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β-Lactam Formation via Rhodium(II) Catalyzed Carbon-Hydrogen Insertion Reactions of α-Diazo Amides

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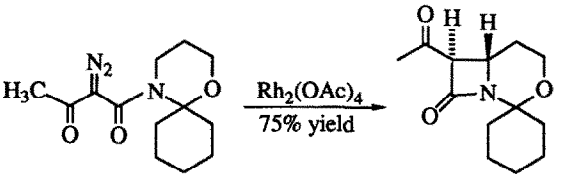
Abstract. Diazoacetoacetamides undergo rhodium(II) catalyzed decomposition to form β-lactam products in high yield and with exceptional stereocontrol. Diazoacetamides generally yield mixtures of β- and γ-lactam products whose preference for β-lactam formation can be enhanced by rhodium(II) 2-phenoxybenzoate. Dirhodium(II) catalysts with chiral carboxamide ligands afford a new enantioselective route to lactams.

The use of α-diazocarbonyl compounds in catalytic N-H insertion reactions is a well established methodology for the synthesis of β-lactam antibiotics[1,2] that has been made more prominent by its commercial use for the synthesis of thienamycin.[3] Less well known are C-H insertion reactions of α-diazocarboxamides that produce β-lactams, often with high regio- and stereoselectivity. Although five-membered ring formation is normally the favored process,[4] insertion reactions can be directed to produce β-lactam products because of heteroatom activation[5] for insertion into the C-H bond adjacent to nitrogen. Dirhodium(II) carboxylates are the catalysts of choice for these processes.[4]

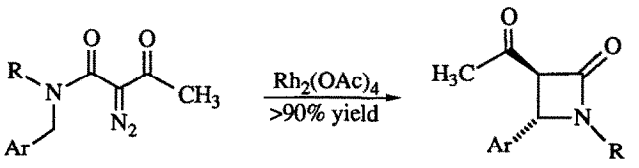
The first reported examples of C-H insertion reactions directed to the formation of β-lactam products were obtained through photolytic and thermal decomposition of diazo amides,[6] but low yields and low selectivities limited their further development. Vastly improved catalytic methods based on dirhodium(II) carboxylates were introduced later, the first examples utilizing piperidine derivatives to form carbapenams (eq. 1).[7] The broad



(1)

1 2

potential of this methodology was suggested only recently when a series of diazoacetoacetamides, prepared by condensation of 2° amines with diketene followed by diazo transfer, was reported to undergo exclusive β-lactam formation in high yield and with exceptional stereocontrol (e.g., eq. 2; R = *t*-Bu, *i*-Pr, CH_2Ph; Ar = *p*-

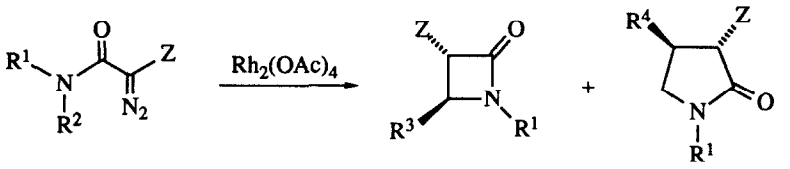


(2)

3 4

$NO_2C_6H_4$, *m*-BrC_6H_4, *m*-$MeOC_6H_4$, Ph, 3,4-$(MeO)_2C_6H_3$).[8] β-Lactam products having only the trans stereochemistry were formed by this catalytic process. However, diazoacetamides often formed mixtures of β-

Table 1. Lactam Formation From $Rh_2(OAc)_4$-Catalyzed Reactions of Diazo Amides[8,9]



(3)

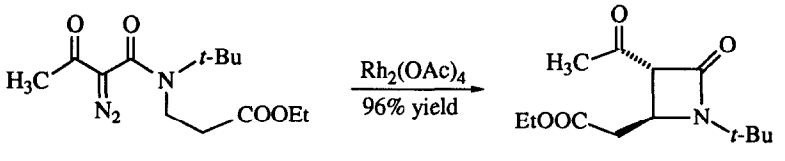
5 **6** **7**

R^1	R^2	Z[a]	yield, %	% 6	% 7
i-Pr	*i*-Pr	CH_3CO	89	>99	<1
i-Pr	*i*-Pr	H	95	81	19
t-Bu	*n*-Bu	CH_3CO	92	37	63
t-Bu	*n*-Bu	H	95	<1	>99
t-Bu	$PhCH_2CH_2$	CH_3CO	94	49	51
t-Bu	$PhCH_2CH_2$	H	85	<1	68[b]
R^1R^2N = *trans*-2,6-dimethylpiperidinyl		CH_3CO	90	>99	<1
R^1R^2N = *trans*-2,6-dimethylpiperidinyl		H	92	94	6

[a]For Z = CH_3CO, reactions performed in refluxing benzene. For Z = H, reactions performed in refluxing dichloromethane. [b]38% of product from aromatic cycloaddition; 97% **7** with the use of rhodium(II) caprolactam.

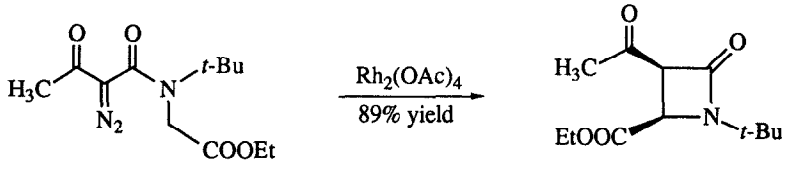
and γ-lactam products in rhodium(II) acetate catalyzed reactions[8,9] (e.g., Table 1) or, in the case of N-benzyl derivatives, exclusive aromatic cycloaddition occurred.[10] Ligands of the dirhodium(II) catalyst can influence selectivity for insertion,[8] but the full extent of their control has yet to be revealed.

Insertion into C-H positions that are β or α to strongly electron withdrawing carboxylate substituents occurs with relative ease and, once again, with high yield and high stereocontrol (eq. 4,5).[11] However, unlike



(4)

8 **9**



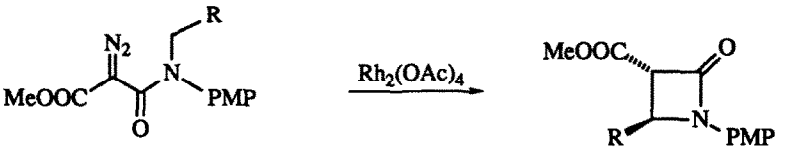
(5)

10 **11**

the stereochemical course of reactions described in eq. 1-4, **11** is produced with a cis stereochemistry. The cause of this stereochemical control, and of regio- and chemoselectivity in insertion into normally deactivated posi-

tions,[12] has been attributed to the activating influence of the amide nitrogen in the transition state for C-H insertion and to conformationally-dependent orientation of substituents in the intermediate metal carbene.[13] Modification of **8** by substituting the *N-tert*-butyl group for neopentyl or *n*-butyl, or by exchanging the ethyl ester for a *tert*-butyl ester, all influence selectivity for β-lactam formation. The *N-tert*-butyl group is superior to the others in directing preference for β-lactam formation.

The bulky *tert*-butyl group has been assumed to be a major factor in conformational determination of selectivity in rhodium(II) catalyzed reactions of diazo amides.[13] However, removal of this *N*-alkyl group from lactam products is synthetically unattractive, and recent investigations of *N-p*-methoxyphenyl derivatives have suggested a solution to this problem in two cases where aromatic substitution was not competitive (eq. 6: PMP = *p*-methoxyphenyl).[14] Evidence is accumulating that carboxylate or carboxamide ligand modification on



(6)

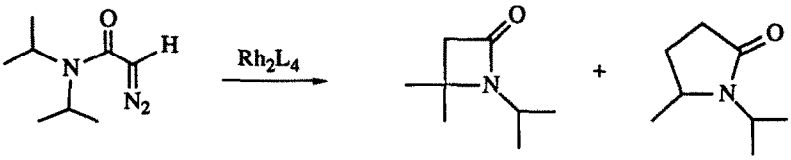
12 **13**

R = Ph 41% yield 100% trans
CH_2COO-*t*-Bu 53% yield 60% trans

dirhodium(II) strongly influences chemoselectivity,[15] and further studies may reveal a broader applicability of *N-p*-methoxyphenyldiazoamides.

In our efforts to develop highly selective metal carbene processes, we have examined the regioselectivity for β-lactam formation with a series of dirhodium(II) catalysts. In reactions of *N,N*-diisopropyldiazoacetamide (eq. 7) only moderate regiocontrol, comparable to that found with $Rh_2(OAc)_4$, occurs for β-lactam formation with a broad selection of dirhodium(II) catalysts (Table 2). Electronic effects from dirhodium(II) ligands that have been

Table 2. Dirhodium(II) Ligand Effects on Regioselectivity for β-Lactam Formation

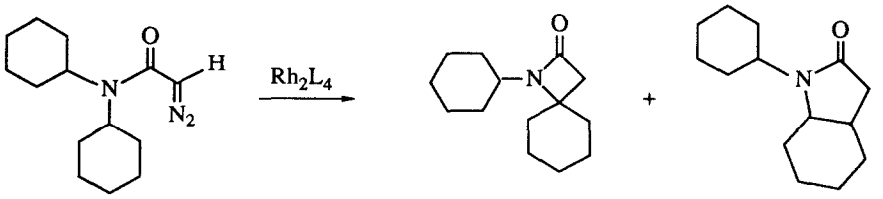


(7)

14 **15** **16**

Rh_2L_4, L =	yield, %	% 15	% 16	Rh_2L_4, L =	yield, %	% 15	% 16
perfluorobutyrate (pfb)	92	71	29	benzoate	90	80	20
acetate (OAc)	95	81	19	2,6-dimethoxybenzoate	92	78	22
acetamide (acam)	95	75	25	2,4,6-triisopropylbenzoate	82	79	21
butyrate	90	75	25	2-phenyoxybenzoate	98	92	8

effective for increased regioselectivity in C-H insertion reactions of diazoacetoacetates (pfb < OAc < acam)[16] do not greatly influence the relative percentage of the β-lactam product. The exception is rhodium(II) 2-phenoxybenzoate which increases the **15:16** ratio to 92:8. Similar selectivity enhancement with this catalyst occurs in reactions with *N,N*-dicyclohexyldiazoacetamide (eq. 8): rhodium(II) 2-phenoxybenzoate, 81% yield, **18:19** =

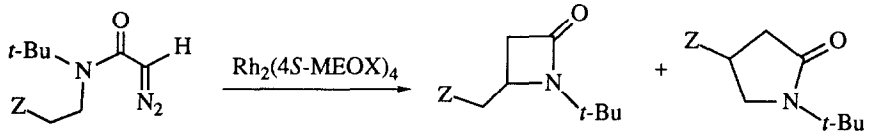


(8)

17 **18** **19**

90:10; rhodium(II) acetate, 82% yield, **18:19** = 80:20. Both cis and trans isomers of **19** are formed in an approximate 1:1 ratio, independent of catalyst. However, β-lactam formation from *trans*-2,6-dimethylpiperidinyldiazoacetamide (**20**) was not increased beyond the 94:6 β-/γ- selectivity ratio (Table 1) with the use of rhodium(II) phenoxybenzoate. Selectivity enhancement in these examples is likely due to steric effects. Further ligand modifications may lead to even greater control of selectivity.

Enantioselective C-H insertion reactions that result in β-lactam products have recently been made possible through the use of dirhodium(II) catalysts that possess chiral ligands. With binaphthyl-derived (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate as ligands in (S-Binap$O_2PO_2)_2Rh_2(HCO_3)_2$, reaction with **8** resulted in the formation of **9** in 93% yield with an enantiomeric excess of 26%.[17] Dirhodium(II) catalysts possessing chiral pyrrolidone or oxazolidinone ligands that are effective for enantioselective C-H insertion reactions of diazoesters[18] also promote C-H insertion reactions of diazoacetamides (60-80% ee); however, except with diazoacetamides having strong electron withdrawing substituents in the β-position (eq. 9, Z = COOEt), γ-lactam



(9)

21 **22** **23**

Z = Et	82% yield	9 (80% ee)	91 (71% ee)
OEt	97% yield	0	100 (78% ee)
COOEt	54% yield	93 (46% ee)	7

products dominate.[19] Catalysts such as Rh_2(4*S*-MEOX)$_4$, dirhodium(II) tetrakis(methyl 2-oxazolidinone-4(*S*)-carboxylate), are not generally effective in reactions with diazoacetoacetamides because of their relative inability to cause dinitrogen loss from diazoacetoacetamides. Nevertheless, these dirhodium(II) carboxamides are the most promising for highly enantioselective catalytic carbon-hydrogen insertion reactions. These investigations have just begun, and further enhancements in selectivity can be anticipated.

Experimental Procedures

***N,N*-Diisopropyldiazoacetamide (14)** was prepared in 49% overall yield by condensation with diketene, diazo transfer using methanesulfonyl azide, and deacylation with lithium hydroxide according to procedures that have been reported.[13] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.95 (s, 1H), 3.65 (hept, J = 6.9 Hz, 2H), 1.29 (d, J = 6.9 Hz, 6H). IR (thin film): 2120 and 1630 cm^{-1}. Anal. Calcd for $C_8H_{15}N_3$, 56.78; H, 8.94; N, 24.83. Found: C, 56.88; H, 8.81; N, 24.83.

Catalytic Decomposition of 14. To a suspension of Rh_2L_4 (0.02 mmol) in 20 mL of anhydrous CH_2Cl_2 was added, dropwise over 1.5 h via syringe pump, 1.0 mmol of **14** in 2.0 mL of CH_2Cl_2. After gas evolution was complete, the reaction solution was passed through a short plug of alumina followed by 2 mL of ethyl acetate to separate the catalyst. Solvent was removed under reduced pressure and the residue was purified by bulb-to-bulb distillation. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.70. Found: C, 68.09; H, 10.66. ***N*-Isopropyl-4,4-dimethyl-2-azetidinone.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.58 (hept, J = 6.9 Hz, 1H), 2.66 (s, 2H), 1.41 (s, 6H), 1.31 (d, J = 6.9 Hz, 6H). IR (thin film): 1743 cm^{-1}. ***N*-Isopropyl-5-methyl-2-pyrrolidone.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.22-4.10 (m, 1H), 4.09-4.00 (m, 1H), 2.52-2.35 (m, 2H), 2.15-2.03 (m, 2H), 1.26-1.15 (9H).

***N,N*-Dicyclohexyldiazoacetamide (17)** was prepared in 41% overall yield by the same procedure as **14**, mp 121-123°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.97 (s, 1H), 3.22-3.08 (m, 2H), 1.88-1.05 (m, 20H). IR (CCl_4): 2106 and 1622 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N_3$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.32; H, 9.26; N, 16.87.

Catalytic Decomposition of 17. The same procedure as that for **14** was followed. ***N*-Cyclohexyl-4,4-pentamethylene-2-azetidinone.** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.21-3.10 (m, 1H), 2.56 (s, 2H), 1.90-1.60 (m, 14H), 1.40-1.08 (m, 6H). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.87; H, 10.52; N, 6.31.

***trans*-2,6-Dimethylpiperidinyldiazoacetamide (20)** was prepared in 48% overall yield by the same procedure as **14**, mp 103-104°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.00 (s, 1H), 4.21-4.12 (m, 2H), 1.45-1.86 (m, 6H), 1.24 (d, J = 7.1 Hz, 6H). IR (KBr): 2095 and 1585 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.72; H, 8.38; N, 23.15.

Catalytic Decomposition of 20. The same procedure as that for **14** was followed. **8-Oxo-2,6-dimethyl-1-azabicyclo[4.2.0^{1,6}]octane,** bp 66-68°C (0.4 Torr). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.16-4.06 (m, 1H), 2.82 (d, J = 14.4 Hz, 1H), 2.62 (d, J = 14.4 Hz, 1H), 1.95-1.45 (m, 6H), 1.44 (s, 3H), 1.18 (d, J = 7.1 Hz, 3H). IR (thin film): 1745 cm^{-1}. Anal. Calcd for $C_9H_{15}NO$: C, 70.54; H, 9.87; N, 9.14. Found: C, 70.52; H, 9.88; N, 9.16.

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