ORGANIC LETTERS

2005
Vol. 7, No. 20
4439−4441

Asymmetric Synthesis of 5-Arylcyclohexenones by Rhodium(I)-Catalyzed Conjugate Arylation of Racemic 5-(Trimethylsilyl)cyclohexenone with Arylboronic Acids

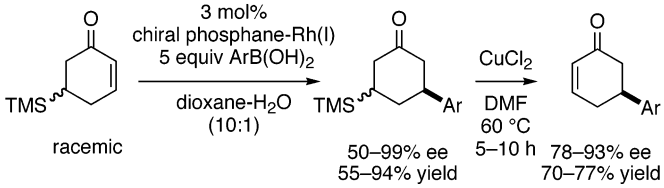
Qian Chen, Masami Kuriyama, Takahiro Soeta, Xinyu Hao, Ken-ichi Yamada, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

tomioka@pharm.kyoto-u.ac.jp

Received July 20, 2005

ABSTRACT



A catalytic asymmetric conjugate arylation of racemic 5-(trimethylsilyl)cyclohex-2-enone with arylboronic acids was catalyzed by 3 mol % chiral amidophosphane- or BINAP-Rh(I) in dioxane–water (10:1) to afford *trans*- and *cis*-3-aryl-5-(trimethylsilyl)cyclohexanones in high enantioselectivity. Dehydrosilylation of the product mixture with cupric chloride in DMF gave 5-arylcyclohex-2-enones with up to 93% ee in good yield. Enantiofacial selectivity with chiral phosphane-Rh(I) exceeds the *trans*-diastereoselectivity that is maintained in the achiral or racemic phosphane-Rh(I)-catalyzed conjugate arylation of 5-(trimethylsilyl)cyclohexenone.

Enantiomerically enriched substituted cyclohexenones have been utilized as versatile chiral building blocks for the synthesis of biologically important compounds.[1] Among a variety of methods for the preparation of these chiral cyclohexenones,[2,3] kinetic resolution of racemic substituted cyclohexenones by catalytic asymmetric reactions[4] and enzymatic reactions[5] has proven to be the most effective method, resulting in recovery of a nearly pure enantiomer.

(1) Ho, T.-L. *Enantioselective Synthesis: Natural Products Synthesis from Chiral Terpenes*; Wiley: New York, 1992.

(2) Derivation of natural and unnatural products: (a) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640−3650. (b) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984−3988. (c) Barton, D. H. R.; Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1551−1558. (d) Chapuis, C.; Brauchli, R.; Thommen, W. *Helv. Chim. Acta* **1993**, *76*, 535−544. (e) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831. (f) Tomioka, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 903−906.

(3) Asymmetric synthesis: (a) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166. (c) Schwarz, J. B.; Devine, P. N.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795−8806. (d) O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 8057−8058. (e) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637−1640. (f) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

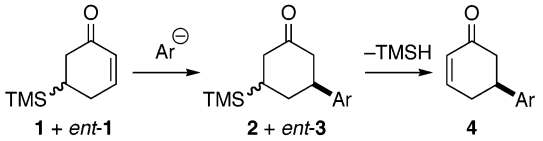
(4) (a) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927−930. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431. (c) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, G.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009−1010. (d) Yun, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 767−774. (e) Feng, X.; Shu, L.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11002−11003. (f) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669−5672.

(5) (a) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811−814. (b) Ogasawara, K. *Pure Appl. Chem.* **1994**, *66*, 2119−2122.

10.1021/ol051704m CCC: $30.25
Published on Web 09/01/2005

However, kinetic resolution involves a fatal disadvantage because half of the starting material is discarded. It should also be emphasized that careful control of the reaction progress is required to maximize the recovery yield and ee of the unreacted starting material. Since the enantioenriched 5-(trialkylsilyl)cyclohexenones themselves have been the choice of starting material for the preparation of 5-substituted cyclohexenones, 5-(trialkylsilyl)cyclohexenones have been the target of kinetic resolution.[4a,f,5a] We describe herein the straightforward asymmetric synthesis of 5-arylcyclohexenones **4** with high ee from racemic 5-(trimethylsilyl)-cyclohexenone **1** via chiral phosphane-rhodium(I)-catalyzed conjugate arylation[6,7] and subsequent oxidative dehydrosilylation (Scheme 1). Namely, the idea is based on the utility

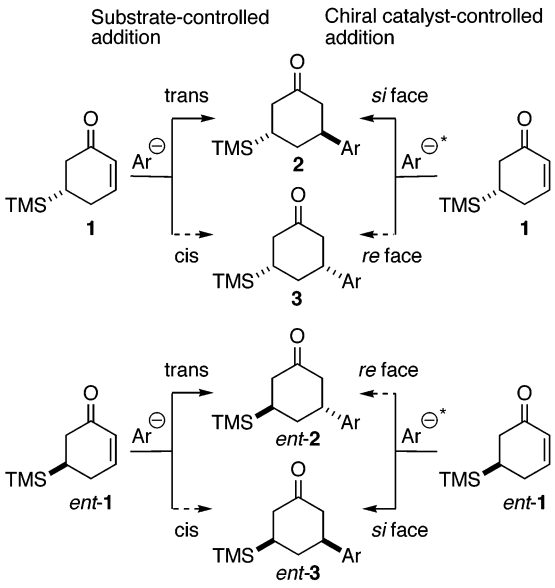
Scheme 1. Two-Step Catalytic Asymmetric Synthesis of **4** from Racemic **1**



of racemic **1** as a synthetic equivalent of cyclohex-2,5-dienone, which readily isomerizes to phenol.

Generally, 5-substituted cyclohexenones undergo *trans*-selective conjugate addition.[2a,8] Although this substrate control is operative in the reaction of racemic **1** (**1** and *ent*-**1**) to stereoselectively produce racemic **2** (**2** and *ent*-**2**), the enantiofacial control of a chiral catalyst, if favoring *si* face addition, produces **2** as a major product over *ent*-**2**, allowing kinetic resolution to recover *ent*-**1** as has been reported (Scheme 2).[4,5] However, if the chiral catalyst control overcomes the *trans*-diastereoselectivity of the substrate control,[9] **2** and *ent*-**3** are the major products that bear the same stereochemistry at the newly created chiral centers. Dehydrosilylation[4f,5a] thereof completes an asymmetric synthesis of 5-substituted cyclohexenones **4** from the racemic mixture of **1** and *ent*-**1**.

Scheme 2. Substrate Control versus Chiral Catalyst Control in Conjugate Arylation of Racemic **1**



We anticipated that the high enantioselectivity up to 97% ee observed with an amidophosphane **5**-rhodium(I) catalyst in the conjugate arylation of cyclohexenone[10] would overcome the *trans*-diastereoselectivity, providing a mixture of **2** and *ent*-**3** with high ee (Figure 1). The difference of the

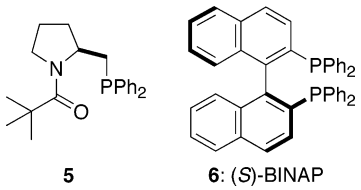


Figure 1. Chiral phosphane ligands **5** and **6** for Rh(I).

present proposal from kinetic resolution protocol is the full conversion of racemic **1** to ideally a 1:1 mixture of **2** and *ent*-**3**, whereas in the kinetic resolution the formation of *ent*-**3** is suppressed to recover *ent*-**1**.

The *trans*-diastereoselectivity by the substrate control was confirmed by the dppb-[RhCl(C_2H_4)$_2$]$_2$-KOH-catalyzed Miyaura arylation[11] of racemic **1**[4f] with phenylboronic acid in dioxane−water at 100 °C, giving a 91:9 racemic mixture of *trans*-**2a** (Ar = Ph) and *cis*-**3a** (Ar = Ph) in 57% yield, apparently indicating that *trans*-diastereoselectivity is maintained in the Rh(I)-catalyzed arylation of **1**. With *dl*-BINAP **6** in place of dppb, the same substrate control was observed to give a 89:11 *trans* major mixture in 90% yield.

The reaction of racemic **1** with phenylboronic acid was successfully catalyzed by 3 mol % **5**-[RhCl(C_2H_4)$_2$]$_2$ and 1

(6) (a) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240−6241. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628−1629. (c) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508−11509. (d) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481−9484. (e) Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* **2003**, 1040−1042. (f) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (g) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580.

(7) Reviews on asymmetric conjugate addition: (a) Tomioka, K. in *Comprehensive Asymmetric Catalysis*, Supplement to Chapter 31.1; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004, pp 109−124. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (c) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 2000, p 569. (d) Tomioka, K. *Synthesis* **1990**, 541−549.

(8) (a) Yamamoto, Y. In *Methoden Organischen Chemie*, Engl. Ed.; Helmchen, G., Houben, J., Wely, T., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E21b, pp 2041−2067. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1990**, *31*, 1393−1396.

(9) *cis*-Diastereoseletivity by chiral catalyst- and reagent-control has been reported in the reaction of cyclohexenones bearing an ether appendage: Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485−2489. See also ref 2a.

(10) (a) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932−8939. (b) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921−923.

(11) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4231.

Table 1. Phosphane-Rh(acac)(C_2H_4)$_2$-Catalyzed Asymmetric Arylation of Racemic **1** at 100 °C and Dehydrosilylation to **4**[a]

				2 + *ent*-**3**				(*S*)-**4**[b]		
entry	Ar	**5**/**6**	time (h)	yield (%)	ratio	**2** ee (%)	*ent*-**3** ee (%)	**4**	yield (%)	ee (%)
1	Ph	**5**[c,d]	3	91	59:41	76	98	**4a**	73	83
2	Ph	**6**	10	91	61:39	89	99	**4a**	75	93
3	3-MeOC$_6$H$_4$	**5**[c]	2	93	65:35	72	99	**4b**	73	84
4	3-MeOC$_6$H$_4$	**6**	5	92	61:39	83	99	**4b**	73	93
5	3-ClC$_6$H$_4$	**5**[c]	2	93	67:33	70	97	**4c**	72	78
6	3-ClC$_6$H$_4$	**6**	6	82	63:37			**4c**	77	90
7	4-CF$_3$C$_6$H$_4$	**5**[c]	11	88	68:32	72	99	**4d**	74	80
8	4-CF$_3$C$_6$H$_4$	**6**	22	82	63:37	88	99	**4d**	74	93
9	2-Naph	**5**[c,d]	32	55	87:13	50	98			
10	2-Naph	**6**[c]	3	94	51:49	83	99	**4e**	70	90

[a] Percent ee was determined by HPLC (Supporting Information). [b] The absolute configuration was assigned to be (*S*) by comparing specific rotation of the 3-arylcyclohexanones obtained by hydrogenation of **4**. [c] [RhCl(C_2H_4)$_2$]$_2$ (1.5 mol %) and KOH (1 equiv) were used. [d] At 60 °C.

equiv of KOH in dioxane−water (10:1) at 60 °C to afford a 59:41 mixture of **2a** and *ent*-**3a** in 91% yield (Table 1, entry 1). The enantioselectivity was determined by chiral stationary phase HPLC to be 76% and 98% ee, respectively. Treatment of the above mixture of **2a** and *ent*-**3a** with cupric chloride in DMF[12] at 60 °C for 5 h gave (*S*)-**4a** (Ar = Ph) with 83% ee in 73% yield. (*S*)-BINAP **6** was more effective to give a 61:39 mixture of **2** with 89% ee and *ent*-**3** with 99% ee in 91% combined yield. Dehydrosilylation to (*S*)-**4a** with 93% ee was carried out in 68% overall yield from racemic **1** (entry 2).

Aryl groups having electron-donating and -withdrawing substituents, for example, 3-methoxyphenyl, 3-chlorophenyl, 4-trifluoromethylphenyl, and 2-naphthyl groups, were successfully introduced into racemic **1**, giving the corresponding **2** and *ent*-**3** with reasonably high ee (50−99%) in high yields (55−94%). In the production of **2**, **6** is superior to **5**, giving higher enantioselectivity (entries 2, 4, 6, 8, and 10). In the production of *ent*-**3** both phosphanes **5** and **6** behave equally efficiently, giving selectivity over 97% ee. Dehydrosilylation of a mixture of **2b**−**e** and *ent*-**3b**−**e** successfully afforded the corresponding **4b**−**e** with 90−93% ee by **6** and 78−84% ee by **5** in 70−77% yield. It is also important to note that with use of *dl*-**6** as a ligand *trans*-diastereoselectivity (racemic **2**:**3** = 83:17−89:11**)** due to the conformational and stereoelectronic effects of **1** was confirmed without exception.

In conclusion, a chiral phosphane-Rh(I)-catalyzed asymmetric conjugate arylation of racemic 5-(trimethylsilyl)-cyclohexenone with arylboronic acids and subsequent dehydrosilylation gave 5-arylcyclohex-2-enones in high enantioselectivity and good two-step yield. The present asymmetric reaction protocol overcomes the drawback involved in catalytic kinetic resolution. Enantiofacial selectivity with chiral phosphane-Rh(I) exceeds the *trans*-diastereoselectivity that is maintained in achiral or racemic phosphane-rhodium-catalyzed conjugate arylation of 5-(trimethylsilyl)cyclohexenone.

Acknowledgment. This research was supported by the COE Program "Knowledge Information Infrastructure for Genome Science" and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Reaction procedure and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051704M

(12) Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430−431.