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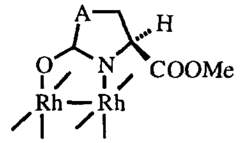
IMPROVED ENANTIOSELECTION FOR CHIRAL DIRHODIUM(II) CARBOXAMIDE-CATALYSED CARBON-HYDROGEN INSERTION REACTIONS OF TERTIARY ALKYL DIAZOACETATES

Michael P. Doyle* and Qi-Lin Zhou
Department of Chemistry, Trinity University, San Antonio, Texas 78212, U.S.A.

Conrad E. Raab and Gregory H. P. Roos[†]
Department of Chemistry and Chemical Technology, University of Natal, Pietermaritzburg, Natal 3200, South Africa

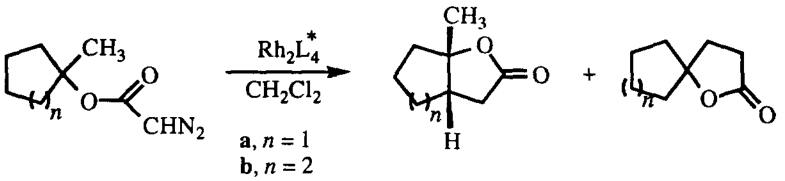
Summary: *Enantiocontrol in C-H insertion reactions of 3° alkyl diazoacetates, which is highly dependent on the catalyst ligand, is greatly enhanced with the use of dirhodium(II) tetrakis[methyl 1-acetylimidazolidin-2-one-4(S)-carboxylate],* Rh$_2$(4*S*-MACIM)$_4$.

The intramolecular carbon-hydrogen insertion reactions of metal carbenes generated by dirhodium(II) catalysed diazo decomposition of diazocarbonyl compounds have proven to be efficient and selective carbon-carbon bond forming processes.[1-3] Regioselectivity is generally subject to defined electronic effects,[4,5] with 5-membered rings being preferentially formed,[6,7] although there are exceptions.[8-10] Enantiocontrol in C-H insertion reactions has been achieved with α-diazo-β-ketoesters (24-76% ee)[11] and selected methyldiazoketones (62-82% ee) using homochiral dirhodium(II) carboxylates.[12] With chiral dirhodium(II) carboxamides, particularly dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(*S*)-carboxylate], Rh$_2$(5*S*-MEPY)$_4$, and its enantiomeric form Rh$_2$(5*R*-MEPY)$_4$,[13] enantiocontrol in C-H insertion reactions of 1° and 2° alkyl diazoacetates has been extraordinary, often exceeding 90% ee.[14-17] The exception has been diazoacetates derived from 3° alcohols which produce the corresponding γ-lactone products in moderate to high yield but with enantioselectivities that range from 31-79% ee.[14,17] We now report that enantiocontrol in C-H insertion reactions of 3° alkyl diazoacetates is remarkably dependent on the catalyst ligand and that the highest enantioselectivities can be achieved with the use of dirhodium(II) tetrakis[methyl 1-acetylimidazolidin-2-one-4(*S*)-carboxylate], Rh$_2$(4*S*-MACIM)$_4$.



A = CH$_2$: Rh$_2$(5*S*-MEPY)$_4$
= NCOCH$_3$: Rh$_2$(4*S*-MACIM)$_4$
= O: Rh$_2$(4*S*-MEOX)$_4$

Addition of 1-methylcyclopentyl diazoacetate to Rh$_2$(5*S*-MEPY)$_4$ in refluxing dichloromethane produced the *cis*-fused bicyclic lactone **2a** (eq. 1) in moderate yield along with the product from C-H insertion into the 1-methyl substituent, **3a**. The molar ratio of **2a**:**3a** was 94:6, demonstrating a high degree of regioselectivity for insertion into the secondary CH_2 group relative to insertion into the primary CH_3 group, but enantiocontrol was low (36% ee). The *trans*-fused bicyclic analogue to **2a** was not detected. Use of dirhodium(II) tetrakis-[methyl 2-oxazolidinone-4(*S*)-carboxylate], $Rh_2(4S\text{-MEOX})_4$,[18] which has provided higher levels of enantiocontrol in select C-H insertion reactions,[18,19] was actually inferior to $Rh_2(5S\text{-MEPY})_4$ in this case. However, $Rh_2(4S\text{-MACIM})_4$, whose advantages for diastereocontrol in highly enantioselective C-H insertion reactions of secondary cycloalkyl diazoacetates have recently been demonstrated,[15] provided **2a** in 85% ee and with a regioselectivity of 9:1. Similar results were obtained with 1-methylcyclohexyl diazoacetate (Table 1), which afforded **2b** in 90% ee with the use of $Rh_2(4S\text{-MACIM})_4$. Isolated yields are those of the pure lactone products obtained after distillation.



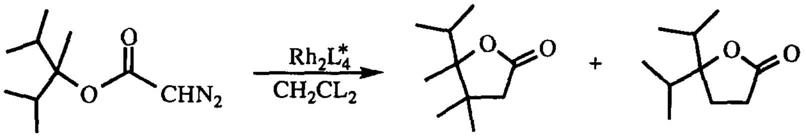
1 **2** **3** (1)

Table 1. Enantiocontrol and Regiocontrol for Dirhodium(II)-Catalysed C-H Insertion Reactions of Tertiary Cycloalkyl Diazoacetates[a]

diazoacetate	catalyst	isolated yield, %	2:3[b]	2, % ee[c]	2, $[\alpha]_D^{23}$
1a	$Rh_2(4S\text{-MEOX})_4$	61	83:17	33	-14.2°
	$Rh_2(5S\text{-MEPY})_4$	52	94:6	36 (31)[d]	-15.6°
	$Rh_2(4S\text{-MACIM})_4$	56	90:10	85	-36.7°[e]
1b	$Rh_2(4S\text{-MEOX})_4$	60	78:22	40	+4.2°
	$Rh_2(5S\text{-MEPY})_4$	63	90:10	75 (74)[d]	+7.9°
	$Rh_2(4S\text{-MACIM})_4$	68	90:10	90	+9.5°[f]

[a] Reactions were performed in refluxing dichloromethane using 1.0 mol % catalyst. [b] GC ratios obtained on a methyl silicone column. [c] Determined by GC on a Chiraldex G-TA column with baseline resolution. [d] Reference 17. [e] (c = 1.84, $CHCl_3$). [f] (c = 2.10, $CHCl_3$)

Extensions of this methodology to 3° acyclic diazoacetates provided results which demonstrated the overall effectiveness of $Rh_2(4S\text{-MACIM})_4$, relative to $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(4S\text{-MEOX})_4$, for enantioselective C-H insertion reactions. 2,3,4-Trimethyl-3-pentyl diazoacetate (**4**) formed the γ-lactone from insertion into an isopropyl methine C-H bond (eq. 2) vicinal to the incipient chiral center (**5**) in 85% ee (Table 2). With $Rh_2(4S\text{-MEOX})_4$



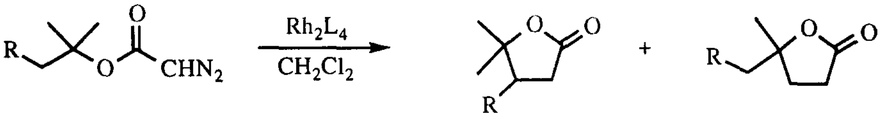
4 **5** **6** (2)

Table 2. Enantiocontrol and Regiocontrol for Dirhodium(II)-Catalysed C-H Insertion Reactions of 2,3,4-Trimethyl-3-pentyl Diazoacetate[a]

diazoacetate	catalyst	isolated yield, %	**5**:**6**[b]	% ee **5**[c]	$[\alpha]_D^{23}$ **5**
4	$Rh_2(4S\text{-}MEOX)_4$	70	70:30	0	0.0°
	$Rh_2(5S\text{-}MEPY)_4$	66	93:7	61	-12.3°
	$Rh_2(4S\text{-}MACIM)_4$	73	83:17	85	-17.1°[d]

[a]Reactions were performed in refluxing dichloromethane using 1 mol% catalyst. [b]GC ratios obtained on a methyl silicone column. [c]Determined by GC on a Chiraldex A-DA column with baseline resolution. [d](c = 0.95, $CHCl_3$).

enantioselectivity was negligible. Regiocontrol was highest with $Rh_2(5S\text{-}MEPY)_4$ (13:1), and that for $Rh_2(4S\text{-}MACIM)_4$ favored formation of **5** by 5:1.[20] Analogous results were obtained with **10 a-c** (eq. 3) where $Rh_2(4S\text{-}MACIM)_4$ provided the highest levels of enantiocontrol, and the use of $Rh_2(4S\text{-}MEOX)_4$ actually brought about a reversal in configuration for **8a,b** and **9b** (Table 3). This reversal in configuration is believed to be due to a change in the preferential conformational alignment of R relative to the ester's ether oxygen in the transition state for C-H insertion. The absolute configurations of **8c** and **8d** are *S*.[14]



7 **8** **9** (3)

Table 3. Enantiocontrol and Regiocontrol for Dirhodium(II)-Catalysed C-H Insertion Reactions of Tertiary Alkyl Diazoacetates[a]

				ee, %		$[\alpha]_D^{23c}$	
diazoacetate	catalyst	isolated yield, %	**8**:**9**[b]	**8**	**9**	**8**	**9**
7a ($R=CH_3$)[d]	$Rh_2(4S\text{-}MEOX)_4$	42	100:0	21	-	-4.2°	-
	$Rh_2(5S\text{-}MEPY)_4$	54	100:0	0	-	0.0°	-
	$Rh_2(4S\text{-}MACIM)_4$	47	100:0	62	-	+12.3°	-
7b (R=Ph)[e]	$Rh_2(4S\text{-}MEOX)_4$	75	20:80	34	10	+20.5°	-2.7°
	$Rh_2(5S\text{-}MEPY)_4$	62	30:70	53	70	-31.9°	+18.9°
	$Rh_2(4S\text{-}MACIM)_4$	74	32:68	77	83	-46.4°	+22.4°
7c (R=OMe)[f]	$Rh_2(4S\text{-}MACIM)_4$	85	87:13	56	*g*	+28.8°[i]	-
7d (R=OBn)[h]	$Rh_2(4S\text{-}MACIM)_4$	74	84:16	58	50	+30.6°[i]	-

[a]Reactions were performed in refluxing dichloromethane using 1 mol% catalyst. [b]GC ratios obtained on a methyl silicone column. [c]In $CHCl_3$, c = 0.7 to 2.0. [d]% ee determined by GC on a Chiraldex A-DA column with baseline resolution. [e]% ee determined by GC on a Chiraldex G-TA column with baseline resolution. [f]56% ee for **8c** with $Rh_2(5S\text{-}MEPY)_4$ (ref. 14). [g]Not determined. [h]59% ee for **8d** with $Rh_2(5S\text{-}MEPY)_4$ and 94:6 for **8**:**9**. [i]In EtOH, c = 1.30 (**8c**), 1.72 (**8d**).

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†Current address: Department of Chemistry, School of Mathematical and Physical Sciences, Murdoch University, Murdoch, Western Australia 6150.

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