Pergamon

Tetrahedron Letters 43 (2002) 9561–9564

TETRAHEDRON LETTERS

Dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate]: a new chiral Rh(II) catalyst for enantioselective amidation of C–H bonds

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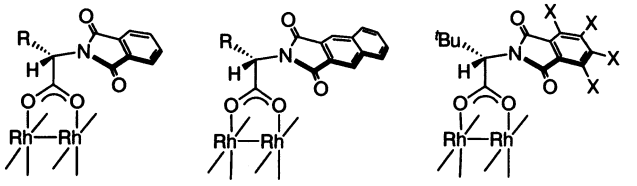
Received 25 September 2002; revised 21 October 2002; accepted 25 October 2002

Abstract—Dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], characterized by substitution of chlorine atoms for four hydrogen atoms on the phthalimido group in the parent dirhodium(II) complex has been found to be well suited for enantioselective amidation of benzylic C–H bonds with [(4-nitrophenyl)sulfonylimino]phenyliodinane. The observed enantioselectivity of up to 84% ee is the highest reported to date for dirhodium(II) complex-catalyzed C–H amidations. © 2002 Elsevier Science Ltd. All rights reserved.

Pioneered by the groups of Breslow[1] and Mansuy[2] in the early 1980s, transition metal-catalyzed nitrene transfer reactions with (arenesufonylimino)phenyliodinanes have been recognized as potentially powerful methods for the synthesis of aziridines, amides, or amines.[3] Consequently, a great deal of effort has recently been directed toward the development of enantioselective version of these catalytic processes. While high levels of enantiocontrol in aziridinations have already been achieved using well-designed chiral catalysts,[4] such as Cu(I)–bis(oxazoline),[5] Cu(I)–diimine,[6] Mn(III)–salen[7] or Mn(III)–porphyrin[8] complexes, only a few examples of enantioselective amidation of C–H bonds have been reported. Müller and co-workers were the first to demonstrate asymmetric induction (up to 33% ee) in the reaction of [(4-nitrophenyl)sulfonylimino]phenyliodinane, NsN=IPh (**1**, Ns = 4-$NO_2C_6H_4SO_2$) and indan (**2**) employing dirhodium(II) tetrakis[(*R*)-binaphthylphosphate], Rh_2(*R*-BNP)$_4$, as a chiral catalyst.[9] Thereafter, Che and co-workers explored amidation of a series of benzylic hydrocarbons with TsN=IPh in the presence of chiral Ru(III)- or Mn(III)-porphyrin-catalysts, wherein modest enantioselectivity of 54% ee was obtained with 1-ethylnaphthalene.[8b,10] More recently, Katsuki and co-worker have disclosed that a chiral Mn(III)–salen complex modified with an electron-withdrawing group is an efficient catalyst for the reaction of TsN=IPh with various allylic and benzylic hydrocarbons, and it displays the highest degree of enantioselectivity (89% ee) known for this type of transformations.[11] In recent years we have achieved high levels of enantiocontrol in a range of catalytic Rh(II)–carbene transformations by developing dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acids as bridging ligands.[12] Using the analogy between carbenes and nitrenes, we now address the issue of enantiocontrol in Rh(II)-catalyzed C–H amidation reactions.



Following the pioneering work of Müller,[9] we initially explored C–H insertion of **1** with 5 equiv. of **2** in the presence of 2 mol% of our chiral dirhodium(II) carboxylates (Table 1).[13] The use of tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate], Rh_2(*S*-PTPA)$_4$, in dichloromethane at 0°C provided amidation product **3** in 68% yield (entry 1).[14] The enantioselectivity in this reaction was determined to be 15% ee by HPLC analysis (Daicel Chiralpak AD).[15] The preferred absolute stereochemistry of **3** [$[\alpha]_D^{24}$ +5.67 (*c* 1.07, $CHCl_3$)] was established as *R* by comparing the sign of the optical rotation with

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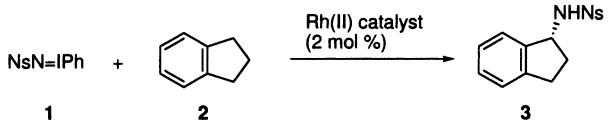
PII: S0040-4039(02)02432-2

(*R*)-**3** [$[\alpha]_D^{25}$ +34.5 (*c* 1.10, $CHCl_3$)], which was prepared from (*R*)-1-aminoindan[16] (*p*-$NO_2C_6H_4SO_2Cl$, aq. NaOH–CH_2Cl_2, 0°C, 1 h, 76%). We next screened other chiral dirhodium(II) carboxylates, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$, and Rh_2(*S*-PTTL)$_4$, derived from *N*-phthaloyl-(*S*)-alanine, -valine, and -*tert*-leucine, respectively (entries 2–4). While a uniform sense of asymmetric induction was observed in all cases, the highest levels of enantioselectivity were only 27 and 28% ee obtained with Rh_2(*S*-PTA)$_4$ and Rh_2(*S*-PTTL)$_4$, respectively (entries 2 and 4).[17] Focusing on these two catalysts, we then evaluated the abilities of Rh_2(*S*-BPTA)$_4$ and Rh_2(*S*-BPTTL)$_4$ which are characterized by an extension of the phthalimido group with one more benzene ring.[12b] Surprisingly, the use of Rh_2(*S*-BPTA)$_4$ markedly diminished product yield,[18] although the drop in enantioselectivity was slight (entry 5). The use of Rh_2(*S*-BPTTL)$_4$ resulted in similar levels of product yield and enantioselectivity as found with Rh_2(*S*-PTTL)$_4$ (entry 6).

It has recently been demonstrated that ligand modification by incorporating electron-donating[19] or electron-withdrawing[11,20] substituents can have a profound influence on the rate and enantioselectivity of catalytic asymmetric reactions. Based on these precedents, we envisaged that the development of dirhodium(II) carboxylates characterized by substitution of electron-withdrawing groups for four hydrogen atoms on the phthalimido group could facilitate the formation and ensuing C–H insertion of the presumed Rh(II)-complexed sulfonyl nitrene intermediate, leading to further enhancement of the enantioselectivity.[21] Thus, new dirhodium(II) carboxylates, Rh_2(*S*-TFPTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$ were prepared from $Rh_2(OAc)_4$ by ligand exchange reaction[22] with *N*-tetrafluorophthaloyl- and *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucines,[23] respectively.[24,26] Indeed, we were gratified to find that Rh_2(*S*-TFPTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$ exhibited even higher enantioselectivities (54% and 66% ee, respectively) than the unsubstituted parent dirhodium(II) complex, Rh_2(*S*-PTTL)$_4$ (entries 7 and 8). Using Rh_2(*S*-TCPTTL)$_4$ as a catalyst, we then studied the effects of solvent and temperature on enantioselectivity. The solvent survey revealed that dichloromethane was the optimal solvent for this transformation. While benzene and benzotrifluoride exhibited nearly the same yields and enantioselectivities as dichloromethane, reaction times to complete the reaction in these solvents were extended (entries 9 and 10). Toluene was found to be the least effective due to the formation of substantial amounts (30%) of *N*-benzyl-4-nitrobenzenesulfonamide arising from the C–H insertion into a methyl group of toluene (entry 11). When the reaction in dichloromethane was conducted at −23°C, the enantioselectivity was increased to 70% ee without affecting product yield (entry 12). Although reaction times at −23°C were extended (6 h) compared to those at 0°C (0.5 h), much longer reaction times (24 h) were necessary with the case of Rh_2(*S*-PTTL)$_4$ where product yield was substantially reduced (entry 13). These results strongly suggest that the chlorinated ligand did confer higher

Table 1. Enantioselective amidation of indan (**2**) with NsN=IPh (**1**) catalyzed by chiral dirhodium(II) complexes[a]



Entry	Rh(II) catalyst	R		Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	Rh_2(*S*-PTPA)$_4$	Bn		CH_2Cl_2	0	0.5	68	15
2	Rh_2(*S*-PTA)$_4$	Me		CH_2Cl_2	0	0.5	75	27
3	Rh_2(*S*-PTV)$_4$	^{i}Pr		CH_2Cl_2	0	0.5	69	15
4	Rh_2(*S*-PTTL)$_4$	^{t}Bu		CH_2Cl_2	0	0.5	79	28
5	Rh_2(*S*-BPTA)$_4$	Me		CH_2Cl_2	0	0.5	23	25
6	Rh_2(*S*-BPTTL)$_4$	^{t}Bu		CH_2Cl_2	0	0.5	80	33
7	Rh_2(*S*-TFPTTL)$_4$	^{t}Bu	(X = F)	CH_2Cl_2	0	0.5	89	54
8	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	CH_2Cl_2	0	0.5	87	66
9	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	Benzene	10	3.5	89	63
10	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	$CF_3C_6H_5$	0	2.0	81	59
11	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	Toluene	0	3.5	57[d]	62
12	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	CH_2Cl_2	−23	6.0	82	70
13	Rh_2(*S*-PTTL)$_4$	^{t}Bu		CH_2Cl_2	−23	24.0	53	27
14	Rh_2(*S*-TCPTTL)$_4$	^{t}Bu	(X = Cl)	CH_2Cl_2	−40	12.0	51	73

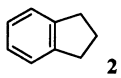
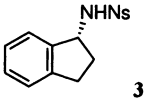
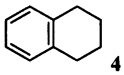
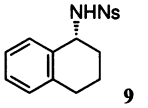
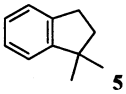
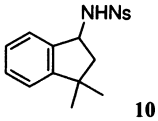
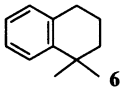
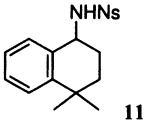
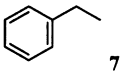
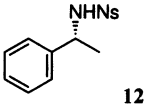
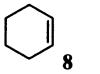
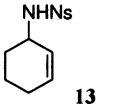
[a] Reactions were carried out as follows: **1** (40.4 mg, 0.10 mmol) was added in one portion to a solution of **2** (59 mg, 0.5 mmol, 5 equiv.) and Rh(II) catalyst (0.002 mmol, 2 mol%) in the indicated solvent (1.0 mL) at the indicated temperature under argon.

[b] Isolated yield based on **1**.

[c] Determined by HPLC [column, Daicel Chiralpak AD; eluent, 3:1 *n*-hexane:*i*-PrOH; flow rate, 1.0 mL/min; retention time 11.8 min [(*R*)-**3**] and 16.7 min [(*S*)-**3**]].

[d] BnNHNs (ca. 30%) was formed by way of C–H insertion reaction of **1** with a methyl group of toluene.

Table 2. Enantioselective intermolecular C–H amidation with NsN=IPh (**1**) catalyzed by $Rh_2(S\text{-TCPTTL})_4$

entry	substrate	product	yield %[a]	$[\alpha]_D$ (c, $CHCl_3$)	ee %	confign
1	 **2**	 **3**	82	+22.7 (1.30)	70[b]	*R*[c]
2	 **4**	 **9**	88	+44.3 (1.40)	76[b]	*R*[d]
3	 **5**	 **10**	69	+19.7 (1.18)	76[b]	–[e]
4	 **6**	 **11**	52	+42.6 (0.94)	84[b]	–[e]
5	 **7**	 **12**	61	+6.23 (0.80)	33[f]	*R*[g]
6	 **8**	 **13**	54[h]	+9.33 (0.73)	19[f]	–[e]

[a]Isolated yield based on **1**. [b]Determined by HPLC (Daicel Chiralpak AD). [c]Determined by chemical correlation, see the text. [d]Preferred absolute stereochemistry of the product was not determined. [e]Determined by comparing the sign of the optical rotation with that of (*R*)-**9** derived from (*R*)-1-aminotetralin.[29] [f]Determined by HPLC (Daicel Chiralpak AS). [g]Determined by comparing the sign of the optical rotation with that of (*R*)-**12** derived from (*R*)-1-phenylethylamine.[30] [h]Azridination product (23%) was also obtained.

reactivity to the associated dirhodium(II) catalyst in this transformation. While further enhancement of up to 73% ee was possible by lowering the reaction temperature to −40°C (entry 14), −23°C was found to be the temperature limit in terms of both reaction rate and product yield.

Having identified the effectiveness of the combinational use of $Rh_2(S\text{-TCPTTL})_4$ as a catalyst and dichloromethane as a solvent, we then investigated the scope and limitation of this process (Table 2). The amidation of tetralin (**4**) under the optimized conditions for indan (**2**) gave amidation product **9** in high yield with 76% ee (entry 2). As already demonstrated by Katsuki,[11] 1,1-dimethylindan(**5**)[27] and 1,1-dimethyltetralin (**6**)[28] provided even higher enantioselectivities than the unsubstituted parent substrates (entries 1 versus 3 and 2 versus 4). It is worth noting that the enantioselectivity of 84% ee obtained with **6** is the highest reported to date for dirhodium(II) complex-catalyzed C–H amidations. In contrast to these results, the present protocol was found to be less effective for ethylbenzene (**7**) and cyclohexene (**8**).

In summary, we have demonstrated that $Rh_2(S\text{-TCPTTL})_4$ developed through the electronic tuning of $Rh_2(S\text{-PTTL})_4$ is effective for enantioselective amidation of C–H bonds, wherein this catalyst has been found to exhibit even higher reactivity and enantioselectivity (up to 84% ee) than the parent dirhodium(II) complex.[31] Further application of this catalyst to enantioselective aziridinations as well as mechanistic and stereochemical studies are currently in progress.

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Ms. S. Oka and Ms. M. Kiuchi of Center for Instrumental Analysis at Hokkaido University for mass measurements.

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14. The C–H amidation of indan (**2**) with 1.5 equiv. of **1** in the presence of 2 mol% of Rh_2(*S*-PTPA)$_4$ afforded the amidation product **3** in 18% yield with 19% ee.
15. Previously, Müller reported that Rh_2(*S*-PTPA)$_4$-catalyzed amidation of **2** with **1** in CH_2Cl_2 afforded **3** in 77% yield with 7% ee.[9]
16. R-1-Aminoindan was purchased from Aldrich Chemical Company, Inc.
17. We also examined Rh_2(*S*-PTTL)$_4$-catalyzed C–H amidation of TsN=IPh with **2**, which gave the amidation product in 16% yield with 38% ee. On the other hand, a similar reaction of [[(4-methoxyphenyl)sulfonyl]imino]-phenyliodinane gave a complex mixture of products.
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24. According to the procedure of Bose,[25] *N*-tetrafluorophthaloyl-(*S*)-*tert*-leucine [$[\alpha]_D^{20}$ −40.8 (*c* 1.58, EtOH)] and *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucine [$[\alpha]_D^{20}$ −34.7 (*c* 1.69, EtOH)] were prepared from (*S*)-*tert*-leucine and tetrafluoro- or tetrachlorophthalic anhydride without any racemization.
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26. The new dirhodium(II) carboxylates exhibited satisfactory spectral (IR, 270 MHz ^{1}H NMR and 67.8 MHz ^{13}C NMR), analytical, and mass spectral characteristics.
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30. (*R*)-1-Phenylethylamine was purchased from Wako Chemical Industries, Ltd.
31. Representative procedure (Table 2, entry 1): **1** (80.8 mg, 0.20 mmol) was added in one portion to a solution of **2** (118 mg, 1.00 mmol, 5.0 equiv.) and bis(ethyl acetate) adduct of Rh_2(*S*-TCPTTL)$_4$ (7.9 mg, 0.004 mmol, 2 mol%) in CH_2Cl_2 (2.0 mL) at −23°C. After 6.0 h of stirring at this temperature, the whole mixture was concentrated in vacuo and purified by column chromatography (silica gel, 5:1 *n*-hexane:ethyl acetate) to provide (*R*)-**3**[9] (52.4 mg, 82%); $[\alpha]_D^{25}$ +22.7 (*c* 1.30, $CHCl_3$). Enantiomeric excess was determined to be 70% by HPLC analysis [column, Daicel Chiralpak AD; eluent, 3:1 *n*-hexane:*i*-PrOH; flow rate, 1.0 mL/min; retention time, 11.8 min [major (*R*)-isomer] and 16.7 min [minor (*S*)-isomer].