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Enantioselective Synthesis of 4-Substituted 2-Pyrrolidinones by Site-selective C-H Insertion of α-Methoxycarbonyl-α-diazoacetanilides Catalyzed by Dirhodium(II) Tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate]

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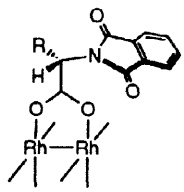
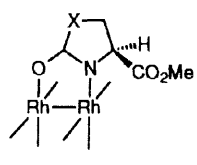
Abstract: *Site- and enantioselective intramolecular C-H insertion of α-methoxycarbonyl-α-diazoacetamides has been achieved by exploiting a p-nitrophenyl group as the N-substituent and dirhodium(II) tetrakis[N-phthaloyl-(S)-tert-leucinate] as catalyst, leading to the formation of 4-substituted 2-pyrrolidinone derivatives of up to 82% ee. The efficiency of the present protocol has been verified well by a short-step synthesis of (R)-(-)-baclofen.*

Enantioselective C-H insertion reaction of α-diazo carbonyl compounds catalyzed by chiral dirhodium(II) complexes is rapidly becoming recognized as a potentially powerful means for the construction of both carbocyclic and heterocyclic systems in optically active form.[1] Our efforts in this area have led to the development of dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids as the bridging ligands, which catalyze intramolecular C-H insertion reactions of α-diazo carbonyl compounds site-selectively to give optically active cyclopentanone, 2-indanone, and 2-azetidinone derivatives with up to 80%, 98%, and 74% ee, respectively.[2-4] As a logical extension of our studies, we have addressed enantioselective construction of 4-substituted 2-pyrrolidinones *via* a site-selective C-H insertion process.

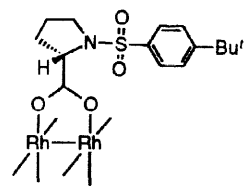
Apart from enantiocontrol, site-control has remained a major challenge in the enantioselective construction of heterocycles *via* an intramolecular C-H insertion process in an acyclic system. It is well documented that site-selectivities in the rhodium(II)-catalyzed C-H insertion reaction of α-diazo amides are highly dependent on the α-substituents of the diazo carbon as well as the *N*-substituents on the amide moiety.[5,6] For example, cyclization of *N*-alkyl-*N*-*tert*-butyl-α-diazoacetamides pioneered by Doyle and his coworkers with Rh_2(5*S*-MEPY)$_4$ and Rh_2(4*S*-MEOX)$_4$ gave a mixture of 2-pyrrolidinone and 2-azetidinone derivatives of up to 71% and 80% ee, respectively, with the former being favored.[7] In this context, we demonstrated that Rh_2(*S*-PTPA)$_4$-catalyzed cyclization of *N*-alkyl-*N*-*tert*-butyl-α-methoxycarbonyl-α-diazoacetamides led to the exclusive formation of 2-azetidinone derivatives of up to 74% ee.[4] On the other hand, Wee and his coworkers recently reported that Rh_2(OAc)$_4$-catalyzed cyclization of *N*-alkyl-*N*-*p*-methoxyphenyl-α-alkoxycarbonyl-α-diazoacetamides bearing a chiral auxiliary alcohol resulted in the predominant or exclusive formation of 2-



R = Me: Rh_2(*S*-PTA)$_4$, R = Bn: Rh_2(*S*-PTPA)$_4$
R = *i*-Pr: Rh_2(*S*-PTV)$_4$, R = *t*-Bu: Rh_2(*S*-PTTL)$_4$



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



Rh_2(*S*-TBSP)$_4$

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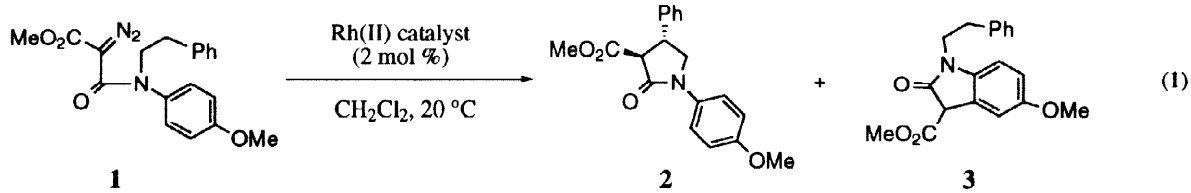
pyrrolidinone derivatives of up to 98% de, wherein the *N*-*p*-methoxyphenyl substituent played a dual role as a practical nitrogen protective group as well as a site-control element.[6,8]

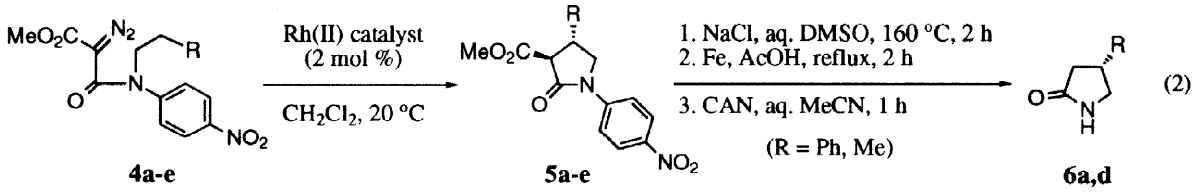
Inspired by Wee's site- and diastereoselective construction of 4-substituted 2-pyrrolidinones, we initially explored cyclization of *N*-phenylethyl-*N*-*p*-methoxyphenyl-α-methoxycarbonyl-α-diazoacetamide (**1**) with the aid of 2 mol % of Rh_2(*S*-PTPA)$_4$ (eq 1). While $Rh_2(OAc)_4$-catalyzed cyclization of **1** afforded *trans*-3-methoxycarbonyl-4-phenyl-2-pyrrolidinone **2**[6,9] *via* aliphatic C-H insertion and 2(3*H*)-indolinone **3** *via* aromatic C-H insertion in 64% and 12% yields, respectively, Rh_2(*S*-PTPA)$_4$-catalysis of **1** was found to produce **3** in 68% yield along with less than 5% of **2**. No trace of 2-azetidinone derivatives could be detected in either case. The difference in predominant insertion sites with $Rh_2(OAc)_4$ and Rh_2(*S*-PTPA)$_4$ can be rationalized by assuming that aromatic C-H insertion proceeds *via* an electrophilic addition of the rhodium(II) carbene carbon to the aromatic ring rather than *via* a direct C-H insertion mechanism as pointed out by ourselves and other groups,[3a,10-12] wherein aliphatic C-H insertion is presumed to be more sensitive to nonbonding interactions with the bridging ligands on the rhodium relative to aromatic C-H insertion.



1 **2** **3**

$Rh_2(OAc)_4$	64%	12%
Rh_2(*S*-PTPA)$_4$	<5%	68%

At this point, we envisaged that, by switching the substituent at the para position on the benzene ring from the electron-donating methoxy group to the electron-withdrawing nitro group, formation of 2(3*H*)-indolinones *via* an electrophilic aromatic substitution-type reaction could be suppressed in favor of the ring closure leading to 2-pyrrolidinones. Indeed, we found that cyclization of *N*-phenylethyl-*N*-*p*-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide (**4a**) in the presence of Rh_2(*S*-PTPA)$_4$ gave exclusively *trans*-3-methoxycarbonyl-4-phenyl-2-pyrrolidinone **5a**[9] in 82% yield, with no trace of 2(3*H*)-indolinone or 2-azetidinone derivatives (eq 2). The



4a-e **5a-e** **6a,d**

a: R = Ph, **b**: R = *p*-$MeOC_6H_4$, **c**: R = *p*-$NO_2C_6H_4$, **d**: R = Me, **e**: R = Et

enantioselectivity in this reaction was determined to be 47% ee by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent.[13] The preferred absolute configuration at the insertion site was established as *R* by its transformation [(1) NaCl, aq. DMSO, 160 °C, 2 h; (2) Fe,[14] AcOH, reflux, 2 h; (3) ceric ammonium nitrate (CAN),[15] MeCN] to the known 4-phenyl-2-pyrrolidinone (**6a**), $[\alpha]_D^{25}$ -17.9 (*c* 1.07, MeOH) [lit.,[16] $[\alpha]_D^{25}$ -37.8 (*c* 0.95, MeOH) for (*R*)-**6a**]; undoubtedly, the above % ee value was virtually consistent with that based on the optical rotation value. We next screened other chiral dirhodium(II) carboxylates, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$, Rh_2(*S*-PTTL)$_4$, and Rh_2(*S*-TBSP)$_4$[17], and the results are summarized in Table 1. While a consistent sense of enantioselection was observed in all cases, % ee values were dependent on the catalyst. Of dirhodium(II) carboxylates incorporating *N*-phthaloyl-(*S*)-amino acids, Rh_2(*S*-PTTL)$_4$ characterized by a bulky *tert*-butyl group proved to be the catalyst of choice for displaying the highest degree of enantioselectivity (74% ee, entry 4), though we cannot presently rationalize the effect of the bridging ligands on the degree of enantioselection. It is worthy of note that the enantioselectivity observed with Rh_2(*S*-TBSP)$_4$ developed by

Davies[17] was 6% ee (entry 5), suggesting the unique ability of our dirhodium(II) complexes.[18]

With the effectiveness of Rh_2(*S*-PTTL)$_4$ as the catalyst identified, we then explored cyclization of α-diazoacetanilides **4b-e** possessing substituents other than a phenyl group at the insertion site. The results are summarized in Table 2. While the same sense of enantioselection as that with **4a** was observed in every case, the aryl group at the insertion site was found to exhibit much higher enantioselectivities than the alkyl group (73-81% ee vs 33-34% ee, entries 1-3 vs 4 and 5). We previously observed similar substituent effects in enantioselective synthesis of 3-substituted cyclopentanones *via* C-H insertion, where the introduction of an electron-donating methoxy group at the para position on the benzene ring sharply diminished the enantioselectivity.[2b] In the present reaction, however, a little variation in enantioselectivities was observed by the introduction of electron-donating or electron-withdrawing groups on the benzene ring (entries 1-3), which provides added flexibility in the present protocol.

Table 1. Enantioselective Intramolecular C-H Insertion of α-Diazoacetamide **4a** Catalyzed by Chiral Rh(II) Catalyst

entry	Rh(II) catalyst	time, h	% yield[a]	% ee[b]	config[c]
1	Rh_2(*S*-PTPA)$_4$	4	82	47	3*S*, 4*R*
2	Rh_2(*S*-PTA)$_4$	5	83	47	3*S*, 4*R*
3	Rh_2(*S*-PTV)$_4$	3	82	26	3*S*, 4*R*
4	Rh_2(*S*-PTTL)$_4$	5	80	74	3*S*, 4*R*
5	Rh_2(*S*-TBSP)$_4$	4	87	6	3*S*, 4*R*

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent. [c]See the text.

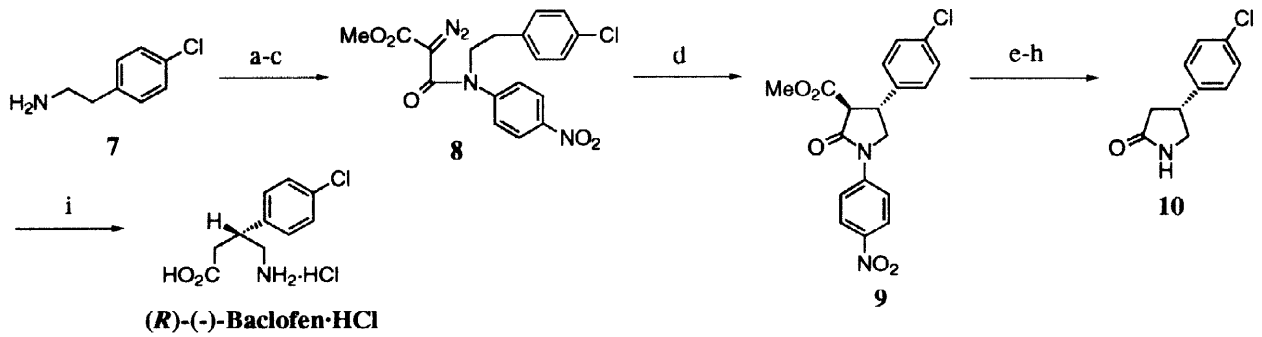
Table 2. Enantioselective Synthesis of 4-Substituted 2-Pyrrolidinones Catalyzed by Rh_2(*S*-PTTL)$_4$

	substrate			2-pyrrolidinones			
entry		R	time, h	% yield[a]	$[\alpha]_D$ (*c*, $CHCl_3$)	% ee[b]	config
1	**4a**	Ph	5	**5a** 80	+7.18 (1.12)	74	3*S*, 4*R*[c]
2	**4b**	*p*-$MeOC_6H_4$	4	**5b** 72	+12.6 (1.17)	81	(3*S*, 4*R*)[d]
3	**4c**	*p*-$NO_2C_6H_4$	8	**5c** 81	+14.0 (1.05)	73	(3*S*, 4*R*)[d]
4	**4d**	Me	3	**5d** 82	-2.11 (1.06)	33	3*S*, 4*S*[e]
5	**4e**	Et	4	**5e** 84	-4.67 (1.07)	34	(3*S*, 4*S*)[d]

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent. [c]See the text. [d]Assigned by analogy. [e]The preferred absolute configuration at insertion site of **5d** was established as *S* by its transformation to the known (*S*)-4-methyl-2-pyrrolidinone. See ref 19.

Finally, we applied the present method to the synthesis of (*R*)-(-)-baclofen, a typical $GABA_B$ receptor agonist (Scheme 1).[20] There have recently been reported a number of syntheses of (*R*)-(-)-baclofen *via* chemoenzymatic[21] and diastereoselective[22] approaches, but a catalytic, enantioselective synthesis has not yet been addressed. Toward this end, *N*-2-(*p*-chlorophenyl)ethyl-*N*-*p*-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide (**8**) was prepared from commercially available 2-(*p*-chlorophenyl)ethylamine (**7**) by condensation with 4-fluoronitrobenzene[23] followed by *N*-acylation and subsequent diazo transfer in 87% overall yield. Cyclization of **8** with the aid of 2 mol % of Rh_2(*S*-PTTL)$_4$ proceeded uneventfully to afford the desired 2-pyrrolidinone **9**, $[\alpha]_D^{25}$ +16.8 (*c* 0.85, $CHCl_3$), in 83% yield, the enantioselectivity of which was determined to be 82% ee by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent. Successive removal of the methoxycarbonyl and *p*-nitrophenyl groups from **9** furnished the known lactam **10**, mp 108-115 °C, $[\alpha]_D^{25}$ -33.4 (*c* 1.01, EtOH), in 76% yield, which, upon one recrystallization from AcOEt-hexane, produced the optically pure sample, mp 113-114 °C , $[\alpha]_D^{25}$ -39.1 (*c* 1.03, EtOH) [lit.,[22b] mp 112 °C, $[\alpha]_D^{25}$ -39 (*c* 1, EtOH) for (*R*)-**10**] in 79% yield. Acidic hydrolysis of **10** afforded (*R*)-(-)-baclofen as its hydrochloride, mp 214-215 °C (dec), $[\alpha]_D^{25}$ -1.42 (*c* 1.12, H_2O) [lit.,[24] mp 215 °C (dec), $[\alpha]_D^{25}$ -1.4 (*c* 1, H_2O)].

In summary, we have achieved the first catalytic, enantioselective synthesis of 4-aryl-substituted 2-pyrrolidinones of up to 82% ee *via* Rh_2(*S*-PTTL)$_4$-mediated C-H insertion of α-methoxycarbonyl-α-diazoacetamides, wherein the dual role of the *N*-*p*-nitrophenyl substitutent as a practical nitrogen protective group as



Scheme 1. *Reagents and conditions*: (a) 4-fluoronitrobenzene, K_2CO_3, EtOH, 160 °C, 18 h, 95%; (b) MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 96%; (c) *p*-acetamidobenzenesulfonyl azide, DBU, MeCN, 0 °C, 3 h, 95%; (d) Rh_2(*S*-PTTL)$_4$ (2 mol %), CH_2Cl_2, 23 °C, 6 h, 83% (82% ee); (e) NaCl, aq. DMSO, 160 °C, 2 h, 96%; (f) Fe, AcOH, reflux, 2 h, 97%; (g) CAN, MeCN, H_2O, 0 °C, 1.5 h, 81%; (h) recrystallization from AcOEt-*n*-hexane (>99% ee), 79%; (i) 6N HCl, reflux, 6 h, 74%.

well as a site-control element has proven to be crucial to the success. The efficiency of the present protocol has been verified well by a short-step synthesis of (*R*)-(-)-baclofen, thus providing great potential for a facile access to its novel analogues for biological and pharmacological investigations.[25]

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