ortho-Halogeno Substituents Effect in Asymmetric Cyclization of 4-Aryl-4-pentenals Using a Rhodium Catalyst

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Asymmetric cyclization of 4-aryl-4-pentenals by using a cationic [Rh((*R*)-BINAP)]ClO_4 afforded (3*R*)-3-substituted cyclopentanones; on the other hand, the cyclization of 4-pentenals bearing *ortho*-halogeno phenyl groups afforded the opposite (3*S*)-ones.

Highly enantioselective cyclization of 4-pentenals using a rhodium catalyst with chiral ligands was independently reported by us[1] and Bosnich's group.[2] The intramolecular hydroacylation of 4-pentenal catalyzed by a cationic [Rh(BINAP)]ClO_4 complex afforded highly enantiomerically enriched cyclopentanones, in the case that the substituents at the C4-position of 4-pentenal were bulky tertiary groups, or ketonic carbonyl functions. However, in the case of the substrate bearing a phenyl group, the cyclization gave cyclopentanones in moderate to poor enantiomeric excess. Here, we report the effect of substituents in the aromatic ring on the enantioselection of cyclization.

The electron-withdrawing and/or electron-releasing functional groups were introduced in various positions of the phenyl ring as follows: methyl and methoxy groups, as an electron-releasing functional group, and nitro and halogen (Br and Cl) groups as an electron-withdrawing functional group. Two substituents (2,4-di-Cl, and also 2-Cl-4-NO_2) in the aromatic ring were also introduced simultaneously. Furthermore,

Scheme 1.

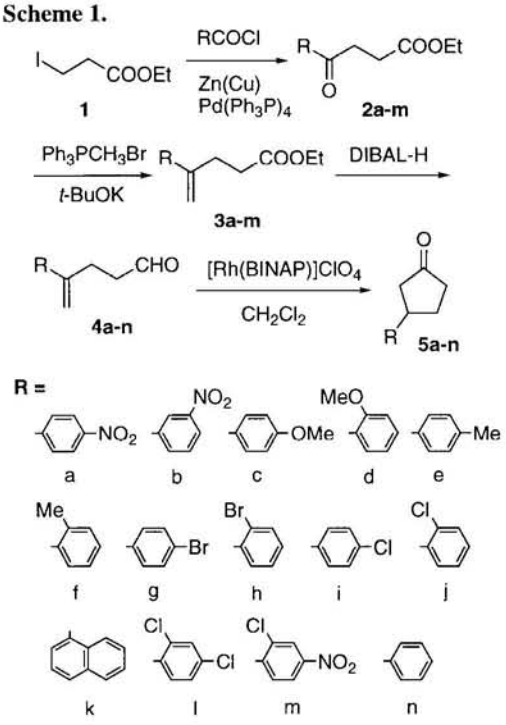


Table 1. Asymmetric cyclization by cationic rhodium complex [Rh(BINAP)]ClO_4[a]

Run	Sub.	BINAP	Product	Isolated Yield (%)	Opt. Purity (% ee)	Abs. Config.
1	**4a**	*R*	(+)-**5a**	87	82	*R*
2	**4a**	*S*	(-)-**5a**	86	77	*S*
3	**4b**	*R*	(+)-**5b**	81	83	*R*
4	**4b**	*S*	(-)-**5b**	95	80	*S*
5	**4c**	*R*	(+)-**5c**	88	18	*R*
6	**4c**	*S*	(-)-**5c**	84	24 (25)[c]	*S*
7	**4d**	*R*	(+)-**5d**	83	19	*R*
8	**4d**	*S*	(-)-**5d**	80	20 (17)[c]	*S*
9	**4e**	*R*	(+)-**5e**	45[b]	25	*R*
10	**4e**	*S*	(-)-**5e**	51	29 (44)[c]	*S*
11	**4f**	*R*	(+)-**5f**	86	18	*R*
12	**4f**	*S*	(-)-**5f**	81	17	*S*
13	**4g**	*R*	(+)-**5g**	90	49	*R*
14	**4g**	*S*	(-)-**5g**	84	44	*S*
15	**4h**	*R*	(-)-**5h**	82	63	*S*
16	**4h**	*S*	(+)-**5h**	79	60	*R*
17	**4i**	*R*	(+)-**5i**	70	57	*R*
18	**4i**	*S*	(-)-**5i**	83	63	*S*
19	**4j**	*R*	(-)-**5j**	75	63	*S*
20	**4j**	*S*	(+)-**5j**	74	61	*R*
21	**4k**	*R*	(+)-**5k**	78	26	*R*
22	**4k**	*S*	(-)-**5k**	76	26	*S*
23	**4l**	*R*	(-)-**5l**	74	81	*S*
24	**4l**	*S*	(+)-**5l**	82	80	*R*
25	**4m**	*R*	(-)-**5m**	90	87	*S*
26	**4m**	*S*	(+)-**5m**	95	83	*R*
27	**4n**	*R*	(+)-**5n**	94	48[d]	*R*
28	**4n**	*S*	(-)-**5n**	95	48[d]	*S*

[a]Reactions were completed within 2 h, except for substrates **4c** and **4e**. [b]Reaction was not completed after 10 h, and the substrate was recovered. [c]Data in parentheses are Bosnich's report.[2] [d]These data were already reported by us.[1]

a 1-naphthyl group was introduced as a substituent in 4-substituted 4-pentenal. The substrates were prepared as shown in Scheme 1. Ethyl 3-iodopropionate **1** was coupled with various benzoyl chlorides according to Yoshida's procedure[3] [Zn(Cu), $Pd(Ph_3P)_4$] to give γ-keto esters **2a-m**. Wittig reaction, followed by reduction of ester with DIBAL-H afforded 4-aryl-4-pentenals **4a-m**.

The results of cyclization by [Rh(BINAP)]ClO_4 are summarized in Table 1. The reaction was carried out using 1.0 mmol of substrate and 0.10 mmol of the Rh-complex under an Ar atmosphere. The products were obtained in moderate to good

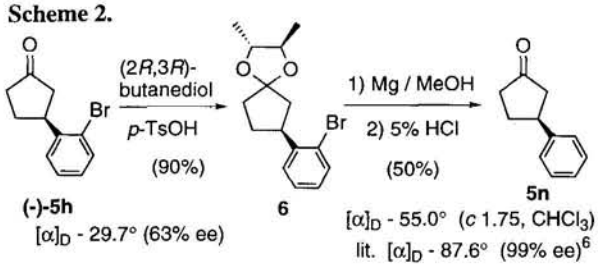
yields. The structures of products were determined by spectroscopic analyses. For example, the signals due to aldehyde [δ 9.81 (t, J = 1.1 Hz, 1H)] and olefin [5.48 (d, J = 0.7 Hz, 1H) and 5.29 (m, 1H)] which were observed in the ^{1}H NMR spectrum of **4a**, disappeared, and the signal due to the methine proton [δ 3.54 (m, 1H)] appeared in that of **5a**. The IR spectrum of **5a** showed the absorption band at 1740 cm^{-1}, and also the MS spectrum [m/z 205 (M^+)] supported the structure. The enantiomeric excess of the cyclopentanone products was definitively determined by ^{13}C NMR spectra,[4] after acetalization of ketone with (2*R*,3*R*)-butanediol using *p*-TsOH in refluxing benzene. For example, the ^{13}C NMR spectrum of the acetal derived from (3*S*)-(-)-**5a** showed the splitting methylene carbon signals at δ 45.79 (C2, minor), 45.56 (C2, major), 38.29 (C5, minor), 37.97 (C5, major), 32.27 (C4, minor), and 32.12 (C4, major), respectively. Based on the intensity of these signals, the enantiomeric excess of (3*S*)-(-)-**5a** was estimated to be 77% ee. The cyclization of 4-pentenals **4a**,**b**,**g**-**j**,**l**,**m** with the electron-withdrawing group in the phenyl ring afforded cyclopentanones of moderate enantiomeric excess (44-87% ee), but the cyclization with the electron-releasing group **4c**-**f** gave products of low enantiomeric excess (17-29% ee). The cyclization of **4k** bearing 1-naphthyl group afforded cyclopentanone **5k** of 26% ee. The position of the substituent in the phenyl ring did not affect the enantiomeric excess, excepting the substrates bearing halogeno groups (Br and Cl).

The absolute configurations of the products were assigned based on the chemical shifts of the ^{13}C NMR signals of (2*R*,3*R*)-butanediol acetals. The (2*R*,3*R*)-butanediol acetal of (*S*)-cyclopentanone enantiomer of the established absolute configuration always showed a ^{13}C NMR signals upfield from the acetal of the *R* enantiomer.[1,4] Based on this assumption, the absolute stereochemistry of the unknown configurations was determined. On the whole, the cyclization of 4-pentenals by a cationic [Rh((*S*)-BINAP)]ClO$_4$ gave the (3*S*)-arylcyclopentanones, and by (*R*)-BINAP afforded the (3*R*)-products. These enantioselections were consistent with the previous results.

Contrary to this empirical rule, the cyclization of 4-pentenal bearing *ortho*-bromophenyl **4h** by [Rh((*R*)-BINAP)]ClO$_4$ afforded the (3*S*)-(-)-cyclopentanone **5h**, and the cyclization by (*S*)-BINAP gave (3*R*)-(+)-**5h**. The stereochemistry of (-)-**5h** was unambiguously determined by chemical correlation with (3*S*)-phenylcyclopentanone **5n**. (Scheme 2).[5] The opposite enantioselectivity was also found in the case of substrates **4j**,**l**,**m**.

The cyclization of 4-pentenals bearing two substituents

Scheme 2.



4l,**m** afforded the cyclopentanones **5l**,**m** of high enantiomeric excess (80-87% ee). These high enantioselectivities would be attributed to the multiple effects of two electron-withdrawing groups. At this time, we are not able to offer a reasonable explanation why the cyclization of 4-pentenals bearing an *ortho*-halophenyl group showed the opposite enantioselectivity to the other cases.

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References and Notes

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5 The absolute configuration of cyclopentanone (+)-**5g** was also determined by chemical correlation with **6**, and the stereochemistry of (+)-**5g** was 3*R*.

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