ORGANIC LETTERS

2003
Vol. 5, No. 4
407−410

Influences of Catalyst Configuration and Catalyst Loading on Selectivities in Reactions of Diazoacetamides. Barrier to Equilibrium between Diastereomeric Conformations

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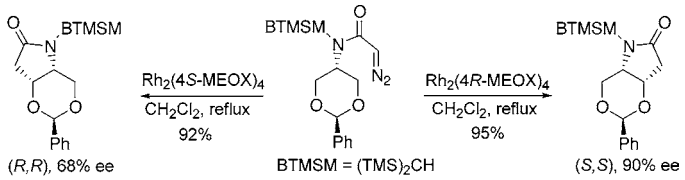
Received October 23, 2002

ABSTRACT

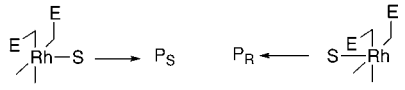


Stereoelectronic factors present a barrier to equilibrium between diastereomeric conformations resulting in differences in selectivity as a function of catalyst configuration. The bis(trimethylsilyl)-methyl protective group is inert to insertion but directs carbon–hydrogen insertion with enhanced enantiocontrol.

In asymmetric catalysis, standard practice assumes that with achiral substrates the selectivities achieved with one enantiomeric catalyst under a specified set of conditions will be equal, but opposite, to those from use of its mirror image.[1] This is well established in reactions involving metal carbene intermediates, and there are no published exceptions.[2−4] The possibility that chiral catalysts of opposite configuration could induce different outcomes with the same achiral substrate has not been examined.

However, there is growing documentation that, since flexible achiral and meso ligands possess chiral conformations,[5] interaction with a metal can produce diastereomeric complexes whose reactivities and selectivities in a chemical transformation are different.[6,7] This could occur in reactions of diazocarbonyl compounds if diastereomeric conformations are formed from mirror image catalysts (e.g., Scheme 1, **1a** and **1b** are diastereomeric in the attached substrate, S). A test of this concept has been undertaken with conformation-

Scheme 1



1a **1b**

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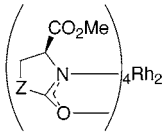
10.1021/ol027157b CCC: $25.00
Published on Web 01/21/2003

Table 1. Catalyst-Dependent Reactions of **8** as a Function of Configuration and Loading[a]

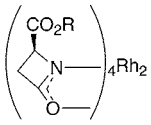
catalyst	S/C[b]	configuration[c]	isolated yield, %[d]	**9**:**10**:**11**[e]	% ee[f] **9**	% ee[f] **11**	configuration[c]	isolated yield, %[d]	**9**:**10**:**11**[e]	% ee[f] **9**	% ee[f] **11**
$Rh_2(MEPY)_4$	10	*R*	98	1:3:96		3	*S*	52	35:30:35	94	28
	100	*R*	81	10:9:81	88	50	*S*	52	34:28:38	95	22
	1000	*R*	87	12:10:78	78	32	*S*	66	18:32:50	>95	33
$Rh_2(MEOX)_4$	100	*R*	48	35:42:23	86	62	*S*	61	32:33:35	87	38
	1000	*R*	55	18:35:47	82	13					
$Rh_2(MPPIM)_4$	100	*R*	85	10:21:69	29	20	*S*	82	8:37:55	64	5

[a] All reactions were carried out in refluxing dichloromethane containing diazoamide (0.009 M) and catalyst for 5 min (S/C ≤ 100) or 1 h (S/C = 1000). [b] Molar ratio of **8** to catalyst. [c] Configuration of catalyst. [d] Yield determined after chromatographic removal of catalyst. [e] Determined by ^{1}H NMR of reaction mixture; imine **12** was present in amounts that were 0.8 that of **10**. [f] Determined by HPLC using a Chiralpak OD column; opposite catalyst configurations give opposite mirror image isomers of **9** and **11**.

ally and configurationally well-defined chiral dirhodium(II) carboxamidates ((*S*)-forms, **2**−**5**). They have been fully characterized[8−11] and are well-known for their conformational rigidity.[12]

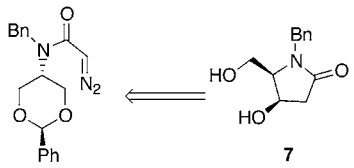


2: Z = CH_2, Rh_2(5*S*-MEPY)$_4$
3: Z = O, Rh_2(4*S*-MEOX)$_4$
4: Z = $Ph(CH_2)_2C(O)N$, Rh_2(4*S*-MPPIM)$_4$



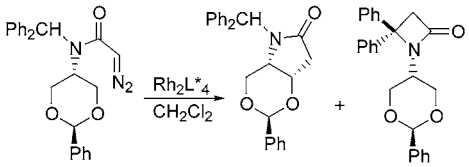
5a: R = Me, Rh_2(4*S*-MEAZ)$_4$
5b: R = *i*-Bu, Rh_2(4*S*-IBAZ)$_4$

We have previously reported that C−H insertion reactions from 1,3-dioxan-5-yl diazoacetamide **6** provides a convenient route to 2-deoxyxylolactams **7** and *ent*-**7**, and uses of **2**−**5** were explored to determine optimum catalysts and conditions.[13] The $Rh_2(MEPY)_4$ catalysts gave the highest level of enantiocontrol (85% ee) and the least complications from competing reactions (5%). However, the benzyl protective group could not be conveniently removed, and a search for an alternative led us to evaluate the *N*-benzhydryl compound **8**.

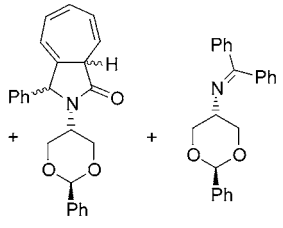


6 **7**

However, treatment of **8** with **2**−**4** and their enantiomeric forms gave very different results that were dependent on the configuration of the catalysts (eq 1). For example, with Rh_2(5*R*-MEPY)$_4$, aromatic cycloaddition was dominant, and insertion into the benzhydryl C−H group (or fragmentation to imine **12**) was competitive with insertion into the 1,3-dioxane ring.



8 **9** **10** (1)



11 **12**

With Rh_2(5*S*-MEPY)$_4$, chemoselectivity, regioselectivity, and enantioselectivity were greatly different. Similar catalyst configuration-dependent outcomes were seen with Rh_2(MEOX)$_4$ and Rh_2(MPPIM)$_4$ catalysts (Table 1), and selectivities also varied as a function of catalyst loading. Increasing the concentration of **8** by 30-fold had very limited influence on selectivities,[14] as did performing this reaction in refluxing dichloroethane.[15]

To ensure that these differences were not due to differential catalyst purity, the same catalyst pairs were used with the *N*-benzyl analogue of **6**. Here chemoselectivity and enantioselectivity did not vary with catalyst configuration. Indeed, in all reactions previously reported from our laboratories that used chiral dirhodium(II) carboxamidate catalysts, we did not observe different outcomes from the use of the (*R*)- or (*S*)-configured catalysts.

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(14) For Rh_2(5*R*-MEPY)$_4$ at S/C = 1000 and [**8**] = 0.27 M in refluxing CH_2Cl_2: % yield = 75; **9**:**10**:**11** = 9:16:75; % ee **9** = 81; % ee **11** = 34.
(15) For Rh_2(5*R*-MEPY)$_4$ at S/C = 1000 and [**8**] = 0.009 M in refluxing $ClCH_2CH_2Cl$: % yield = 74; **9**:**10**:**11** = 19:15:66; % ee **9** = 75; % ee **11** = 7.

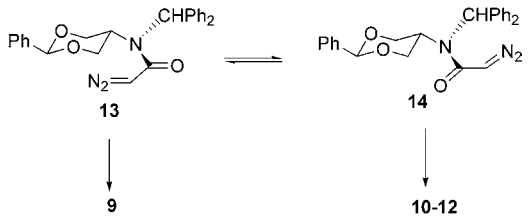
Table 2. Catalyst-Dependent Reactions of **15** as a Function of Configuration[a]

catalyst	catalyst configuration[b]	**16** at room temperature[c]		**16** at reflux [d]		absolute configuration[e]
		% yield	% ee[f]	% yield	% ee[f]	(4a,7a)-**16**
$Rh_2(MEPY)_4$	*R*	72	66	80	44	*S*,*S*
	S	82	50	84	43	*R*,*R*
$Rh_2(MEOX)_4$	*R*	72	84	95	90	*S*,*S*
	S	76	70	92	68	*R*,*R*
$Rh_2(MPPIM)_4$	*R*	g		62	1	
	S	g		88	4	
$Rh_2(MEAZ)_4$	*R*	81	78	77	77	*S*,*S*
	S	69	66	80	70	*R*,*R*
$Rh_2(PTTL)_4$	*S*	g		71	29	*R*,*R*

[a] All reactions were carried out in dry dichloromethane (0.02 M) containing diazoamide and 2.5 mol % Rh(II) catalyst. [b] Configuration of catalyst ligands. [c] Reaction time was 40 min except with $Rh_2(MEAZ)_4$ for which the reaction time was 20 min. [d] Reaction time was 15−20 min except with $Rh_2(MPPIM)_4$ (20 h) and Rh_2(*S*-PTTL)$_4$ (3 h). [e] Configuration assigned based on comparison of $[\alpha]_D^{20}$ of **17**, prepared from **16**, with known (4*S*,5*S*)-**17**. The configuration at carbons 4a and 7a in **16** prepared using other Rh(II) catalysts was inferred. [f] Determined by chiral HPLC analysis using a Chiralcel OD column. [g] No reaction at room temperature.

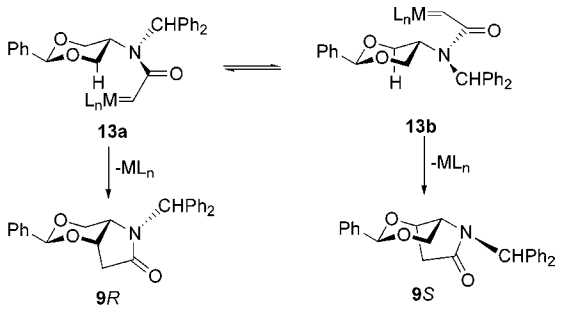
The influences of catalyst configuration and loading on selectivities can be attributed to basic conformational differences in the intermediate metal carbene. Regioselectivities and chemoselectivities are a function of the populations of **13** and **14** (Scheme 2), and the data demonstrate that the pathway through **14** is dominant.

Scheme 2



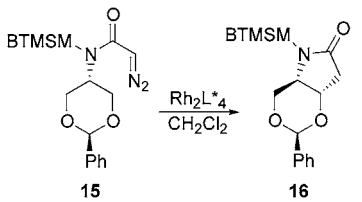
Differences in enantioselectivity, however, are related to the relative access through competing diastereomeric conformations, as through **13a** and **13b** (Scheme 3). Here, the

Scheme 3



relative energy difference between **13a** and **13b** is the normal determinant of the extent of enantiocontrol. However, if equilibrium between diastereomeric **13a** and **13b** cannot be achieved within the time scale for insertion, then the enantioselectivity will differ with the configuration of the catalyst that is employed. Furthermore, the favored conformation (**13a**/**13b**) is dependent on the configuration of the catalyst so that the conformational distribution of **13** with Rh_2(5*S*-MEPY)$_4$, for example, will not be the same as that with Rh_2(5*R*-MEPY)$_4$. And because trapping of diazoacetamide **8** configurations leading to **13** and **14** is a function of the S/C ratio, selectivities also vary with catalyst loading.[16]

To focus only on enantiocontrol in C−H insertion, we have taken advantage of Wee's recent report of bis(trimethylsilyl)-methyl (BTMSM) as a nitrogen protective group in diazo decomposition reactions.[17] With $Rh_2(OAc)_4$, racemic insertion product **16** (eq 2) was obtained in 72% yield. Catalysts **2**−**5** were used, and only **16** was produced. Results from these reactions, reported in Table 2, show significant differences in enantioselectivity as a function of catalyst configuration. Unlike **8**, however, higher enantioselectivity was realized for **16** with the (*R*)-configured catalysts for an enantiomeric set of Rh(II) carboxamidates when the reaction was conducted either at room temperature or at reflux. It is also instructive to compare the levels of enantioselection for the conversions **8** → **9** and **15** → **16** to the structure of the catalyst. In the formation of **9**, $Rh_2(MEPY)_4$ (**2**) gave good to excellent enantioselection, whereas for the formation of **16**, $Rh_2(MEOX)_4$ (**3**) provided superior results. For catalysts of type **5**, **5a** was more effective in providing higher enantioselection in the formation of **16** than **5b**.

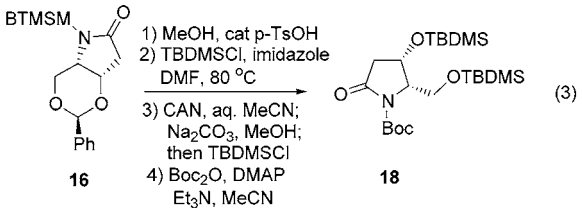


(2)

On the other hand, **5b** gave a higher % ee for **9** compared to that for **16**. There was a marked difference in the performance of $Rh_2(MPPIM)_4$ in effecting enantioselection during

the formation of **9** and **16**; for **9**, higher ees were realized with Rh_2(4*S*-MPPIM)$_4$, whereas for **16**, an almost racemic mixture was produced with each of the enantiomeric forms of this catalyst.

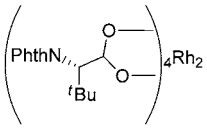
The absolute configuration at C-4a and C-7a in **16**, formed with Rh_2(4*R*-MEOX)$_4$, was assigned as *S*,*S* by conversion of **16** to the known[18] **18** (eq 3) and comparison of the specific optical rotation of **18** ($[a]_D^{20} = +40.9$) with the reported[18] value ($[a]_D^{20} = +51.53$).



(3)

Thus, the (*R*)-configured catalysts afforded (4a*S*,7a*S*)-**16** and the (*S*)-configured catalysts gave (4a*R*,7a*R*)-**16**.

The Hashimoto catalyst **17**[19] was also evaluated against **15** and found to be not as effective as the dirhodium(II) carboxamidates [except Rh_2(MPPIM)$_4$] for enantiocontrol during formation of **16**, but interestingly, the sense of induction is the same as that obtained with (*S*)-configured dirhodium(II) carboxamidates.



17: Rh_2(*S*-PTTL)$_4$

With the use of diazoamide **15** and Rh_2(4*R*-MEOX)$_4$, an enantioselectivity of 90% ee has been achieved for the C−H insertion reaction to form **16**, and because of the ease of removal of BTMSM, this methodology is optimal for the construction of 2-deoxyxylolactam. Applications to other synthetic targets are presently under investigation.

Acknowledgment. Support for this research by grants from the National Science Foundation and National Institutes of Health (GM-46503) to M.P.D. is gratefully acknowledged. A.G.H.W. thanks the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for support. We thank Professor S.-I. Hashimoto for providing A.G.H.W. with a sample of Rh_2(*S*-PTTL)$_4$ catalyst for initial studies on *N*-BTMSM diazoamide chemistry.

Supporting Information Available: Experimental procedures and product characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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