High β-Stereoselectivity in Asymmetric Radical Addition to α-Sulfinylcyclopentenones

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Received June 11, 1993

A number of attempts at selective carbon–carbon bond formation via radical processes have been made in recent years.[1] As compared with the high α-stereoselection[2] observed in radical reactions which occur α to a center substituted with a chiral auxiliary, diastereofacial control in the addition of achiral radicals at the carbon β to the chiral auxiliary is difficult to achieve. Quite recently, high β-stereoselection was reported in the addition of a limited class of carbon radicals such as *tert*-butyl or sulfonylmethyl radicals to chiral α,β-unsaturated amides[3a] or C_2 chiral enamines.[3b] A few examples using sulfoxides as chiral auxiliaries for radical reactions have been studied, but they have also been limited to α-stereoselection.[4] We now report extremely high β-stereoselection in the addition of tertiary, secondary, and even primary alkyl radicals to chiral α-sulfinylcyclopentenones which have sterically demanding substituents.

Initially, we examined the addition of *tert*-butyl radical, generated from *tert*-butyl iodide and triethylborane,[5] to (*S*)-(+)-2-(*p*-toluenesulfinyl)-2-cyclopentenone[6] (**1a**) (Scheme I). To fix the conformation of the reactive intermediate, the reaction was carried out in the presence of $ZnBr_2$ or $TiCl_2(Oi\text{-}Pr)_2$. The radical addition proceeded efficiently to give alkylated products, but the diastereoselectivity was low under these conditions (entries 1 and 2, Table I). Therefore, we designed a new chiral sulfoxide which would effectively shield one face of the cyclopentenone ring. Chiral (*R*)-(–)-2-((3,5-di-*tert*-butyl-4-methoxyphenyl)-sulfinyl)-2-cyclopentenone[7] (**1b**) was prepared from 2,6-di-*tert*-butylphenol in five steps through the reaction of menthyl arylsulfinate and 2-lithiocyclopentenone ethylene acetal.[6] The stereoselectivity was significantly improved in the reaction of **1b** (Table I). $TiCl_2(Oi\text{-}Pr)_2$ gave the highest selectivity among the Lewis acids tested.[8] CH_2Cl_2 was most suitable among the solvents examined (entry 4). Interestingly, the reaction under higher dilution gave products with higher selectivities (entries 5 and 9).[9] These data suggest that effective 1:1 coordination of the sulfinyl enone and the Lewis acid is crucial for fixing the reactive conformer and therefore for giving high stereoselection. Indeed, the reaction without Lewis acid gave almost equal amounts of **2** and **3** (entry 10). In the reaction using *tert*-butyl iodide and triethylborane, the competitive addition of *tert*-butyl and ethyl radicals could not be avoided, the latter radical being formed from triethylborane as initiator, and the reaction of **1b** afforded *tert*-butyl and ethyl addition products in a ratio of 95:5.[10] To avoid the formation of the ethyl adduct, we next examined the reaction using trialkylboranes as alkyl radical sources.[11] As summarized in Table II, the desired alkyl adducts were obtained in high yield in the reaction of **1b** with a variety of trialkylboranes[12] either in the presence of Lewis acid or without Lewis acid. Stereoselectivities depended on the bulkiness of the alkyl radicals. Thus, the reaction afforded adducts **2** and **3** in a ratio of 77:23 with triethylborane, 84:16 with triisopropylborane, 89:11 with tricyclohexylborane, and 98:2 with tri-*tert*-butylborane. In those reactions the corresponding cis isomers were not detected. The

Scheme I

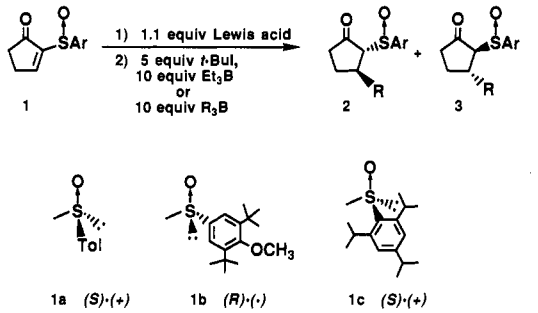

Table I. Reaction of α-Sulfinylcyclopentenones **1a** and **1b** with *tert*-Butyl Iodide and Triethylborane in the Presence of Lewis Acids[a]

entry	sulfinylcyclopentenone	Lewis acid	solvent	concn, M	*t*, °C	time, h	yield, %	ratio[b] 2:3
1	**1a**	$ZnBr_2$	THF	0.1	–78	1	48	38:62
2	**1a**	$TiCl_2(Oi\text{-}Pr)_2$	CH_2Cl_2	0.1	0	8	60	28:72
3	**1b**	$ZnBr_2$	THF	0.1	0		*c*	59:41
4	**1b**	$Ti(Oi\text{-}Pr)_4$	CH_2Cl_2	0.1	0	3	70	56:44
5	**1b**	$TiCl_2(Oi\text{-}Pr)_2$	CH_2Cl_2	0.1	0	2	85	91:9
6	**1b**	$TiCl_2(Oi\text{-}Pr)_2$	CH_3CN	0.1	0	2	66	89:11
7	**1b**	$TiCl_2(Oi\text{-}Pr)_2$	toluene	0.1	0	2	66	85:15
8	**1b**	$TiCl_2(Oi\text{-}Pr)_2$	CH_2Cl_2	0.01	–78	8	83	75:25
9	**1b**	$TiCl_2(Oi\text{-}Pr)_2$	CH_2Cl_2	0.01	0	5	86	95:5
10	**1b**		CH_2Cl_2	0.01	–78	4	94	49:51

[a] To a solution of **1a** or **1b** was added 1.1 equiv of Lewis acid at 0 °C or at –78 °C, and the mixture was stirred for 1 h. To this mixture were added 5 equiv of *tert*-butyl iodide and 10 equiv of triethylborane, and the mixture was stirred for the time shown in table. The mixture was quenched with aqueous sodium dihydrogenphosphate and extracted with ether. The crude product was purified by silica gel column chromatography. [b] Determined by HPLC. [c] Not isolated.

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Table II. Reaction of α-Sulfinylcyclopentenones **1b** and **1c** with Various Trialkylboranes[a]

entry	sulfinylcyclopentenone	R_3B	Lewis acid	time, h	yield, %	ratio[b] 2:3
1	**1b**	Et_3B	$TiCl_2(Oi\text{-}Pr)_2$	12	72	77:23
2	**1b**	$(i\text{-}Pr)_3B$	$TiCl_2(Oi\text{-}Pr)_2$	10	61	84:16
3	**1b**	$(c\text{-}C_6H_{11})_3B$	$TiCl_2(Oi\text{-}Pr)_2$	3	90	89:11
4	**1b**	$(t\text{-}Bu)_3B$	$TiCl_2(Oi\text{-}Pr)_2$	8	94	98:2
5	**1b**	$(t\text{-}Bu)_3B$		8	91	38:62
6	**1c**	Et_3B	$TiCl_2(Oi\text{-}Pr)_2$	2	60	42:58
7	**1c**	Et_3B	Et_2AlCl	1.5	92	45:55
8[c]	**1c**	Et_3B	$ZnBr_2$	2	52	>98:<2
9[c]	**1c**	Et_3B	$MgCl_2$	1	30	>98:<2
10[c]	**1c**	Et_3B	$ZrCl_4$	8	82	>98:<2
11	**1c**	Et_3B		6	95	>98:<2
12	**1c**	$(i\text{-}Pr)_3B$		2	94	>98:<2
13	**1c**	$(c\text{-}C_6H_{11})_3B$		3	71	>98:<2
14	**1c**	$(t\text{-}Bu)_3B$		8	66	>98:<2

[a] To a 0.01 M solution of **1b** or **1c** was added 1.1 equiv of Lewis acid at 0 °C, and the mixture was stirred for 1 h. To the mixture was added dropwise 10 equiv of trialkylborane, and the mixture was stirred for the time shown in table. It took longer to complete the reaction when a lesser amount of trialkylborane was used. CH_2Cl_2 was used as solvent unless otherwise noted. [b] Determined by ^1H NMR. [c] THF was used as solvent.

selectivity was reversed when the reaction was performed without Lewis acid (entry 5). These data showed again that the *syn*-periplanar orientation of the S→O and C=O bonds formed by chelating with bidentate Lewis acid is crucial for controlling the stereoselectivity.

We next studied the reaction of chiral (*S*)-(+)-2-((2,4,6-triisopropylphenyl)sulfinyl)-2-cyclopentenone (**1c**), which was successfully prepared from the DAG ester instead of the menthyl ester.[13] In the reaction of **1c**, Lewis acids such as $TiCl_2(Oi\text{-}Pr)_2$ or Et_2AlCl showed no selectivity (entries 6 and 7). The lack of selectivity suggests that the Lewis acid is only weakly or partially coordinated with the sulfinyl and/or carbonyl oxygens and that the two sterically bulky isopropyl groups on the phenyl ring of **1c** interfere in the chelation with Ti or Al. This interference was more prominent in the reaction using $ZnBr_2$, $MgCl_2$, and $ZrCl_4$ in THF solution, leading to high stereoselection but to reversed-face selection. In this case, the face selection is the same as that observed in the reaction without Lewis acid (entries 8–11). Surprisingly, the reaction of **1c** with triethylborane without Lewis acid afforded only a single diastereomer (**2**), and **3** was not detected by careful analyses of ^1H NMR spectra and HPLC of the crude product. Complete β-stereoselection was also achieved in the additions of isopropyl, cyclohexyl, and *tert*-butyl radicals to **1c**.

In the radical reactions studied, unprecedentedly high β-stereoselection using chiral sulfinylcyclopentenones was achieved. Further studies of radical reactions of acyclic enones having a chiral sulfoxide auxiliary are now in progress in our laboratory.

Supplementary Material Available: Determination of the absolute configurations of **1b** and **1c**; determination of the stereochemistry of **2** and **3**; the reaction mechanism (2 pages). Ordering information is given on any current masthead page.

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