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SYNTHESIS OF PYRROLIZIDINE BASES BY HIGHLY DIASTEREOSELECTIVE AND REGIOSELECTIVE CATALYTIC CARBON-HYDROGEN INSERTION REACTIONS OF CHIRAL PYRROLIDINEDIAZOACETAMIDES

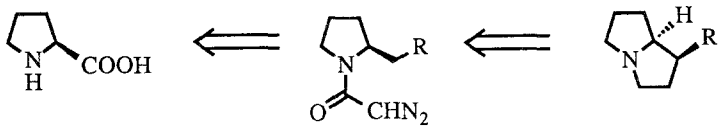
Michael P. Doyle* and Alexey V. Kalinin

Department of Chemistry, Trinity University, San Antonio, Texas 78212, U.S.A.

Summary: *Pyrrolizidines, (1S,8S)-1-hydroxypyrrolizidin-3-one and (-)-heliotridane, have been prepared in high yield from diazoacetamides of 2-substituted-pyrrolidines by carbon-hydrogen insertion catalyzed by dirhodium(II) tetrakis[methyl 1-acylimidazolidin-2-one-4(S)-carboxylates].*

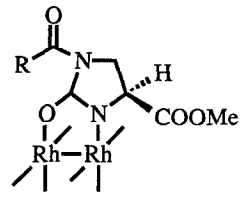
Intramolecular carbon-hydrogen insertion reactions of metal carbenes catalytically generated from diazoacetate esters with chiral dirhodium(II) carboxamidates can be achieved with high stereocontrol.[1,2] With symmetric systems such as cycloalkyl diazoacetates, one of four possible isomeric bicyclic dihydro-2(3*H*)-furanone products is formed,[3] demonstrating exceptional enantio- and diastereocontrol, and similar results have been reported with acyclic systems.[4-8] With unsymmetric systems regiocontrol adds to the complexity of an already stereochemically demanding problem, where at least eight isomeric products are possible. To examine the potential of chiral dirhodium(II) carboxamidates for highly selective intramolecular C-H insertion reactions with such complex systems, we have selected conveniently accessible chiral 2-substituted pyrrolidines as potential precursors to pyrrolizidine bases (Scheme 1),[9,10] whose natural

Scheme 1



1 **2** **3**

constituents generally have the thermodynamically less stable *syn*-stereochemistry of **3**.[9,10] We now report that the high diastereoselectivity and regiocontrol required for C-H insertion in this synthetic strategy can be achieved with the use of catalytic amounts of dirhodium(II) tetrakis[methyl 1-acylimidazolidin-2-one-4(*S*)-carboxylates] (**4**).



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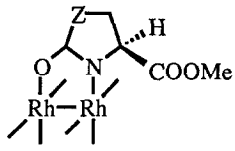

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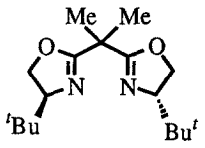
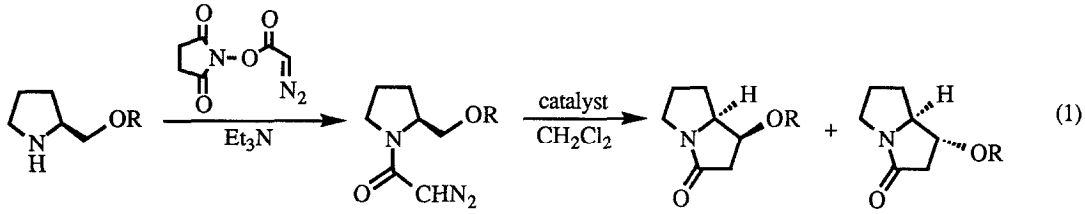


S-6

R = Me: Rh_2(4*S*-MACIM)$_4$
R = $PhCH_2CH_2$: Rh_2(4*S*-MPPIM)$_4$

Z = CH_2: Rh_2(5*S*-MEPY)$_4$
Z = O: Rh_2(4*S*-MEOX)$_4$

The methyl ether of (*S*)-2-pyrrolidinemethanol (**8a**) was converted into the corresponding diazoacetamide in 90% yield using succinimidyl diazoacetate.[11] Diazo decomposition of **8a** in refluxing dichloromethane induced with an extensive array of dirhodium(II) as well as selected copper(I) catalysts provided results (eq 1), representatives of which

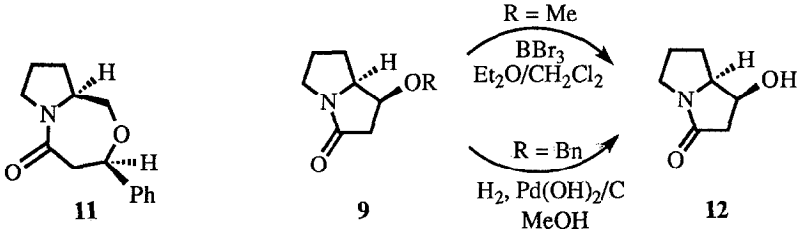


(1)

7a (R = Me)
7b (R = Bn)

8 **9** **10**

are reported in Table 1. Surprisingly little diastereoselection is observed with either achiral dirhodium(II) catalysts or even the bis-oxazoline (**6**) complex of copper(I) triflate, which provides exceptional enantiocontrol in selected intermolecular cyclopropanation reactions.[12] Of the chiral dirhodium(II) carboxamidates (**4** and **5**), there is an obvious dependence of diastereoselectivity on catalyst configuration, and with either Rh_2(4*S*-MACIM)$_4$ or Rh_2(4*S*-MPPIM)$_4$ **9a** could be formed in high yield and with 94% de. Similar results were obtained with the corresponding benzyl ether **8b**, which was formed from (*S*)-2-pyrrolidinemethanol in 67% overall yield by a standard sequence of steps (a. $(Boc)_2O$/THF; b. NaH, BnBr, Bu_4NI/THF; c. HCl/MeOH). However, in this case C-H insertion also occurred into the benzylic position to give **11** whose stereochemistry was determined by NMR methods to be (4*R*,7*S*). Once again, Rh_2(4*S*-MACIM)$_4$ provided the highest level of diastereocontrol and, in addition, regiocontrol was exceptional. Neither homochiral prolinate[13] nor phenylalanate[14] dirhodium(II) catalysts provided any advantage (low yields and



11 **9** **12**

Table 1. Catalyst Dependent Diastereoselectivity and Regioselectivity in Carbon-Hydrogen Insertion Reactions of **8** and **15**[a]

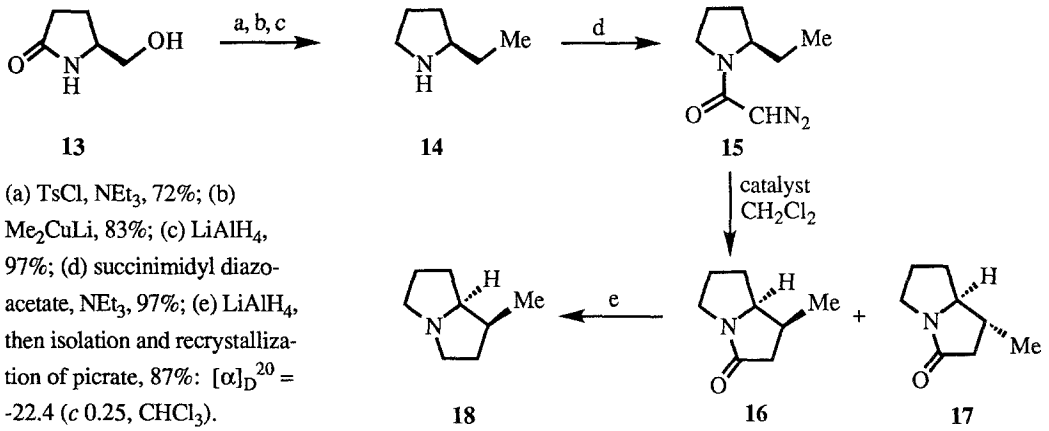
Catalyst	yield[b] **9a + 10a**	from **8a**: **9a:10a**	yield[b] **9b+10b+11**	from **8b**: **9b:10b:11**	yield[b] **16+17**	from **15**: **16:17**
Rh_2(5*S*-MEPY)$_4$	95	90:10	81	90:9:1		
Rh_2(5*R*-MEPY)$_4$	96	73:27	87	55:36:9		
Rh_2(4*S*-MEOX)$_4$	99	89:11	90	89:11:<1	98	71:29
Rh_2(4*S*-MACIM)$_4$	88	97:3	94	97:3:0	86	98:2
Rh_2(4*S*-MPPIM)$_4$	97	97:3	93	96:4:0	95	96:4
Rh_2(cap)$_4$[c]	45	63:37	27	33:23:44	20[d]	29:71
Rh_2(OAc)$_4$	45	53:47	41	49:35:16	32[d]	18:82
CuOTf[e]	55	38:62			30	20:80
CuOTf/***S*-6**	83	50:50			57	29:71
CuOTf/**R-6**	91	47:53			55	35:65

[a]Reactions performed in refluxing CH_2Cl_2 with 1.0-1.5 mol % catalyst. Diastereomeric ratios were determined by GC analyses. [b]Weight yield of product after chromatography or distillation. [c]cap = caprolactamate. [d]Yield by GC in reaction mixture. [e]Benzene complex; with $CuPF_6$, yield of **9a+10a** was 61% (**9a:10a** = 36:64).

selectivities). Insertion products **9a** and **9b** were readily converted to (1*S*,8*S*)-1-hydroxypyrrolizidin-3-one (**12**, eq 2), and the overall synthesis of **12** is the most efficient yet reported.[15,16]

The synthesis of (-)-heliotridane (**18**), which was recently prepared from (+)-carvone in more than ten steps[17] and from (*S*)-proline in seven steps,[18] was accomplished in six steps from 2-oxopyrrolidine-5(*S*)-methanol (Scheme 2) in greater than 45% overall yield. Diastereoselectivity in the key step, catalytic C-H insertion with **15**, exhibited catalyst dependence that was even more variable than with **8** (Table 1). However, Rh_2(4*S*-MACIM)$_4$ and

Scheme 2



13 **14** **15** **16** **17** **18**

(a) TsCl, NEt_3, 72%; (b) Me_2CuLi, 83%; (c) $LiAlH_4$, 97%; (d) succinimidyl diazoacetate, NEt_3, 97%; (e) $LiAlH_4$, then isolation and recrystallization of picrate, 87%: $[\alpha]_D^{20}$ = -22.4 (*c* 0.25, $CHCl_3$).

Rh_2(4*S*-MPPIM)$_4$ provided exceptional diastereocontrol for the formation of **16**. The need for a match of reactant configuration with catalyst configuration is seen in comparative results with Rh_2(4*R*-MPPIM)$_4$ (**16**:**17** = 75:25).

Significantly, with catalysts other than chiral dirhodium(II) carboxamides, a reversal in **16**:**17** selectivity is observed, and **17** is the predominant diastereoisomer from C-H insertion. However, the yields of **16**+**17** are low with these catalysts, multiple products are formed, and the limit in diastereocontrol is that achieved with $Rh_2(OAc)_4$. Also, with CuOTf/***R*-6** the **16**:**17** diastereomer ratio was 35:65 (55% yield) compared to 29:71 (57% yield) with CuOTf/-***S*-6**, demonstrating here a lack of dependence of diastereoselectivity on catalyst configuration. Thus, the chiral dirhodium(II) imidazolidinone catalysts Rh_2(4*S*-MACIM)$_4$ and Rh_2(4*S*-MPPIM)$_4$ exhibit remarkable diastereocontrol in these C-H insertion reactions that is not matched by other dirhodium(II) catalysts or by copper(I) catalysts.[19]

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19. All reactions were performed by controlled addition of the diazoacetamide in anhydrous CH_2Cl_2 to the catalyst in the same solvent.[6]

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