Asymmetric Carboalkoxyalkylidenation with a Chiral Horner–Wadsworth–Emmons Reagent

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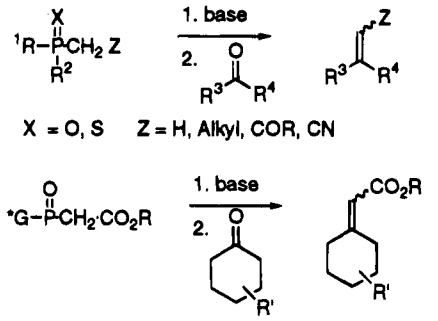
Summary: The asymmetric carboalkoxyalkylidenation of 4-substituted cyclohexanones was effected by the use of chirally modified Horner–Wadsworth–Emmons (HWE) reagents in good yields (78–82%) as well as high levels of enantioselectivity (78–86% ee).

The Horner–Wadsworth–Emmons (HWE) reaction between phosphorus-stabilized carbanions and aldehydes or ketones is an important and practical method for the construction of carbon–carbon double bonds (Scheme 1).[1] The reaction generally occurs at lower temperatures and encompasses a greater spectrum of carbonyl compounds than the conventional Wittig reaction of phosphorus ylides.[2]

Many attempts to develop an asymmetric version of the HWE reaction have been reported over the past three decades. Since the pioneering work by Bestmann, which employed chiral phosphoranes for the synthesis of optically active allenes and cycloalkylidenes,[3a–d] other phosphorus-based reagents have been developed. Chirally modified phosphinothioic amides,[4a] phosphonamides,[4b–d] phosphine oxides,[4e,f] and oxazaphosphorinanes[4g] have been used for the selective preparation of alkyl- or aryl-substituted chiral alkylidenes.

In addition, the synthesis of functionalized, optically active olefins has been addressed and acyl- and carbalkoxyalkylidenes have been prepared as well from phosphorus reagents.[5] For example, chiral phosphinates,[5a,b] phosphonates,[5c–h] oxathiaphosphorinanes,[5i] and phosphoranes[5j,k] have been employed with variable success. The highest selectivity obtained with 4-substituted cyclohexanones is 46% de of the corresponding esters using a menthol-derived phosphonate.[5d] In addition, other non-phosphorus-based methods have been reported.[6]

Scheme 1



In continuation of our examination and development of chiral, phosphorus carbanionic reagents,[4g,7] we have devised a general procedure for the synthesis of (carboxyalkylidene)cycloalkanes from the corresponding ketones. To accomplish this transformation we have investigated the use oxazaphospholidine 2-oxides (**6** and **7**), which employ readily available, camphor-derived amino alcohol auxiliaries for the asymmetric modification of phosphorus (Scheme 2).

The synthesis of the amino alcohols **3** and **5** began with camphorquinone[8] (**1**), which was condensed with different primary amines to produce the corresponding keto imines **2** in good yields.[9] Amino alcohols **3** were obtained by direct hydride reduction of the keto imines with either $NaBH_4$ or $Ca(BH_4)_2$.[10] In the case of the endo isomer, **5**, a stepwise sequence of reductions was employed. Selective reduction of the imine double bond using either Zn/KOH or hydrogen over Raney nickel afforded the α-amino ketones **4**, which upon reduction with $Ca(BH_4)_2$ produced the endo amino alcohols **5**.[11] The exo phosphorus reagents (*cis*- and *trans*-**6**)[12] were synthesized by treatment

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Scheme 2

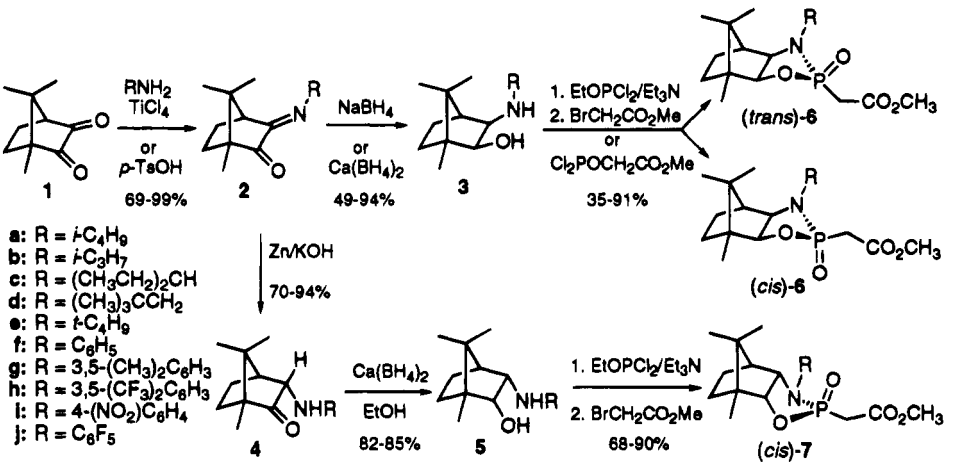
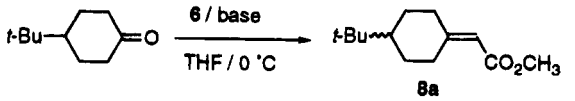


Table 1. Olefination of 4-*tert*-Butylcyclohexanone with *cis*- and *trans*-6



8a

entry	R	compd	base	time, h	yield,[a] %	ee,[b] % (confgn)
1	i-C_4H_9	*trans*-**6a**	KHMDS	1	60	0
2	i-C_3H_7	*trans*-**6b**	KHMDS	1.5	70	11 (*R*)
3	$(CH_3)_3CCH_2$	*trans*-**6d**	KHMDS	3	92	44 (*R*)
4	i-C_4H_9	*cis*-**6a**	KHMDS	1	47	56 (*R*)
5	i-C_4H_9	*cis*-**6a**	NaHMDS	1	58	6 (*R*)
6	i-C_3H_7	*cis*-**6b**	KHMDS	1	68	54 (*R*)
7	i-C_3H_7	*cis*-**6b**	KHMDS[c]	2.5	16	35 (*R*)
8	i-C_3H_7	*cis*-**6b**	LDA	3.5	49	23 (*R*)
9	$(CH_3)_3CCH_2$	*cis*-**6d**	KHMDS	2	59	53 (*R*)
10[d]	t-C_4H_9	*cis*-**6e**	KHMDS	24	<5	45 (*S*)
11	C_6H_5	*cis*-**6f**	KHMDS	2	54	54 (*R*)
12	3,5-$(CF_3)_2C_6H_3$	*cis*-**6h**	KHMDS	9	36	70 (*R*)
13[e]	3,5-$(CF_3)_2C_6H_3$	*cis*-**6h**	KHMDS	48	67	81 (*R*)

[a] Yield of isolated, purified products (not optimized). [b] See refs 17 and 18. [c] Two equiv of 18-crown-6 as additive. [d] Reaction run at 66 °C. [e] Reaction run at −18 °C, 1.6 equiv of anion used.

of **3** with either the corresponding phosphonic dichloride[13] or ethyl dichlorophosphite followed by methyl bromoacetate (Arbuzov reaction). The phosphorus epimers were formed in ratios between 1/1 and 12/1 (*cis/trans*) depending on the *N*-substituent and could be easily separated by column chromatography. The endo counterparts (*cis*- and *trans*-**7**)[12] were prepared in a similar fashion, but in this series the trans isomers, if formed, were produced in trace quantities and were not investigated.

The olefination studies began with the more accessible oxazaphospholidine 2-oxides, *trans*- and *cis*-**6** (Table 1), and 4-*tert*-butylcyclohexanone as the test substrate. In intial experiments, the potassium salt (KHMDS) of the phosphonamidates was found to give appreciably faster reactions than other counterions (vide infra). With 1 equiv of the reagent, the reactions proceeded rapidly at 0 °C affording (*R*)-(−)-**8a** in good yields from both phosphorus epimers. The trans series displayed disappointing selectivity and a modest dependence on the *N*-substituent. On the other hand, reagents derived from *cis*-**6** produced the olefin in much higher ee than the *trans*-**6** counterparts, but remarkably in the same enantiomeric series.[14] The size of the R group on nitrogen again did not show a marked effect on the selectivity, (entries 4, 6, 9, 10, and 11). However, an electron-withdrawing substituent increased the selectivity but the reactions were significantly slower (compare entries 11, 12, and 13). Lowering the temperature had a beneficial effect on selectivity, but extended reaction times were necessary. Interestingly, reactions of the Li^+ or Na^+ reagents were sluggish and afforded poor yields and enantioselectivities (compare entries 4 and 5, 6 and 8).[15] The presence of additives either retarded (18-crown-6, entry 7) or completely inhibited (Kryptofix) the reaction.[16] In addition, the use of solvents more coordinating than THF, such as DME or DMF, slowed down the reactions considerably.

Olefinations carried out with *cis*-**7** were more successful, and the results with the aromatic amine dervied reagents are shown in Table 2. The reaction with 4-*tert*-butylcyclohexanone was conducted using 1.5 equiv of the reagent K^+*cis*-**7f**$^-$ (THF/0 °C) and yielded (*S*)-(+)-**8a** in 77% ee (entry 1). Conducting the reaction at −35 °C increased the selectivity to 86% (entry 2). When Et_2O was used as solvent a significant rate acceleration was observed, but the enantioselectivity dropped (entry 3). An electronic effect was also manisfested in these series. Replacing phenyl with a more electron-rich substituent (R = 3,5-$(CH_3)_2C_6H_3$, K^+*cis*-**7g**$^-$) accelerated the reaction, but had a deleterious effect on the selectivity (compare entries 1 and 4 and 3 and 5). In contrast, K^+*cis*-**7h**, bearing an elecron-wtihdrawing substituent (R = 3,5-$(CF_3)_2C_6H_3$), afforded (*S*)-(+)-**8a** in 91% ee, however, with a significant reduction in rate (entry 6). Thus, we have discovered important structural and medium effects on the reaction which acted with complimentarity and therefore required considerable optimization: (1) the endo series is significantly more selective than the exo

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(12) The cis and trans relationships in compounds **6** and **7** are defined according to the relative disposition of the camphor ring system and the carbomethoxymethylene substituents on the 1,3,2-oxazaphospholidine 2-oxide ring.

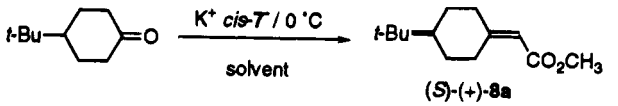
(13) Bodnarchuk, N. D.; Malovik, V. V.; Dercach, G. I. *Zh. Obshch. Khim.* **1970**, *40*, 1210.

(14) In asymmetric alkylation reactions with other phosphorus heterocycles, we have found that the configuration at phosphorus determines the stereochemical outcome of the reaction. See ref 7e and references cited therein.

(15) This phenomenon has been noted by others. See ref 5d.

(16) The presence of such additives in the Horner–Wadsworth–Emmons reaction of aldehydes is known to accelerate the reaction rates. See: Baker, R.; Sims, R. J. *Synthesis* **1981**, 117.

Table 2. Optimization of the Olefination of 4-*tert*-Butylcyclohexanone with *cis*-7

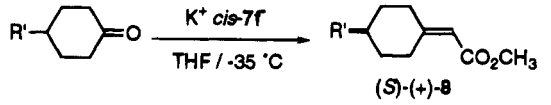


(*S*)-(+)-**8a**

entry	R	compd	time, h	solvent	yield,[a] %	ee,[b] % (confgn)
1	C_6H_5	*cis*-**7f**	22	THF	78	77(*S*)
2	C_6H_5	*cis*-**7f**	48[c]	THF	79	86(*S*)
3	C_6H_5	*cis*-**7f**	6	Et_2O	(100)	62(*S*)
4	3,5-$(CH_3)_2C_6H_3$	*cis*-**7g**	7.5	THF	(98)	63(*S*)
5	3,5-$(CH_3)_2C_6H_3$	*cis*-**7g**	2.5	Et_2O	(100)	61(*S*)
6	3,5-$(CF_3)_2C_6H_3$	*cis*-**7h**	48[c]	THF	68	91(*S*)

[a] Yield of isolated, purified products. GC conversions in parentheses. [b] See refs 17 and 18. [c] Reaction run at −35 °C.

Table 3. Asymmetric Olefination of 4-Substituted Cyclohexanones with *cis*-7f[a]



(*S*)-(+)-**8**

entry	R'	yield,[b] %	ee,[c] % (confgn)	$[\alpha]^{22}_D$ (solv, concn)
1	$C(CH_3)_3$ (**8a**)	78	86 (*S*)	+64° (acetone, 1.50)
2	CH_3 (**8b**)	79	82 (*S*)	+65° (ethanol, 1.20)
3	C_6H_5 (**8c**)	82	82 (*S*)	+87° ($CHCl_3$, 1.00)
4	$CO_2C(CH_3)_3$ (**8d**)	82	78 (*S*)	+34° ($CHCl_3$, 1.05)

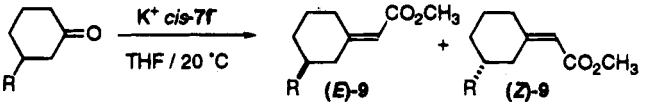
[a] See footnote 21. [b] Yield of isolated, purified products. [c] See refs 17 and 18.

series, (2) the bulk of the *N*-substituent is not important, (3) electron-withdrawing *N*-substituents lead to slower reaction but higher selectivities, and (4) increasing solvent polarity (Et_2O < THF < DME < DMF) decreases rate and increases enantioselectivity.

Other substrates were examined in the carboalkoxyolefination reaction, and the results are collected in Table 3. Because of its ease of preparation and the availability of the starting materials, K+*cis*-**7f**− was selected as the reagent of choice. The reactions were conducted in THF at −35 °C, and after 48 h, good yields as well as respectable levels of enantioselectivity were obtained. The highest selectivity was observed with 4-*tert*-butylcyclohexanone as substrate (entry 1).

To evaluate the scope and limitations of this asymmetric HWE reaction, other ketones were tested. While 2-methylcyclohexanone was almost unreactive to K+*cis*-**7f**− (KHMDS/THF/rt/24 h), 3-methylcyclohexanone provided interesting results (Scheme 3). Reaction of K+*cis*-**7f**− with 3-methylcyclohexanone afforded a 60/40, *E*/*Z* mixture of the corresponding esters **9a** in 58 and 84% ee, respectively (97% conversion). Under similar conditions, 3-*tert*-butylcyclohexanone gave an 83% yield of a 53/47 *E*/*Z* mixture of **9b** in 90 and 83% ee, respectively.[19,20]

Scheme 3



a: R = Me 60%, 58% ee 40%, 84% ee
b: R = *t*-Bu 53%, 90% ee 47%, 83% ee

In summary, we developed a new approach for the asymmetric HWE reaction in which good yields and respectable levels of selectivity for the (carboxyalkylidene)cycloalkanes have been obtained. The ease of preparation of the chiral auxiliaries and the mild reaction conditions augur well for application of this method in organic synthesis.

Acknowledgment. We are grateful to the National Institutes of Health (RO1 GM 45532) for support of this research. I.R. thanks the National Institutes of Health for a postdoctoral fellowship.

Supplementary Material Available: Preparation and full spectroscopic characterization of **2b**, **2d**, **2h**, **3b**, **3d**, **3h**, **4f**, **4h**, **5f**, **5h**, *trans*-**6b**, *cis*-**6b**, *trans*-**6d**, *cis*-**6d**, *trans*-**6f**, *cis*-**6f**, *trans*-**6h**, *trans*-**7f**, *cis*-**7f**, *cis*-**7h**, **8a-d**, (*Z*)-**9b**, and (*E*)-**9b** are provided (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) The absolute configurations of **8a** and **8b** have been established. The configurations of **8c** and **8d** are assigned by analogy. (a) Walborsky, H. M.; Goedken, V. L.; Gawronski, J. K. *J. Org. Chem.* **1992**, *57*, 410. (b) Solladié, G.; Zimmerman, R.; Bartsch, R.; Walborsky, H. M. *Synthesis* **1985**, 662.

(18) The ee for **8a** and **8b** was determined by chiral GC (J & W, β-Cyclodex). For **8c**, chiral HPLC was used (Chiralpak AD). The ee for **8d** was determined by NMR using Eu(hfc)$_3$.

(19) The assignment of alkylidene geometry in **9b** was made on the basis of (1) ^{13}C steric compression shifts of C(5) and C(7), (2) coupling of $H_{eq}C(4)$ and HC(5), and (3) mechanistic analogy for the stereochemical course; equatorial attack, *re* face of the anion.

(20) The absolute configuration of the (*E*)-(+)-**9b** was determined to be *S* by ozonolysis of the alkylidene ester to the corresponding ketone and comparing the rotation [−20.2 (*c* = 2.0, $CHCl_3$) (lit. +24.1 (*c* = 2.15, $CHCl_3$))] to a literature value for the opposite (*R*)-(+) enantiomer of 3-*tert*-butylcyclohexanone: Lightner, D. A.; Bouman, T. D.; Gawronski, J. K.; Gawronska, K.; Chappuis, J. L.; Crist, B. V.; Hansen, A. E. *J. Am. Chem. Soc.* **1981**, *103*, 5314.

(21) 1.5 equiv of K+ *cis*-**7f**− was used. The unreacted *cis*-**7f** was recovered in 77% yield. The amino alcohol **5f** was recovered in 48% yield after HCl digestion, Et_2O extraction, and chromatography.