Yield (%)[b] | **7**:**9**[c] or **8**:**10**[c] | R | Yield(%)[d] | e.e (%)[e] | $[\alpha]_D$ | Config. |
| 1 | **5a** | 75 | 1:3.4 | Bu | 80 | 45 | +1.69 | R |
| 2 | **6a** | 69 | 1:4.3 | Bu | 92 | 47 | -2.10 | S |
| 3 | **5b** | 84 | 1:5 | c-$C_6H_{11}$ | 84 | 98 | +4.45 | S |
| 4 | **5c** | 96 | 1:23 | Ph | 98 | 79 | -10.5 | S |
| 5 | **6c** | 90 | 1:44 | Ph | 87 | 80 | +9.98 | R |
| 6 | **5d** | 85 | 0:100 | 3,4-$(MeO)_2$Ph | 84 | 50 | -15.2 | S |
| 7 | **6d** | 78 | 0:100 | 3,4-$(MeO)_2$Ph | 96 | 52 | +15.9 | R |
| 8 | **5e** | 74 | 1:1 | 2-MeOPh | 84 | 37 | +4.13 | S |
| 9 | **5f** | 90 | 0:100 | 3-MeOPh | 76 | 67 | -6.20 | S |
| 10 | **5g** | 82 | n.d.[f] | 3-$NO_2$Ph | 70 | 77 | -5.88 | S |
| 11 | **6h** | 76 | 0:100 | 4-$NO_2$Ph | 80 | 75 | +4.83 | R |

a) All compounds gave satisfactory NMR spectra and elemental and/or HRMS analyses. b) Isolated, combined yield of 2-azetidinones **7/8** and 2-pyrrolidinones **9/10**. c) Ratio was based on the isolated yields of **7**:**9** or **8**:**10**. d) Isolated yields of **11** or **12**. e) Determined using a Chiralcel OB column; eluent: hexanes-isopropyl alcohol or 95% ethanol. f) Obtained as an inseparable mixture of **7** and **9** (R= 3-$NO_2$Ph). The presence of **7** was evidenced by the 2-azetidinone $\upsilon_{max}$(C=O) at 1761 $cm^{-1}$. Ratio could not be determined by $^1H$ NMR, because of extensive signal overlap.

It is clear that the insertion reaction proceeded with good to high regioselectivity to give the 2-pyrrolidinones **9/10** as major products. In the N-arylethyl systems, with the exception of **5e** (entry 8), the 2-

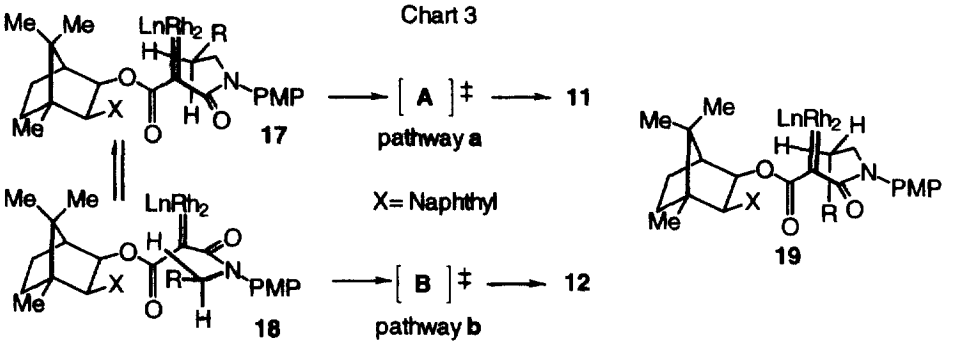
pyrrolidinone is the predominant (entry 4,5,10) and, in some cases, the exclusive product (entry 6,7,9,11). It is useful to note that the electron-withdrawing nitro group did not retard insertion into the benzylic position.[6] The lack of regioselectivity in the cyclization of **5e** can be attributed to the presence of the 2-methoxy group, which sterically shields the benzylic $CH_2$ from the attacking Rh(II) carbenoid (entry 8 vs. 9). This would make insertion into the methylene unit adjacent to the amide nitrogen more competitive.

The lactams **7/8** and **9/10** were readily separated by flash chromatography. The $^1H$ NMR spectra of **7/8** and **9/10** showed that each consisted of a mixture of diastereomers. Unfortunately, we were unable to determine the stereochemistry and the ratio of the diastereomers in each of the lactams. Nevertheless, compounds **9/10** were decarboxylated[7] to give **11/12**. The e.e. of compounds **11/12** (Table) was determined by HPLC analysis using a Chiralcel OB® column. Decarboxylation[7] of **7/8** gave a complex mixture of products. In both cases the chiral auxiliary, (-)-**1** or (+)-**2** was recovered (85–95%) unchanged..

It is evident that the diazoanilides **5/6 a**, bearing a linear N-hexyl group reacted with modest diastereoselectivity (entry 1,2), whereas **5b**, possessing a sterically more demanding (cyclohexyl)ethyl group, reacted with very high diastereoselectivity (entry 3). More interestingly, the diastereoselectivity in the reaction of the N-arylethyl diazoanilides was found to be dependent on the nature of the substituent(s) in the phenyl moiety. Thus, in **5,6 c** (R= Ph), products **11** and **12** (R= Ph) were obtained in 80% e.e (entry 4,5). However, the diastereoselectivity of the reaction decreased when the phenyl moiety was substituted with electron-donating methoxy groups. As well, lower enantiomeric excesses of **11/12** were obtained when a methoxy group was located ortho and/or para to the benzylic position compared to when it was at the meta position. (entry 6,7,8 vs. 9). In contrast, the electron-withdrawing $NO_2$ group had little influence on the diastereoselectivity of the reaction. An e.e. of 75–77% of **11/12** was realized, which was comparable to that of the unsubstituted case, **5,6 c**, (entry 10,11 vs. 4,5).

To establish the sense of asymmetric induction in these reactions, we prepared compounds **13** **14**, **15** and **16** (Eq. 1), and compared the sign of their specific rotation with those reported for known compounds.[8] Thus **13** ($[\alpha]_D^{23}$= +11.1; c, 1.6, $CH_2Cl_2$), prepared from **11** (R= Bu) in two steps (a, CAN, aq. MeCN, 79%; b, $LiAlH_4$, THF, reflux; then $(Boc)_2O$, NaOH, 66%), was found to be dextrorotatory, whereas the known[8a] (S)-enantiomer ($[\alpha]_D$= -30.5) was levorotatory. This result was further confirmed by the specific rotation[9] of **14**, which was prepared from **11** (R= c-$C_6H_{11}$), and from trans-cyclohexyl-*L*-proline.[10] Compounds **11** and **12** (R= Ph) were N-deprotected (CAN, aq. MeCN) to give the known **15** ($[\alpha]_D^{23}$= +27; c, 0.74, MeOH; Lit.[8b] $[\alpha]_D$= +37.5) and **16** ($[\alpha]_D^{23}$= -28.3; c, 0.5, MeOH, Lit.[8b] $[\alpha]_D$= -37.8), respectively. It is apparent from these results that chiral ester diazoanilides of type **5** undergo cyclization to give 2-pyrrolidinones of type **11**, whereas diazoanilides of type **6** cyclize to give **12**.

Chart 3




The results (Table) suggest that steric factors govern the diastereoselectivity of the reaction, but electronic

factors can oppose steric factors in influencing the diastereoselectivity as exemplified by the N-arylethyl systems. The diastereoselectivity of the reaction can be understood if we considered the two conformers **17** and **18** (Chart 3, shown only for diazoanilide **5**), which are rapidly interconvertible. The conformer **19** may also be involved. Conformers **18**, **19** are destabilized by the R/naphthyl and syn $R/CO_2R^*$ interactions, respectively. Reaction via **18** (or **19**) would proceed through a higher energy transition state (T.S.) **B**. The diastereoselectivity of the reaction is, therefore, related to the difference in the relative energies[11] of **A** and **B**. Thus, for a sterically less demanding hexyl group (entry 1) pathways **a**,**b** are competitive, which results in a lower diastereoselectivity. In comparison, the bulkier (cyclohexyl)ethyl group (entry 3) gave a 98% e.e. of **11**, which suggested that insertion involved mainly **17**, and proceeded via the lower energy T.S. **A**. As noted earlier, the presence of electron-donating groups in the phenyl moiety was detrimental to the diastereoselectivity of the reaction. This outcome can be attributed to the enhanced nucleophilicity[12] of the benzylic C–Hs arising from the activation of the benzylic C–Hs by the electron-donating methoxy group(s). This effect either causes the nucleophilic C–H moiety to interact with the electrophilic Rh(II) carbenoid at a greater distance (earlier T.S.)[13] or facilitates the transfer of a hydride anion to the Rh(II) carbenoid;[14] in the latter case, an intimate ion-pair may be involved. Our results, however, do not distinguish between the two. In both cases, the destabilizing interactions in T.S. **B** (via **18** or **19**) would not be fully manifested and, as a result, the difference in relative energies of **A** and **B** would be smaller. Pathways **a**,**b** become competitive leading to a decrease in the diastereoselectivity of the reaction.

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9. Compound **15** from **11**: mp: 60.5–63.0°C, $[\alpha]_D^{23}$ +99.4 (c 0.9, $CH_2Cl_2$); **15** from trans-cyclohexyl-*L*-proline: mp: 58–60°C, $[\alpha]_D^{23}$ +102 (c 0.5, $CH_2Cl_2$). Mixed mp: 58.5–61.5°C
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