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Highly Enantioselective Synthesis of Cyclopropylamine Derivatives via Ru(II)-Pheox-Catalyzed Direct Asymmetric Cyclopropanation of Vinylcarbamates

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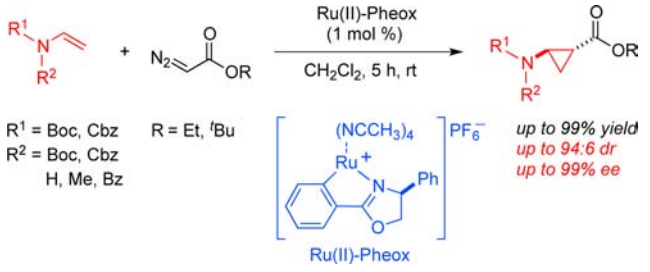
ABSTRACT



The Ru(II)-Pheox-catalyzed asymmetric cyclopropanation of vinylcarbamates with diazoesters resulted in the corresponding cyclopropylamine derivatives in high yield and excellent diastereoselectivity (up to 96:4) and enantioselectivity (up to 99% ee).

Optically active cyclopropylamines have been recognized as useful building blocks for biologically active compounds such as belactosin A,[1] coronamic acid,[2] tcprPNA,[3] tranylcypromine,[4] and trovafloxacin.[5] Several studies in the literature have reported the synthesis of cyclopropylamine derivatives via alkaline hydrolysis of optically active cyclopropanecarboxylic acid esters or cyclopropanecarboxamides and subsequent Curtius rearrangement.[1c,d,3,6] For example, Miyata and co-workers recently applied this procedure to prepare cyclopropylamine **2**, which is a useful intermediate in the synthesis of (1*R*,2*S*)-NCL-1 (see Scheme 1a).[7] In 2003, Nguyen and co-workers[8] developed a synthesis of cyclopropylamine derivative **4** via

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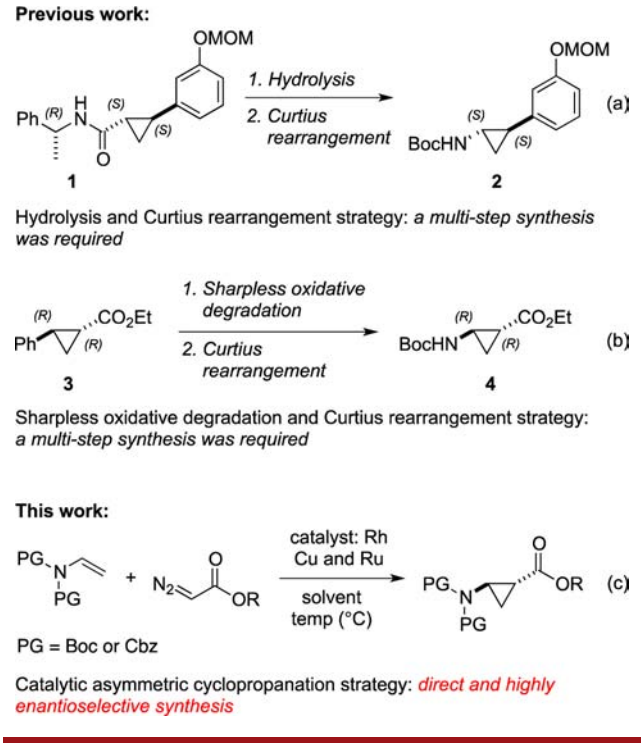
Sharpless oxidative degradation of the phenyl group of optically active cyclopropanecarboxylic acid ester **3** and subsequent Curtius rearrangement (Scheme 1b).

The same authors also reported the asymmetric cyclopropanation of vinylcarbamates with diazoesters using chiral ruthenium(salen) and Doyle's dirhodium catalysts to afford the corresponding protected cyclopropylamines in good yields.[8] Unfortunately, poor diastereoselectivities and no enantioselectivity were obtained. In 2009, a cyclopropanation of *N*-vinyl phthalimide with α-aryl diazoketone was reported by Davies and co-workers.[9] Although the corresponding protected cyclopropylamine was obtained in high yield with excellent diastereoselectivity and enantioselectivity, the removal of phthalimide is not always straightforward and a potentially hazardous hydrazine is commonly used. In summary, the currently available asymmetric cyclopropanation methods present certain drawbacks, and a straightforward route to cyclopropylamines needs to be developed. This prompted us to search for a highly efficient catalytic system that promotes the cyclopropanation of vinylcarbamate derivatives with diazoesters, to give the corresponding cyclopropylamines in high yields with excellent diastereoselectivity and excellent enantioselectivity (Scheme 1c).

Scheme 1. Currently Used Strategies for the Preparation of Optically Active Cyclopropylamines



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In initial investigations, we investigated the cyclopropanation of benzyl vinylcarbamate **5a** with diazoester **6a**, catalyzed by commonly used catalysts such as $Rh_2(OAc)_4$ and $Cu(CH_3CN)_4PF_6$ (Table 1). The desired product was obtained in good yield with low *trans*-diastereoselectivity (65:35) when using either $Rh_2(OAc)_4$ or $Cu(CH_3CN)_4PF_6$ (Table 1, entries 2 and 3). Encouraged by the results obtained with $Rh_2(OAc)_4$, we chose the chiral complex Rh_2-(*S*-TBPTTL)$_4$, which was recently reported by Hashimoto and co-workers to be useful in cyclopropanations,[10] and used it as the catalyst in the asymmetric cyclopropanation of benzyl vinylcarbamate. Indeed, Rh_2(*S*-TBPTTL)$_4$ gave the desired product in good yield (71%), yet both the diastereoselectivity and enantioselectivity were low (46:54 dr, 0% *trans* ee and 7% *cis* ee) (Table 1, entry 4). Although the diastereoselectivity and enantioselectivity were slightly improved by decreasing the temperature to −30 °C, the yield decreased accordingly (Table 1, entry 5). To our delight, $RuCl_2$(pybox-ip)(C_2H_4) catalyst, which was synthesized by Nishiyama's group and is broadly used in cyclopropanation reactions,[11] afforded protected cyclopropylamine **7a** in high yield (90%) with good *trans*-diastereoselectivity (77:23) and enantioselectivity (79% ee) in the presence of 2 mol % of the catalyst (Table 1, entry 6). With the good results obtained with $RuCl_2$-(pybox-ip)(C_2H_4) in hand, the Ru(II)-Pheox complex,[12] a catalyst system recently developed by our research group, was also tested in the cyclopropanation reaction (Table 1, entry 7). Surprisingly, the Ru(II)-Pheox catalyst readily catalyzed the cyclopropanation of benzyl vinylcarbamate **5a** with diazoester **6a**, to give the corresponding protected cyclopropylamine **7a** in excellent yield (99%) and high enantioselectivity (90% ee). To the best of our knowledge, this is the first report of the successful enantioselective carbene transfer cyclopropanation of diazoester into vinylcarbamate.

To improve the diastereoselectivity and enantioselectivity of this catalytic system further, we conducted the cyclopropanation in various solvents (Table 2, entries 1−4). For all tested solvents, cyclopropanation proceeded smoothly in high yield but with differing diastereoselectivities and enantioselectivities. Toluene led to a significant increase in terms of *trans*-selectivity (*trans*/*cis* = 86:14), although enantioselectivity decreased (83% *trans* ee). Dichloromethane was found to be the solvent of choice. The effect of temperature on the reaction was also investigated (Table 2, entries 5−8), showing that enantioselectivity could be improved to 92% ee at a temperature

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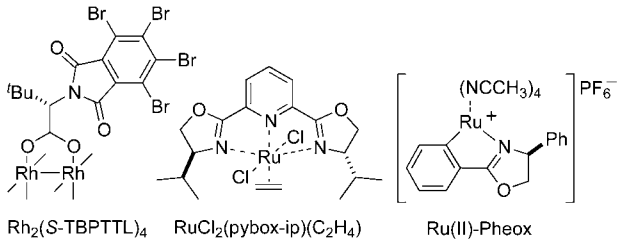
Table 1. Screening of Various Metal Catalysts[a]



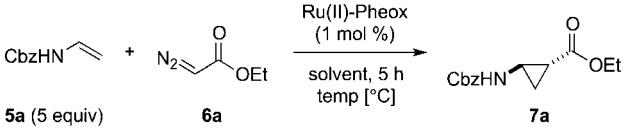
5a (5 equiv) 6a 7a

entry	catalyst	time (h)	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*	ee[d] (%) *cis*
1	$Pd(OAc)_2$	72	0			
2	$Rh_2(OAc)_4$	8	76	65:35		
3	$Cu(CH_3CN)_4PF_6$	6	70	65:35		
4	Rh_2(*S*-TBPTTL)$_4$	5	71	46:54	0	7
5[e]	Rh_2(*S*-TBPTTL)$_4$	72	24	35:65	4	10
6[f]	$RuCl_2$(pybox-ip)(C_2H_4)	8	90	77:23	79	80
7	**Ru(II)-Pheox**	**5**	**99**	**70:30**	**90**	**94**

[a] Reaction conditions: benzyl vinylcarbamate (1 mmol) and ethyl diazoester (0.2 mmol) in the presence of catalyst (1 mol %) under Ar. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out at −30 °C. [f] 2 mol % of catalyst was used. Cbz = benzyloxycarbonyl.

of −30 °C, with diastereoselectivity decreasing to 57:43 (Table 2, entry 8). As such, room temperature was found to be the optimal temperature for this catalytic system.

Table 2. Optimization of Reaction Conditions[a]



5a (5 equiv) 6a 7a

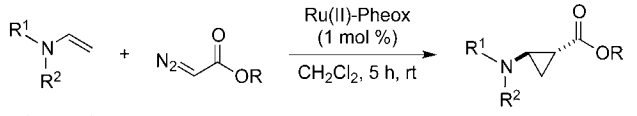
entry	solvent	temp (°C)	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*	ee[d] (%) *cis*
1	THF	rt	97	75:25	85	92
2	toluene	rt	95	86:14	83	78
3	acetone	rt	99	80:20	87	95
4	**CH_2Cl_2**	**rt**	**99**	**70:30**	**90**	**94**
5	CH_2Cl_2	0	97	62:38	90	95
6	CH_2Cl_2	−10	96	61:39	91	97
7	CH_2Cl_2	−20	98	60:40	91	97
8	CH_2Cl_2	−30	99	57:43	92	97

[a] Reaction conditions: benzyl vinylcarbamate (1 mmol) and ethyl diazoester (0.2 mmol) in the presence of Ru(II)-Pheox (1 mol %) under Ar. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis.

Under these optimized conditions, the cyclopropanation of a series of vinylcarbamates and diazoesters was examined (Table 3). Reaction of benzyl vinylcarbamate with the bulky *tert*-butyl diazoester gave the corresponding protected cyclopropylamine product in high yield with excellent enantioselectivity (97% *trans* ee). However, diastereoselectivity was low (Table 3, entry 2). In contrast to the successful use of succinimidyl diazoacetate in the cyclopropanation of styrene derivatives,[12b] low diastereoselectivity and enantioselectivity were obtained in the cyclopropanation of benzyl vinylcarbamate (Table 3, entry 3). *tert*-Butyl vinylcarbamate was also readily cyclopropanated with diazoesters to afford the desired products in high yields (Table 3, entries 4 and 5), where it should be noted that, in particular, the reaction involving the bulky *tert*-butyl diazoester displayed higher diastereoselectivity (*trans*/*cis* = 72:28) and enantioselectivity (93% ee) than the reaction of ethyl diazoester.

In addition, the cyclopropanation of diprotected vinylamines such as benzyl carbobenzyloxy(vinyl)carbamate and *tert*-butyl-*tert*-butoxycarbonyl(vinyl)carbamate was investigated (Table 3, entries 6−9). Interestingly, both diastereoselectivity and enantioselectivity were significantly improved (up to 91:9 dr and up to 97% ee) with a negligible effect on yield. Inspired by these results, we also carried out the experiments using larger R^2 (Bz) and smaller R^2 (Me) substituents (Table 3, entries 10−12). Surprisingly, high diastereoselectivity and enantioselectivity were obtained using a smaller R^2 substituent (R^2 = Me, 93:7 dr and 99% ee), indicating that disubstituted vinylamines

Table 3. Ru(II)-Pheox-Catalyzed Asymmetric Cyclopropanation of Various Vinylcarbamates with Diazoesters[a]

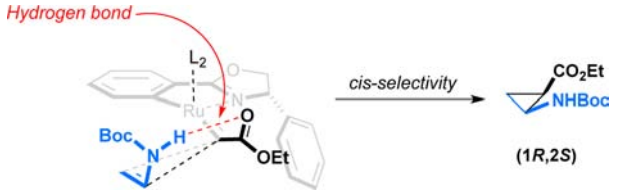


5 (5 equiv) 6 7

	5		6				ee[d] (%)	
entry	R^1	R^2	R	7 yield[b] (%)		*trans*/*cis*[c]	*trans*	*cis*
1	Cbz	H	Et	99	**7a**	70:30	90	94
2	Cbz	H	^{t}Bu	91	**7b**	52:48	97	96
3	Cbz	H	Su	90	**7c**	43:57	49	31
4	Boc	H	Et	89	**7d**	60:40	89	99
5	Boc	H	^{t}Bu	82	**7e**	72:28	93	91
6	Cbz	Cbz	Et	91	**7f**	90:10	96	88
7	Cbz	Cbz	^{t}Bu	77	**7g**	86:14	97	99
8	Boc	Boc	Et	88	**7h**	91:9	96	84
9	Boc	Boc	^{t}Bu	72	**7i**	90:10	95	
10	Cbz	Bz	Et	90	**7j**	92:8	97	
11	Cbz	Bz	^{t}Bu	77	**7k**	94:6	97	
12	Cbz	Me	Et	97	**7l**	93:7	99	

[a] Reaction conditions: vinylcarbamate **5** (1 mmol) and diazoester **6** (0.2 mmol) in the presence of catalyst (1 mol %) under Ar. [b] Isolated yield. [c] Determined by NMR. [d] Determined by chiral HPLC analysis. Su = succinimidyl, Boc = *tert*-butoxycarbonyl, Bz = benzoyl.

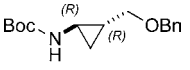
Scheme 2. Plausible Transition State Leading to a *cis*-Selective Approach of the Reactants



gave much higher diastereoselectivity and enantioselectivity (Table 3, entries 6−12) as compared with monosubstituted vinylamines (Table 3, entries 1−5). This may result from a hydrogen bond that forms between the *N*-hydrogen of the vinylcarbamate and the carbonyl oxygen of the carbenoid intermediate, leading to a *cis*-selective approach of the reactants, as shown in Scheme 2.

Finally, to demonstrate the utility of our direct enantioselective cyclopropylamine synthesis, we prepared a key intermediate in the reported synthesis of belactosin A from cyclopropylamine **7h** (Table 3, entry 8), as shown in Scheme 3. The optically active 2-((*tert*-butoxycarbonyl)-amino)cyclopropylmethanol intermediate **8** was readily synthesized by the reduction of cyclopropylamine **7h** with DIBAL in 60% yield with high enantioselectivity (96% ee). Even though the configuration of belactosin A at both chiral carbon centers in the cyclopropane motif is opposite to the configuration of our cyclopropane product **7h**, the desired configuration should, in principle, straightforwardly be obtained using the *R*-enantiomer of Ru(II)-Pheox as a catalyst. Apart from this, we employed this intermediate **8** to determine the absolute configuration of **7h** by reacting it with benzyl chloride in the presence of NaH, to give the corresponding (*R*,*R*)-*tert*-butyl-(2-((benzyloxy)methyl)cyclopropyl) carbamate **9**, of which

(13) Absolute configuration of **9** was determined to be (1*R*,2*R*) by comparing the reported specific optical rotation: $[\alpha]_D^{25}$ −40.0 (*c* 0.40, $CHCl_3$), lit.[1c] $[\alpha]_D^{22}$ −30.0 (*c* 0.40, $CHCl_3$) for 1*R*,2*R*-isomer.



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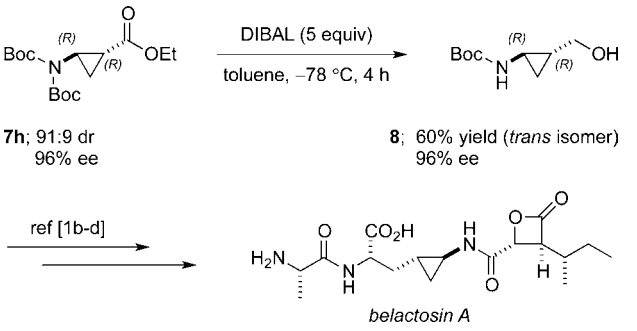
Scheme 3. Preparation of (1*R*,2*R*)-2-((*tert*-Butoxycarbonyl)-amino)cyclopropylmethanol **8**, a Key Intermediate in the Synthesis of Belactosin A



the (1*R*,2*R*) configuration was confirmed by comparison of the optical rotation.[13]

In conclusion, we succeeded in the development of the first highly enantioselective cyclopropanation of vinylcarbamate derivatives with diazoesters, using the Ru(II)-Pheox complex as a catalyst. The reaction proceeds smoothly under mild conditions, giving the corresponding protected cyclopropylamine products in high yield, with excellent diastereoselectivity (up to 96:4) and enantioselectivity (up to 99% ee). Furthermore, the utility of the present asymmetric cyclopropanation is highlighted in the stereoselective and straighforward synthesis of enantioenriched 2-((*tert*-butoxycarbonyl)amino)cyclopropylmethanol **8**, which is a key intermediate in the synthesis of the antitumor antibiotic belactosin A. We hope that this efficient procedure will contribute to the progress of synthetic organic chemistry.

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Supporting Information Available. Experimental procedures, characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.