ORGANIC LETTERS

2011
Vol. 13, No. 23
6284–6287

Catalytic Enantioselective Intermolecular Cycloaddition of Diazodiketoester-Derived Carbonyl Ylides with Indoles Using Chiral Dirhodium(II) Carboxylates

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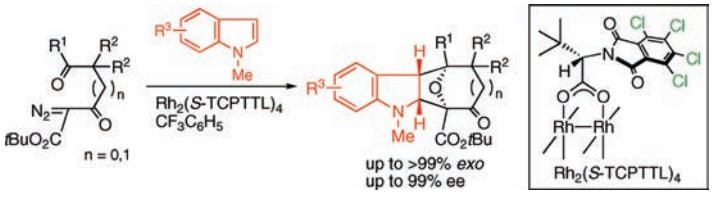
Received October 14, 2011

ABSTRACT



The first example of enantioselective intermolecular cycloaddition of carbonyl ylides with indoles is described. The cycloaddition of five- and six-membered carbonyl ylides derived from diazodiketoesters with *N*-methylindoles under catalysis by dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TCPTTL)$_4$, gave cycloadducts in high yields and with high levels of enantioselectivity (up to 99% ee) as well as excellent *exo* diastereoselectivity.

Fused indolines are important synthetic targets because they are found in a large number of biologically active alkaloids.[1] Consequently, the development of efficient methods for the stereoselective synthesis of these molecules continues to attract considerable attention in the field of synthetic organic chemistry.[2] Among a variety of methods, those based on the annulation of indoles offer a distinctive advantage since a diverse array of indoles are readily available.[3,4] In this context, the dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation–1,3-dipolar cycloaddition reaction sequence[5,6] has been regarded as one of the most powerful methods for the rapid assembly of complex oxapolycyclic indolines. Padwa et al. demonstrated the efficient participation of the indole C2–C3 double bond as a 2π component in intramolecular cycloadditions with push–pull carbonyl ylides.[7] The power of this methodology was verified by the synthesis

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10.1021/ol2027625
Published on Web 11/02/2011

of core skeleta of aspidosperma[8] and kopsifoline alkaloids[9] and by the total synthesis of (±)-aspidophytine.[10] Boger et al. developed an elegant approach to (−)-vindoline and related alkaloids based on a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles.[11] Muthusamy et al. reported the first example of intermolecular cycloaddition of five-membered cyclic carbonyl ylides with a variety of indoles.[12]

Over the past decade, enantioselective carbonyl ylide cycloadditions catalyzed by chiral dirhodium(II) complexes have been developed.[13−15] Recently, we reported catalytic enantioselective cycloadditions of six-membered carbonyl ylides derived from 2-diazo-3,6-diketoesters with arylacetylene, alkoxyacetylene, and styrene dipolarophiles.[16,17] In this process, Rh_2(*S*-TCPTTL)$_4$ (**1a**) (Figure 1),[18−20] the chlorinated analogue of Rh_2(*S*-PTTL)$_4$ (**1c**)[21−23] proved to be the catalyst of choice, providing the corresponding cycloadducts in good to high yields and with high levels of enantioselectivity (up to 99% ee) as well as with perfect *exo* diastereoselectivity for styrenes. From frontier molecular orbital (FMO) analysis for the reaction in the absence of a catalyst, the dominant interaction was found to be between the LUMO of the carbonyl ylide and the HOMO of the dipolarophile,[24] which predicted the regiochemistry exactly as observed. As a logical extension of this catalytic process, we focused on the use of indoles with high HOMO energy levels as dipolarophiles. To the best of our knowledge, no examples of an enantioselective version of this sequence have been reported to date.[25] Herein, we report the first example of enantioselective intermolecular cycloaddition of carbonyl ylides with indoles, in which Rh_2(*S*-TCPTTL)$_4$ (**1a**) provides cycloadducts with high levels of enantioselectivity (up to 99% ee) and excellent *exo* diastereoselectivity.

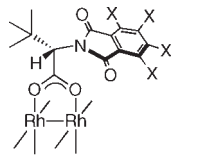

Figure 1. Chiral dirhodium(II) complexes.

On the basis of our previous work,[16] we initially explored the cycloaddition of a six-membered cyclic carbonyl ylide derived from 2-diazo-3,6-diketoester **2a** with 2 equiv of *N*-methylindole (**3a**) in the presence of 1 mol % of Rh_2(*S*-TCPTTL)$_4$ (**1a**).[18−20] As expected from FMO analysis (see Supporting Information (SI)), the reaction in α,α,α-trifluorotoluene proceeded smoothly at rt to give *exo* cycloadduct **4a** as the sole product in 81% yield (Table 1, entry 1). The *exo* stereochemistry of **4a** was established by a NOESY experiment (SI). The enantioselectivity of this reaction was determined to be 99% ee by HPLC analysis

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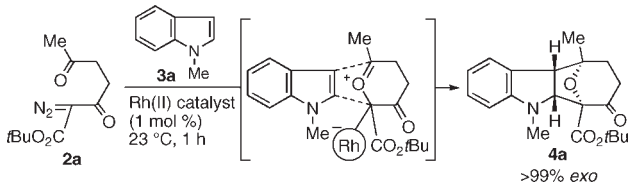
(25) Recently, we reported asymmetric intramolecular carbonyl ylide cycloaddition of diazo imides containing a tethered indoles, in which Rh_2(*S*-TCPTTL)$_4$ (**1a**) provided cycloadducts in moderate yields and with enantioselectivities of up to 66% ee. Nambu, H.; Hikime, M.; Krishnamurthi, J.; Kamiya, M.; Shimada, N.; Hashimoto, S. *Tetrahedron Lett.* **2009**, *50*, 3675–3678.

(26) The preferred absolute stereochemistry of cycloadducts was not determined.

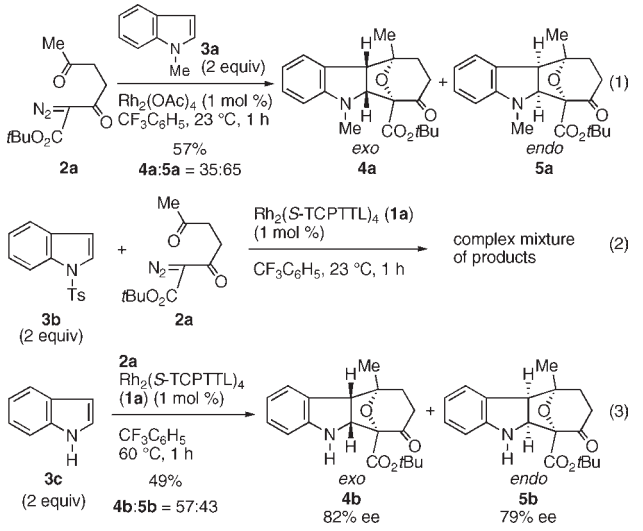
Table 1. Enantioselective Intermolecular Cycloaddition of **2a** with **3a** Catalyzed by **1a**–**c**[a]



entry	Rh(II) catalyst	solvent	yield(%)[b]	ee(%)[c]
1	Rh_2(*S*-TCPTTL)$_4$ (**1a**)	$CF_3C_6H_5$	81	99
2	Rh_2(*S*-TFPTTL)$_4$ (**1b**)	$CF_3C_6H_5$	77	97
3	Rh_2(*S*-PTTL)$_4$ (**1c**)	$CF_3C_6H_5$	71	89
4	Rh_2(*S*-TCPTTL)$_4$ (**1a**)	toluene	75	93
5	Rh_2(*S*-TCPTTL)$_4$ (**1a**)	CH_2Cl_2	33	87

[a] All reactions were carried out as follows: a solution of **2a** (48.0 mg, 0.2 mmol) and **3a** (2 equiv) in $CF_3C_6H_5$ (1 mL) was added over 1 h to a solution of Rh(II) catalyst (1 mol %) in $CF_3C_6H_5$ (1 mL) at rt. [b] Isolated yield. [c] Determined by HPLC.

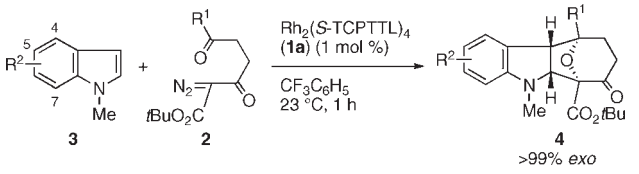
using a Daicel Chiralcel OD-H column.[26] We next evaluated the performance of Rh_2(*S*-TFPTTL)$_4$ (**1b**)[27] and Rh_2(*S*-PTTL)$_4$ (**1c**).[21–23] Although complete *exo* diastereoselectivity was obtained in both cases, product yields and enantioselectivities were lower than those found with **1a** (entries 2 and 3). A survey of solvents with **1a** revealed that α,α,α-trifluorotoluene was the optimal solvent for this transformation (entries 1 vs 4 and 5). It is notable that the use of $Rh_2(OAc)_4$ as an achiral catalyst gave a 35:65 mixture of *exo* and *endo* cycloadducts **4a** and **5a** in 57% combined yield (eq 1). While the mechanistic profile for this reaction is not clear at this time, these results suggest that the presence of phthalimido groups in the bridging ligands of dirhodium(II) catalysts **1a**–**c** is responsible for the complete *exo* selectivity.[14a,c,16,19,23] We then examined the effects of N-substitution of the indole ring. The use of indole **3b** bearing a strongly electron-withdrawing Ts group failed to give the corresponding cycloadducts (eq 2).



The reaction of **2a** with an unmasked indole (**3c**) at 60 °C[28] resulted in only modest product yield as well as poor diastereoselectivity (49% yield, *exo*/*endo* = 57:43, eq 3), though good enantioselectivities were observed (**4b**: 82% ee; **5b**: 79% ee). Clearly, the indole N-substituent has a profound effect on diastereoselectivity as well as on the efficiency of the cycloaddition.

Using Rh_2(*S*-TCPTTL)$_4$ (**1a**) as a catalyst, we then explored the use of phenyl-substituted diazodiketoester **2b** and a range of indole dipolarophiles (Table 2). The reaction of **2b** with **3a** afforded exclusively *exo* cycloadduct **4c** in 83% yield with 97% ee (entry 1). Aside from complete *exo* diastereoselectivity, excellent levels of asymmetric induction (97–99% ee) were consistently observed with either electron-donating or -withdrawing groups at the C5 position on the indole ring (entries 2–4). The use of 4- or 7-methyl-substituted *N*-methylindoles **3g** and **3h** resulted in high yields and enantioselectivities (84–85% yields, 94–95% ee, entries 5 and 6).

Table 2. Enantioselective Cycloaddition of **2a** and **2b** with **3a**, **d**–**h** Catalyzed by Rh_2(*S*-TCPTTL)$_4$ (**1a**)[a]



	diazodiketoester		dipolarophile		product		
entry		R^1		R^2		yield(%)[b]	ee(%)[c]
1	**2b**	C_6H_5	**3a**	H	**4c**	83	97
2	**2a**	Me	**3d**	5-MeO	**4d**	86	97
3	**2a**	Me	**3e**	5-Me	**4e**	80	97
4	**2a**	Me	**3f**	5-Br	**4f**	76	99
5	**2a**	Me	**3g**	4-Me	**4g**	85	95
6	**2a**	Me	**3h**	7-Me	**4h**	84	94

[a] All reactions were performed on a 0.2 mmol scale with 2 equiv of dipolarophile. [b] Isolated yield. [c] Determined by HPLC.

Armed with these positive results, we next examined the cycloaddition with a five-membered cyclic carbonyl ylide for the construction of a hexahydrocarbazole skeleton, which is a common structural unit found in a diverse array of biologically interesting natural products. While a variety of intermolecular cycloadditions with five-membered cyclic carbonyl ylides using achiral dirhodium(II) catalysts have been reported,[5a,b,d–f,i,12] its enantioselective variants using chiral dirhodium(II) catalysts are quite limited.[14a,c] The reaction of diazodiketoester **6a**[29] carrying a *gem*-dimethyl group at C4 with 3 equiv of *N*-methylindole

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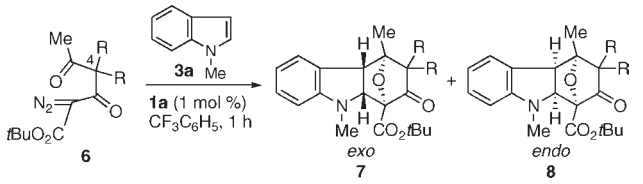
(28) The reaction at rt gave a complex mixture of products.

(29) It was necessary to block the C4 position of **6** with two substituents in order for the cycloaddition to occur without the formation of furanones via proton transfer. (a) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. J. *J. Org. Chem.* **1991**, *56*, 3271–3278. (b) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317–1325.

Table 3. Enantioselective Cycloaddition of **6a** and **6b** with **3a** Catalyzed by Rh_2(*S*-TCPTTL)$_4$ (**1a**)[a]

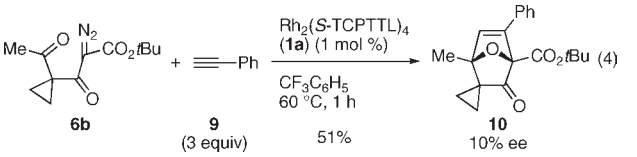


6 7 8

	diazodiketoester					ee (%)[c]	
entry		R	temp(°C)	yield(%)[b]	7:8	7	8
1[d]	**6a**	Me	23	40	>99:1	50	–
2	**6a**	Me	60	84	>99:1	61	–
3	**6a**	Me	80	80	>99:1	59	–
4[e]	**6b**	-CH_2CH_2-	23	69	87:13	82	2
5	**6b**	-CH_2CH_2-	60	88	92:8	92	2

[a] All reactions were performed on a 0.2 mmol scale with 2 equiv (for **6b**) or 3 equiv (for **6a**) of **3a**. [b] Combined yield of **7** and **8**. [c] Determined by HPLC. [d] After the addition of **6a** and **3a** over 1 h, the reaction mixture was stirred for an additional 23 h. [e] After the addition of **6b** and **3a** over 1 h, the reaction mixture was stirred for an additional 7 h.

(**3a**) in the presence of 1 mol % of Rh_2(*S*-TCPTTL)$_4$ (**1a**) at rt required a significantly longer time (24 h) to reach completion, probably due to steric hindrance imposed by the dimethyl groups, and provided exclusively *exo* cycloadduct **7a** in 40% yield with 50% ee (Table 3, entry 1). Gratifyingly, increasing the reaction temperature greatly enhanced product yields and slightly improved enantioselectivities (80−84% yields, 59−61% ee), though 60 °C was found to be the temperature limit (entries 2 and 3). These observations indicate that Rh_2(*S*-TCPTTL)$_4$ (**1a**) is bound to the carbonyl ylide during the cycloaddition process even at higher temperatures, because the carbonyl ylide detached from the catalyst is achiral.[13a,14a] At this stage, we envisaged that a carbonyl ylide containing a sterically less-demanding cyclopropane moiety instead of the *gem*-dimethyl group might react smoothly with the dipolarophile.[30] Indeed, the reaction of diazodiketoester **6b** with **3a** proceeded at rt to completion within 8 h and led to a higher product yield and enantioselectivity (69% yield, 82% ee for **7b**), though a considerable drop in diastereoselectivity was observed (**7b**/**8b** = 87:13, entry 4 vs 1). Not unexpectedly, the reaction conducted at 60 °C greatly improved the product yield as well as diastereo- and enantioselectivity (88% yield, **7b**/**8b** = 92:8, 92% ee for **7b**, entry 5). These results suggest that immediate trapping of the catalyst-bound carbonyl ylide by the indole dipolarophile at a high temperature is crucial for a high yield as well as high levels of enantio- and diastereocontrol. It is noteworthy that the reaction of **6b** with phenylacetylene (**9**) under catalysis by Rh_2(*S*-TCPTTL)$_4$ (**1a**) at 60 °C afforded the corresponding cycloadduct **10** in 51% yield and with only poor enantioselectivity (10% ee, eq 4).[16] These findings clearly demonstrate that *N*-methylindoles are particularly effective dipolarophiles for the LUMO-controlled carbonyl ylide cycloaddition catalyzed by **1a**.



In summary, we have developed a highly enantio- and diastereoselective cycloaddition of carbonyl ylides derived from diazodiketoesters with *N*-methylindole dipolarophiles under the influence of Rh_2(*S*-TCPTTL)$_4$. This is the first example of the use of indoles as dipolarophiles in enantioselective intermolecular carbonyl ylide cycloaddition reactions. The present catalytic protocol is applicable not only to six-membered cyclic carbonyl ylides but also to the five-membered carbonyl ylide containing a cyclopropane ring, providing functionalized indoline derivatives including a hexahydrocarbazole in optically active forms. Further application of this methodology to asymmetric synthesis of biologically active alkaloids as well as mechanistic and stereochemical studies are currently in progress.

Acknowledgment. This research was supported, in part, by a Grant-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration" (No. 2105) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank Ms. S. Oka, and M. Kiuchi of the Center for Instrumental Analysis at Hokkaido University for technical assistance in the MS and elemental analyses.

Supporting Information Available. Experimental details and spectroscopic data. This material is available free of charge via Internet at http://pubs.acs.org.

(30) The effectiveness of the intermolecular cycloaddition of five-membered carbonyl ylides derived from α-diazoketones containing a cyclopropane ring has been demonstrated by the synthesis of biologically active sesquiterpenoids including illudins, ptaquilosin, pterosins, and acylfulvenes. (a) Kinder, F. R., Jr.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965–6967. (b) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73–81. (c) McMorris, T. C.; Hu, Y.; Yu, J.; Kelner, M. J. *Chem. Commun.* **1997**, 315–316. (d) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317–1325. (e) McMorris, T. C.; Staake, M. D.; Kelner, M. J. *J. Org. Chem.* **2004**, *69*, 619–623.