Enantiocontrol in Tandem Carbonyl Ylide Formation and Intermolecular 1,3-Dipolar Cycloaddition of α-Diazo Ketones Mediated by Chiral Dirhodium(II) Carboxylate Catalyst

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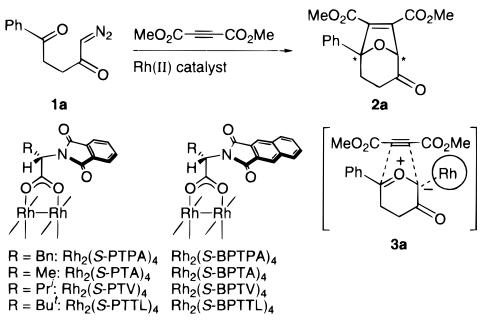
The tandem ylide generation and cycloaddition sequence triggered by copper or dirhodium(II) complex-catalyzed decomposition of α-diazo carbonyl compounds has found numerous applications in organic synthesis.[1] In this context, it has recently been documented that the use of dirhodium(II) carboxylates as catalysts has the advantage of enabling diazo decomposition under much milder conditions than are possible using most copper catalysts, as well as the advantage of higher product yields for many processes.[2] Consequently, the development of the enantioselective version of this sequence catalyzed by chiral dirhodium(II) carboxylates should be a significant addition to the field of asymmetric synthesis.[3] While high levels of enantiocontrol in C−H insertions and cyclopropanations have already been achieved using well-designed dirhodium(II) carboxylates or carboxamidates, the most crucial problem to this aim is that the reactions of ylides generated by catalytic diazo decomposition have generally been believed to proceed through the free ylide instead of the metal complex-associated ylide.[4,5] In this respect, of particular interest are the recent findings of the Padwa group that, in selected cases, the regiochemical outcome of the intramolecular cycloaddition of carbonyl ylides is highly sensitive to ligand substitution in the dirhodium(II) catalyst.[6] Following their suggestion that the catalyst might be bound to the original site of attachment during cycloaddition,[7] we have been interested in the realization of enantioselective tandem carbonyl ylide formation and the 1,3-dipolar cycloaddition sequence mediated by chiral dirhodium(II) carboxylates for the past few years. More recently, Hodgson and co-workers reported enantioselectivities of up to 53% ee in intramolecular trapping of the carbonyl ylide generated using 1 mol % of dirhodium(II) tetrakis[*N*-[(4-dodecylphenyl)sulfonyl]-(*S*)-prolinate],[3c] Rh_2(*S*-DOSP)$_4$, in which intramolecular cycloaddition faster than intermolecular cycloaddition of the ylide was a presumed requirement for asymmetric induction.[8] Herein, we report the first successful example of enantioselective intermolecular cycloaddition of the chiral rhodium(II)-associated carbonyl ylide with dimethyl acetylenedicarboxylate (DMAD), in which Rh_2(*S*-BPTV)$_4$ incorporating *N*-benzene-fused-phthaloyl-(*S*)-valine as a chiral bridging ligand has emerged as the catalyst of choice for achieving high enantioselectivities of up to 92%.[9−11]

Scheme 1



Following the seminal work of Padwa and co-workers,[12] we first explored a six-membered ring carbonyl ylide formation from 1-diazo-5-phenyl-2,5-pentanedione (**1a**) and subsequent 1,3-dipolar cycloaddition with DMAD under the influence of 1 mol % of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate],[13] Rh_2(*S*-PTPA)$_4$, at 23 °C (Scheme 1). After experimentation focusing mostly on the solvent effects, benzotrifluoride[14] was found to be the optimal choice for use in this tandem process, giving cycloadduct **2a** in 81% yield with 60% ee (Table 1, entry 1). While benzene and fluorobenzene allowed for similar levels of enantioselectivities at the expense of product yields (entries 2 and 3),[15] the use of dichloromethane and ether resulted in only poor enantioselectivities (entries 4 and 5). Using benzotrifluoride as the solvent, we next screened other chiral dirhodium(II) carboxylates, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$, and Rh_2(*S*-PTTL)$_4$,

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(4) For examples of enantioselective rearrangement via oxonium, sulfonium, or selenonium ylides generated by catalytic diazo decomposition: (a) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983. (b) Nishibayashi, Y.; Ohe, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1245. (c) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1997**, *38*, 3435. (d) Pierson, N.; Fernández-García, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705. (e) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97. The asymmetric induction observed here has been attributed to the creation of chiral, nonracemic free ylides after dissociation of the catalyst rather than involvement of the catalyst in the product-forming step.

(5) Following the early suggestion by Roskamp and Johnson, Doyle and co-workers have recently demonstrated that a metal-associated ylide is the primary product-forming intermediate in enantioselective intermolecular ylide generation/[2,3]-sigmatropic rearrangement with allyl iodide whose free ylide is achiral: (a) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (b) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653.

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(8) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471.

(9) Ibata and co-workers reported that decomposition of methyl 2-diazoacetylbenzoate in the presence of *N*-phenylmaleimide catalyzed by dirhodium(II) tetrakis[methyl 2-oxapyrrolidine-5(*S*)-carboxylate], Rh_2(5*S*-MEPY)$_4$ afforded 1,3-dipolar cycloadduct in high *exo*-selectivity, albeit in low enantioselectivities (*endo*: 20% ee; *exo*: 5% ee): Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165.

(10) Doyle and co-workers found that ethyl diazoacetate underwent reactions with *p*-nitrobenzaldehyde catalyzed by dirhodium(II) tetrakis[methyl 2-oxooxazolidine-4(*S*)-carboxylate], Rh_2(4*S*-MEOX)$_4$, to form the all-*cis* 1,3-dioxolane as the major product in 28% ee. See ref 3d.

(11) Enantioselective aziridine formation with benzylideneaniline and ethyl diazoacetate catalyzed by Cu(I)L* has been reported, where a free ylide intermediate is improbable: Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.

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(14) Ogawa, A.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 450.

(15) Substantial amounts (ca. 10−15%) of the cycloheptatriene derivatives were formed by way of the bimolecular addition of the rhodium(II) carbene carbon onto the benzene ring.

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Table 1. Enantioselective Intermolecular 1,3-Dipolar Cycloaddition of α-Diazo Ketone **1a** with DMAD Catalyzed by Rh(II) Complexes[a]

entry	Rh(II) catalyst	solvent	yield[b] (%)	% ee[c]
1	Rh_2(*S*-PTPA)$_4$	$CF_3C_6H_5$	81	60
2	Rh_2(*S*-PTPA)$_4$	C_6H_6	64	59
3	Rh_2(*S*-PTPA)$_4$	FC_6H_5	70	58
4	Rh_2(*S*-PTPA)$_4$	CH_2Cl_2	79	20
5	Rh_2(*S*-PTPA)$_4$	Et_2O	63	29
6	Rh_2(*S*-PTA)$_4$	$CF_3C_6H_5$	79	61
7	Rh_2(*S*-PTV)$_4$	$CF_3C_6H_5$	79	59
8	Rh_2(*S*-PTTL)$_4$	$CF_3C_6H_5$	80	69
9	Rh_2(*S*-BPTPA)$_4$	$CF_3C_6H_5$	81	82
10	Rh_2(*S*-BPTA)$_4$	$CF_3C_6H_5$	79	83
11	Rh_2(*S*-BPTV)$_4$	$CF_3C_6H_5$	79	90
12	Rh_2(*S*-BPTTL)$_4$	$CF_3C_6H_5$	83	65

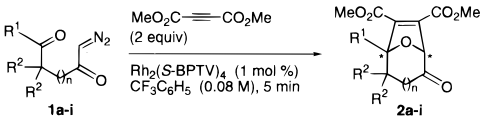
[a] All reactions were carried out as follows: Rh(II) catalyst (1 mol %) was added in one portion to a solution of diazo ketone (50 mg, 0.25 mmol) and DMAD (2 equiv) in the indicated solvent (3 mL) at 23 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent. Absolute configuration of the product was not determined.

derived from *N*-phthaloyl-(*S*)-alanine, -valine, and -*tert*-leucine, respectively.[16] The reactions provided cycloadduct **2a** with the same sign of optical rotation as above in 59−69% ee, in which the highest enantioselectivity was obtained with Rh_2(*S*-PTTL)$_4$ (entry 8). Although these values are modest, they strongly suggest that intermolecular 1,3-dipolar cycloaddition occurred through a rhodium(II)-bound carbonyl ylide **3a**.[17]

In highly enantioselective intramolecular C−H insertion reactions mediated by our dirhodium(II) catalysts, two phthalimido groups in a pair of adjoining ligands orienting to an axial coordination site of each octahedral rhodium have been considered to play a pivotal role as enantiocontrollers.[3b,18] At this stage, we envisaged that the development of dirhodium(II) carboxylates characterized by an extension of the phthalimido wall with one more benzene ring could lead to further enhancement of the enantioselectivity. Thus, new dirhodium(II) carboxylates, Rh_2(*S*-BPTPA)$_4$, Rh_2(*S*-BPTA)$_4$, Rh_2(*S*-BPTV)$_4$, and Rh_2(*S*-BPTTL)$_4$, were prepared from $Rh_2(OAc)_4$ by ligand-exchange reaction with *N*-benzene-fused-phthaloyl-(*S*)-phenylalanine, -alanine, -valine, and -*tert*-leucine, respectively.[19] Indeed, we were gratified to find that this class of catalysts, with the exception of Rh_2(*S*-BPTTL)$_4$, greatly improved the enantioselectivity observed with the respective parent dirhodium(II) complex (entries 9−12). In particular, a dramatic enhancement of up to 90% ee was recorded using Rh_2(*S*-BPTV)$_4$ (entry 11).

With the superiority of Rh_2(*S*-BPTV)$_4$ as a catalyst identified, we then investigated tandem cyclization−cycloaddition of α-diazo ketones possessing substituents other than a phenyl group at the C5 position or with a different chain length of the tether separating the two functionalities. The results are summarized in Table 2. High levels of enantioselectivity (up to 92% ee) were consistently

Table 2. Enantioselective Intermolecular 1,3-Dipolar Cycloaddition of α-Diazo Ketones **1** with DMAD Catalyzed by Rh_2(*S*-BPTV)$_4$



	substrate							
entry		*n*	R^1	R^2	temp, °C	yield, %[a]	$[\alpha]_D$ (*c*, $CHCl_3$)	ee, %[b]
1	**1a**	1	C_6H_5	H	0	77	+400 (1.73)	90[c]
2	**1a**	1	C_6H_5	H	−23	54	+403 (1.62)	92[c]
3	**1b**	1	4-MeC_6H_4	H	0	67	+360 (0.77)	92
4	**1c**	1	4-$MeOC_6H_4$	H	0	65	+366 (1.84)	90
5	**1d**	1	4-ClC_6H_4	H	0	78	+353 (1.90)	87
6	**1e**	1	4-$CF_3C_6H_4$	H	0	65	+306 (1.78)	83
7	**1f**	1	Me	H	23	50	+405 (1.01)	80
8	**1f**	1	Me	H	0	24	+413 (1.21)	82
9	**1g**	1	Et	H	23	53	+339 (1.12)	84
10[d]	**1h**	0	C_6H_5	Me	−23	75	−254 (1.72)	68
11	**1i**	2	C_6H_5	H	−23	51	+325 (1.24)	80[c]

[a] Isolated yield. [b] Determined by HPLC analysis using a Daicel Chiralpak AD or Chiralcel OD, unless otherwise stated. Absolute configuration of the product was not determined. [c] Determined by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent. [d] Reaction required 5 h to go to completion.

maintained with the electron-donating substituents at the *para* position on the benzene ring (entries 3 and 4), whereas a slight drop in enantioselectivities was observed by the introduction of electron-withdrawing groups on the benzene ring as well as with the alkyl substituents at C5 (entries 5−9). A little variation in enantioselectivities was observed by lowering the reaction temperature; however, product yields were substantially reduced (entries 1 vs 2 and 7 vs 8). The present protocol was found to allow for variation of the tether length, with cycloadducts via five- and seven-membered cyclic carbonyl ylide intermediates[20] being formed in 68% and 80% ee, respectively (entries 10 and 11).

In conclusion, we have succeeded in highly enantioselective tandem cyclization−cycloaddition of α-diazo ketones by devising Rh_2(*S*-BPTV)$_4$ as a new chiral dirhodium(II) catalyst. While the precise mechanism remains unclear, the high levels of enantioselection in intermolecular cycloadditions with DMAD provide conclusive evidence for the intermediacy of the chiral rhodium(II)-associated carbonyl ylide in the cycloaddition step. Further extension of the present method to a range of reactions via ylide formation is currently in progress.

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Supporting Information Available: Full details for the preparation of new dirhodium(II) catalysts, ligand synthesis, representative experimental procedures and spectroscopic data of reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The enantioselectivities observed with Rh_2(5*S*-MEPY)$_4$ and Rh_2(*S*-DOSP)$_4$ were 6% and 2%, respectively.

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