Organic LETTERS

Letter

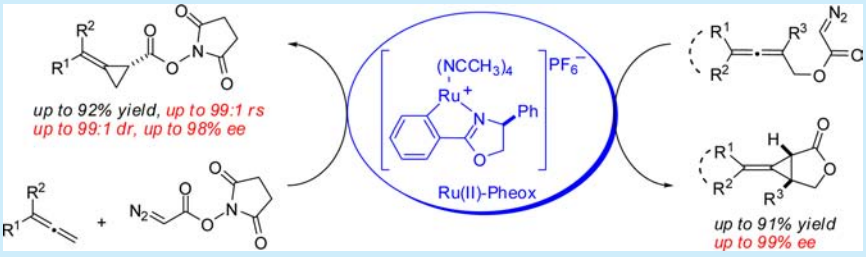
pubs.acs.org/OrgLett

Highly Regio- and Stereoselective Synthesis of Alkylidenecyclopropanes via Ru(II)-Pheox Catalyzed Asymmetric Inter- and Intramolecular Cyclopropanation of Allenes

Soda Chanthamath, Hao Wei Chua, Seiya Kimura, Kazutaka Shibatomi, and Seiji Iwasa*

Department of Environmental, Life Sciences, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi 441-8580, Japan

Supporting Information

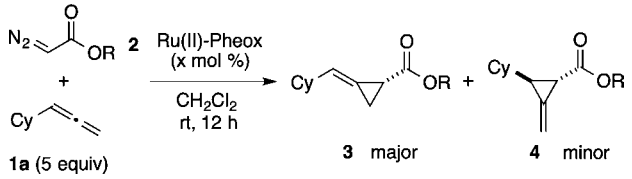


ABSTRACT: An efficient protocol for the synthesis of optically active alkylidenecyclopropanes (ACPs) via the Ru(II)-Pheox catalyzed asymmetric cyclopropanation of allenes has been established. This catalytic system proceeded with high regioselectivity to give the ACP products in high yield with high diastereoselectivity (up to 99/1) and enantioselectivity (up to 99% ee).

Alkylidenecyclopropanes (ACPs) are useful structural motifs that can serve as key intermediates in organic synthesis.[1] Many reports in the literature describe the use of alkylidenecyclopropanes as useful intermediates for the synthesis of biologically important compounds such as 3-methylenecyclobutyl esters,[2] 3-azabicyclo[3.1.0]hexanes,[3] tetrahydropyrans,[4] and 3-ozabicyclo[3.1.0]hexane-2-ones.[5] Although numerous synthetic methods to access ACPs have been developed over the past few decades,[6] methods to access optically active ACPs are rare.[7] Achiral rhodium-catalyzed cyclopropanation of allenes with diazoesters is often employed for the synthesis of ACPs; however, this method poses difficulties regarding control of the regio- and stereochemistry of the product.[8] The most efficient asymmetric catalytic methods for the formation of ACPs has been reported by Frost[7b,c] and Charette.[7d] Their work involved the reaction of disubstituted diazoacetates with allenes using a chiral rhodium(II) catalyst. However, bulky disubstituted diazoacetate was found to be important in providing high regio- and stereocontrol; therefore the reaction of monosubstituted diazoacetate still remains a challenge. Herein, we describe the first asymmetric catalytic inter- and intramolecular cyclopropanation of monosubstituted diazoacetates in the presence of a Ru(II)-Pheox catalyst. Furthermore, the development of the first enantioselective method for the synthesis of *cis*-cyclopropanes via reduction of the ACP products is also disclosed.

Recently, we reported the efficient use of functionalized diazoacetates as the carbene source for the asymmetric cyclopropanation of alkenes using a chiral Ru(II)-Pheox catalyst.[9] Therefore, we began our study by examining the cyclopropanation of cyclohexylallene **1a** with various diazoacetates **2** catalyzed by Ru(II)-Pheox (Table 1). Using ethyl diazoacetate (EDA), the *E*/*Z* ratio of product **3** was low; however, high regio- and enantioselectivity were obtained (Table 1, entry 1). *tert*-Butyl diazoacetate provided an increase in the *E*/*Z* ratio to 95:5 and excellent regioselectivity of product

Table 1. Screening of Various Diazoacetates[a]



entry	R	cat. (mol %)	yield[b] (%)	3/4[c]	product 3 E/Z[c]	Eee[d](%)	Zee[d](%)
1	Et **2a**	3	75	96/4	77:23	94	96
2	^{t}Bu **2b**	3	60	99/1	95:5	95	99
3	 **2c**	5	58	99/1	91:9	89	91
4	 **2d**	1	82	99/1	97:3	92	99

[a]Diazo compound diluted in CH_2Cl_2 was slowly added (11 h) by using a syringe pump. [b]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC. Cy = cyclohexyl.

Received: May 25, 2014
Published: June 11, 2014

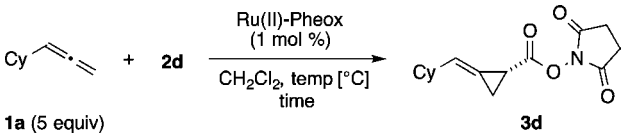
ACS Publications © 2014 American Chemical Society

dx.doi.org/10.1021/ol5014944 | *Org. Lett.* 2014, 16, 3408–3411

3, albeit in lower yield (Table 1, entry 2). Employing methyl (diazoacetoxy)acetate (MDA) failed to improve the yield of product (Table 1, entry 3). Pleasingly, when succinimidyl diazoacetate was used as the carbene source, the desired product **3** was obtained in high yield (82%) with excellent diastereoselectivity (97:3) and enantioselectivity (92% ee) (Table 1, entry 4).

Next, we optimized the reaction conditions as shown in Table 2. Surprisingly, the reaction without the slow addition of

Table 2. Optimization of Reaction Conditions



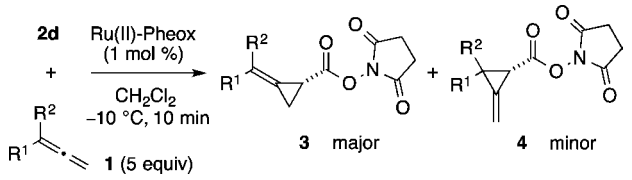
entry	temp (°C)	time	yield[a] (%)	*E*/*Z*[b]	*E* ee[c] (%)	*Z* ee[c] (%)
1[d]	rt	12 h	82	97:3	92	99
2	rt	1 min	86	97:3	85	99
3	0	5 min	86	97:3	91	99
4	**−10**	**10 min**	**90**	**98:2**	**96**	**99**
5	−20	3 h	81	98:2	97	99
6	−30	70 h	87	98:2	98	99

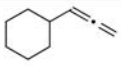
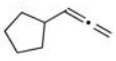
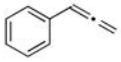
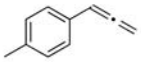
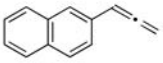
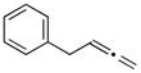
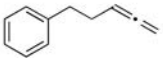
[a]Isolated yield. [b]Determined by NMR. [c]Determined by chiral HPLC analysis. [d]**2d** was slowly added over 11 h.

the diazo compound afforded the desired product **3d** in good yield (86%); however, the enantioselectivity fell to 85% ee (Table 2, entry 2). The effect of the reaction temperature was also investigated (Table 2, entries 2−6). The enantioselectivity of **3d** was improved to 98% ee by decreasing the reaction temperature to −30 °C (entry 6); however, a longer reaction time was required. From these results, it was concluded that carrying out the reaction at −10 °C without slow addition of the diazo compound was optimal for this catalytic system.

Under the optimized reaction conditions, a variety of allenes derivatives were examined for reaction with succinimidyl diazoacetate using the Ru(II)-Pheox catalyst (Table 3). It was observed that monosubstituted aliphatic allenes reacted smoothly with high regioselectivity and excellent enantioselectivity to give the desired product **3** in moderate to high yield (Table 3, entries 1−5). Unfortunately, the diastereoselectivity decreased for the less hindered allene substrates. It is worth noting that the cyclopropanation of 1,2-pentadiene only gave a moderate yield of desired product due to the formation of dimer byproducts (Table 3, entry 3). As a result, we decided to use slow addition of the diazo compound in the presence of 5 mol % catalyst to suppress any dimer formation. Pleasingly, the yield could be improved to 68% without detrimental effects to the diastereo- or enantioselectivity (Table 3, entry 4). Disubstituted allenes also underwent cyclopropanation to give the alkylidenecyclopropane product in high yield and high enantioselectivity; however, the regioselectivity was lower than that for the monosubstituted allenes (Table 3, entries 6 and 7). This may be due to the increase in electron density on the internal carbon−carbon double bond of the allenes. Next, we investigated the cyclopropanation of aromatic allenes: propa-1,2-dien-1-ylbenzene, 2-(propa-1,2-dien-1-yl)naphthalene, and 1-methyl-4-(propa-1,2-dien-1-yl)benzene (Table 3, entries 8−11). The cyclopropanation of propa-1,2-dien-1-ylbenzene proceeded with excellent diastereoselectivity (99:1) and enantioselectivity (97% ee) but in only moderate yield (Table

Table 3. Cyclopropanation of Various Allenes



entry	allene **1**	**3**+**4** yield[a](%)	**3**/**4**[b]	product **3**	*E*/*Z*[b]	Eee[c](%)	Zee[c](%)
1		90	99/1	**3d**	98:2	96	99
2		91	99/1	**3e**	96:4	96	99
3		60	99/1	**3f**	92:8	95	94
4[d]		68	99/1	**3f**	92:8	94	93
5		84	99/1	**3g**	98:2	96	99
6		85	90/10	**3h**		94	
7		79	93/7	**3i**		95	
8		62	95/5	**3j**	99:1	97	
9[d]		85	91/9	**3j**	99:1	97	
10[d]		72	86/14	**3k**	99:1	96	
11[d]		82	86/14	**3l**	99:1	95	
12[e]		92	99/1	**3m**	90:10	84	
13[e]		90	99/1	**3n**	91:9	96	99

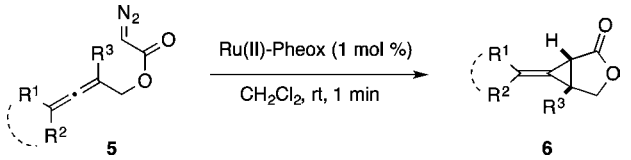
[a]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC. [b]**2d** was slowly added for 4 h at −10 °C by using 5 mol % of catalyst. [e]5 mol % of catalyst was used.

3, entry 8). The yield could be improved to 85% by slow addition of the diazo compound with only a slight decrease in regioselectivity (Table 3, entry 9). Cyclopropanations of the other aromatic allenes were carried out under the same conditions as mentioned above, to give the corresponding alkylidenecyclopropanes in high yield with high diastereo- and enantioselectivity (Table 3, entries 10 and 11). Disappointingly, the regioselectivities were lower compared to the monosubstituted aliphatic allenes. In contrast, the less hindered aromatic allenes gave high regio- and enantioselectivity, while the diastereoselectivity was reduced (Table 3, entries 12 and 13). In addition, we also examined the cyclopropanation of functionalized allenes such as methoxyallene and ethyl 2,3-butadienoate; however, no cyclopropane products were observed due to the decomposition of allene substrates and the formation of a dimer from the diazo compound.

Encouraged by the results from the intermolecular cyclopropanation of allenes with succinimidyl diazoacetate, we decided to investigate the intramolecular cyclopropanation of allenic diazoacetates using the Ru(II)-Pheox catalyst (Table 4). The cyclization of various symmetric allenic diazoacetates (R^1 = R^2 = H, CH_3, and cyclohexyl) proceeded smoothly under mild reaction conditions to afford the bicyclic cyclopropane fused γ-

dx.doi.org/10.1021/ol5014944 | Org. Lett. 2014, 16, 3408−3411

Table 4. Cyclopropanation of Various Allenic Diazoacetates



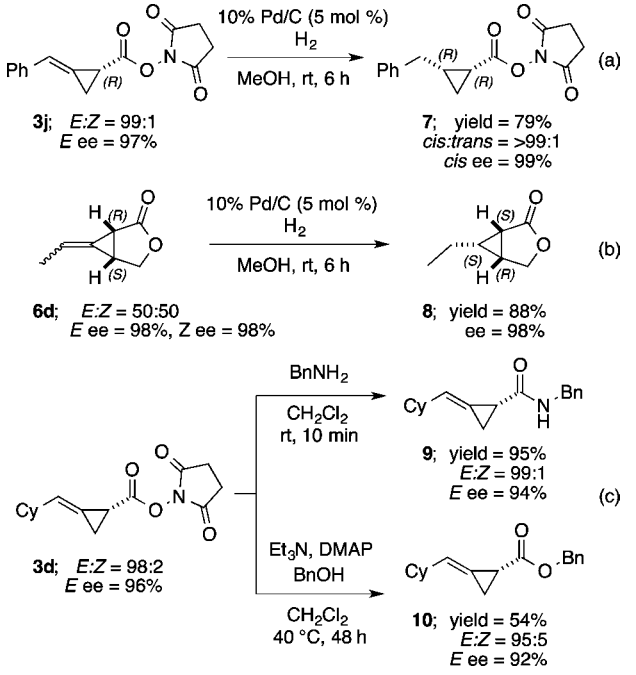
entry	substrate 5 R¹	R²	R³	6	yield[a] (%)	E/Z[b]	ee[c] (%)
1	H	H	H	6a	91		99
		5a					
2	CH_3	CH_3	H	6b	91		99
		5b					
3	Cy		H	6c	84		99
		5c					
4	CH_3	H	H	6d	80	50:50	98 (*E*) 98 (*Z*)
		5d					
5	C_5H_{11}	H	H	6e	91	52:48	98 (*E*) 97 (*Z*)
		5e					
6[d]	Ph	H	H	6f	52	81:19	56 (*E*) 99 (*Z*)
		5f					
7[d]	^{t}Bu	H	H	6g	88	67:33	48 (*E*) 99 (*Z*)
		5g					
8	H	H	CH_3	6h	85		93
		5h					
9[d]	H	H	Ph	6i	40		8
		5i					

[a]Isolated yield. [b]Determined by NMR. [c]Determined by chiral HPLC analysis. [d]Allenic diazoacetate was slowly added over 4 h.

lactones in high yield (up to 91%) and excellent enantioselectivity (99% ee for all substrates) (Table 4, entries 1−3). To the best of our knowledge this is the first example of asymmetric catalytic intramolecular cyclopropanation of allenic diazoacetates. Racemic allenic diazoacetates ($R^1 = CH_3$, $R^2 = H$ and $R^1 = C_5H_{11}$, $R^2 = H$) also underwent intramolecular cyclopropanation to give the corresponding *E* and *Z* bicyclic products in high yield and high enantioselectivity (Table 4, entries 4 and 5). Following this, we also investigated using substrates bearing larger R^1 substituents such as phenyl and *tert*-butyl. It is worth noting that although the cyclopropanation of these substrates had improved diastereoselectivity (*E*/*Z* = 81/19), the enantioselectivity of the *E* isomer fell to 48% ee and slow addition was also required (Table 4, entries 6 and 7). Interestingly, the reaction of allenic diazoacetate bearing a small R^3 (CH_3) substituent proceeded smoothly to give the corresponding bicyclic product in high yield and high enantioselectivity; however, a low yield and enantioselectivity were obtained with a large R^3 (Ph) substituent (Table 4, entries 8 and 9).[10]

The cyclopropanation product succinimidyl 2-benzylidenecyclopropanecarboxylate **3j** was readily hydrogenated to give the corresponding *cis*-cyclopropane **7** in high yield with excellent *cis*-selectivity (>99:1) and enantioselectivity (99% ee) (Scheme 1a). This is the first example for the

Scheme 1. Stereoselective Hydrogenation and Nucleophilic Substitution of Alkylidenecyclopropanes (ACPs)



enantioselective synthesis of *cis*-cyclopropanes via reduction of alkylidenecyclopropanes. The *cis*-isomer was confirmed by comparing the ^{1}H NMR spectral data of **7** with those of the cyclopropane product synthesized from the direct reaction of allylbenzene with succinimidyl diazoacetate **2d** in the presence of the Ru(II)-Pheox catalyst. The absolute configuration of **7** was determined by comparing the optical rotation of the corresponding (+)-2-benzylcyclopropylmethanol obtained from the $LiAlH_4$ reduction of *cis*-cyclopropane **7** with the literature data.[11] Inspired by this result, we also carried out the hydrogenation of bicyclic alkylidenecyclopropane fused γ-lactone **6d** (50:50 *E*:*Z* ratio) under the same reaction conditions as mentioned above to afford bicyclic product **8** in high yield (88%) with excellent enantioselectivity (98% ee) (Scheme 1b). The (1*S*,5*R*,6*S*) configuration of 6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one **8** was confirmed by the comparison of its optical rotation with literature data.[12] By association, the absolute configuration of 6-ethylidene-3-oxabicyclo[3.1.0]-hexan-2-one **6d** was confirmed to be (1*R*,5*S*). Being able to use succinimidyl diazoacetate for cyclopropanation is very useful, as the resulting product **3d** can easily react with benzylamine and benzyl alcohol to form other functionalized alkylidenecyclopropanes (**9** and **10**) in good yield and with high stereoselectivity (Scheme 1c).

In conclusion, we have successfully developed an efficient protocol for the synthesis of optically active ACP derivatives via a Ru(II)-Pheox catalyzed asymmetric intermolecular cyclopropanation of allenes with succinimidyl diazoacetate. This catalytic system gives direct access to ACPs in high yield with high regioselectivity, diastereoselectivity (up to 99/1), and enantioselectivity (up to 98% ee). Additionally, we have successfully carried out the intramolecular cyclopropanation

dx.doi.org/10.1021/ol5014944 | *Org. Lett.* 2014, 16, 3408−3411

of various symmetric and racemic allenic diazoacetates to afford the corresponding bicyclic alkylidenecyclopropane fused γ-lactones in high yield with high enantioselectivity. Furthermore, the utility of the present asymmetric cyclopropanation is highlighted in the stereoselective synthesis of enantioenriched *cis*-cyclopropanes via reduction of the ACP products.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: iwasa@ens.tut.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 23550179) from the Japan Society for the Promotion of Science.

■ REFERENCES

(1) (a) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298−1300. (b) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015−11016. (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111−129. (d) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145−2148. (e) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312−6316. (f) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835−838. (g) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419−4422. (h) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591−593. (i) Tang, X.-Y.; Shi, M. *J. Org. Chem.* **2010**, *75*, 902−905. (j) Tang, X.-Y.; Shi, M. *Eur. J. Org. Chem.* **2010**, 4106−4110.

(2) Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem.—Eur. J.* **2007**, *13*, 862−869.

(3) Fu, W.; Huang, X.; Shi, M. *Tetrahedron Lett.* **2008**, *49*, 562−565.

(4) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 2405−2408.

(5) Ma, S.; Lu, L. *J. Org. Chem.* **2005**, *70*, 7629−7633.

(6) (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77−151. (b) Krief, A. *Top. Curr. Chem.* **1987**, *135*, 1−75. (c) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589−635. (d) Lautens, M.; Meyer, C.; Oeveren, A. V. *Tetrahedron Lett.* **1997**, *38*, 3833−3836. (e) Xu, L.; Huang, X.; Zhong, F. *Org. Lett.* **2006**, *8*, 5061−5064. (f) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575−608. (g) Fujino, D.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2011**, *133*, 9682−9685.

(7) (a) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960−3962. (b) Gregg, T. M.; Farrugia, M. K.; Frost, J. R. *Org. Lett.* **2009**, *11*, 4434−4436. (c) Gregg, T. M.; Algera, R. F.; Frost, J. R.; Hassan, F.; Stewart, R. J. *Tetrahedron Lett.* **2010**, *51*, 6429−6432. (d) Lindsay, N. G. V.; Fiset, D.; Gritsch, P. J.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463−1470.

(8) (a) Cheng, C.; Shimo, T.; Somekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031−2040. (b) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645−9660. (c) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835−838. (d) Scott, M. E.; Schwarz, C. A.; Lautens, M. *Org. Lett.* **2006**, *8*, 5521−5524. (e) Chen, J.; Lu, L.; Ma, S. *Tetrahedron* **2008**, *64*, 8899−8906.

(9) (a) Chanthamath, S.; Phomkeona, K.; Shibatomi, K.; Iwasa, S. *Chem. Commun.* **2012**, *48*, 7750−7752. (b) Chanthamath, S.; Nguyen, D. T.; Shibatomi, K.; Iwasa, S. *Org. Lett.* **2013**, *15*, 772−775. (c) Chanthamath, S.; Takaki, S.; Shibatomi, K.; Iwasa, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5818−5821.

(10) The transition state geometries for the asymmetric intramolecular cyclopropanation were also described: See the Supporting Information.

(11) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (c) Lo, M. M.-C; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271. (d) Hu, S.; Dordick, J. S. *J. Org. Chem.* **2002**, *67*, 314−317.

(12) For the determination of the absolute configuration of 6-ethyl-3-oxabicyclo[3.1.0]hexan-2-one **8**, see: (a) Muller, P.; Lacrampe, F. *Hel. Chim. Acta* **2004**, *87*, 2848−2859. (b) Ghanem, A.; Lacrampe, F.; Schuring, V. *Hel. Chim. Acta.* **2005**, *88*, 216−239.