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Bis(2-*t*-butylphenyl)phosphonoacetamides for the highly cis-selective synthesis of α,β-unsaturated amides

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ABSTRACT

New Horner–Wadsworth–Emmons reagents, $(o\text{-}t\text{-BuPhO})_2P(O)CH_2CONMe(OMe)$ and $(o\text{-}t\text{-BuPhO})_2P(O)CH_2CON(CH_2CH_2)_2O$ were prepared via the Arbuzov reaction in good yields. The HWE reaction of these reagents with a variety of aldehydes gave cis-α,β-unsaturated amides with high selectivity in almost quantitative yields.

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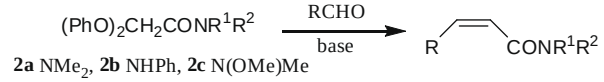
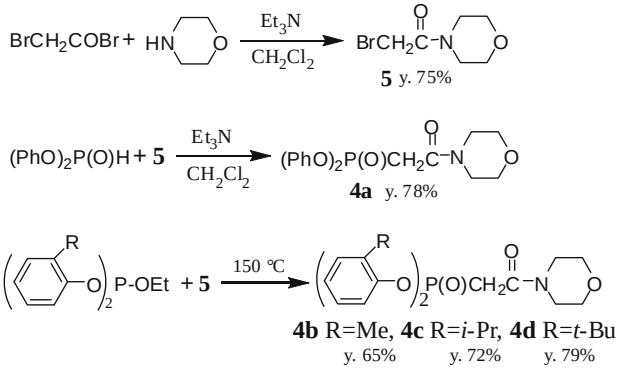
Cis-α,β-unsaturated amides are not only important parts of biologically active natural products[1] but also useful building blocks in organic synthesis.[2] Stereo-defined synthesis of carbon–carbon double bonds with high selectivity is critically important for use in stereoselective reactions. Although it is rather easy to obtain the thermodynamically favored trans isomers, there are only a limited number of methods for preparing the cis isomers.[3–6] During the course of our study on the cis-selective Horner–Wadsworth–Emmons reagents, $(ArO)_2P(O)CH_2CO_2Et$ **1**,[7] which gave cis-α,β-unsaturated esters highly selectively, we prepared (diphenylphosphono)acetamide reagents **2a–c** (Scheme 1). In the presence of base, the reagents **2a–c** react with a variety of aldehydes to give the corresponding cis-α,β-unsaturated amides with moderate to high cis selectivity (75–98% cis) in high yields.[3] After that, Deslongchamps and co-workers reported that the reaction of $(CF_3CH_2O)_2P(O)CH_2CON(Me)OMe$ **3** with *n*-octanal gave more than 20:1 cis selectivity.[4] However, Kojima et al. reported that the HWE reaction of **3** with RCHO (R = $PhCH_2CH_2$, *c*-Hexyl, $PhMe_2C$) gave only moderate to low cis selectivity, 85:15, 68:32, and 43:57, repectively.[5b] Since more general and practical methods are desirable, we decided to improve our reagents **2**. In our study on the cis selective HWE ester reagents **1**, we found ortho-substituted phenyl reagents (*o*-Me and *o*-*i*-Pr) to show higher cis selectivity. After that, Touchard et al. reported the improvement of selectivity at 0 °C using the *o*-*t*-Bu reagent.[8] Here, we wish to report that our new reagents, bis(2-*t*-butylphenyl)phosphonoacetamides react with a variety of aldehydes to give cis-α,β-unsaturated amides in high selectivity.

The *N*-methoxy-*N*-methylamides (Weinreb amides) serve as valuable synthetic intermediates for aldehydes and ketones.[9] The Wittig or HWE reagents containing this amide moiety were reported to show high trans-selectivity.[10] Therefore, cis selective reagents can complement these reactions. However, our reagent **2c** showed only 75–81% cis selectivity, which were lower than the results from dimethylamide reagent **2a** (75–98% cis). Since the morpholine amides have been used as low-cost substitutes for the Weinreb amides,[11] we prepared the morpholine amide reagents **4a–d** (Scheme 2). *N*-Bromoacetylmorpholine **5** was prepared from bromoacetyl bromide and morpholine in the presence of triethylamine in 75% yield. The phenyl reagent **4a** was prepared by the reaction of diphenyl phosphite with **5** in the presence of triethylamine in 78% yield. The reagents **4b–d** were



Scheme 1.



Scheme 2.

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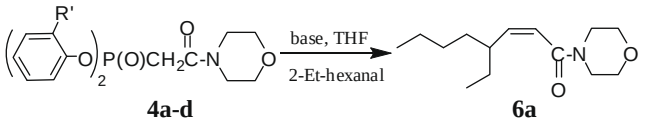
prepared by heating $(ArO)_2POEt$[8] and **5** at 150 °C for 6–8 h in 64–79% yields.

The results of the HWE reaction of **4a–d** with 2-ethylhexanal in THF are summarized in Table 1. After **4a** was treated with NaH at 0 °C for 10 min, the reaction with the aldehyde was performed at −78 to 0 °C over 2 h (entry 1). Only 35% yield of **6a** was obtained in moderate cis selectivity (68:32).[12] The crude NMR showed that no **4a** and about 60% of the aldehyde remained. Although a low yield was also obtained for the reaction of *o*-Me reagent **4b** (entry 2), treating **4b** with NaH in the presence of the aldehyde at 0 °C gave **6a** in 94% yield with 83:17 selectivity (entry 3). These results show that the anion from **4** is labile and easily decomposes at 0 °C. A similar selectivity was observed for the *o*-*i*-Pr reagent **4c** (entry 4). The selectivity was improved by treating **4b** with NaH at −78 °C and allowing the mixture to warm up to 0 °C (89% cis). Furthermore, *o*-*t*-BuPh reagent **4d** gave 94:6 cis selectivity even at 0 °C and 95:5 selectivity at lower temperature (entries 6 and 7). Since NaH does not react with the reagent **4d** at −78 °C and therefore the real reaction temperature is much higher than that, the selectivity did not change much. When *t*-BuOK was used as a base, the selectivity was also 95:5. The selectivity was improved to 97% by the use of *t*-BuONa (entry 9). Thus, the cis selectivity is highest with the biggest *t*-Bu substituted reagent **4d** (R′:H<Me≈*i*-Pr<*t*-Bu).

We examined the HWE reaction of **4** with other types of aldehydes in THF (Table 2). The reaction of the Ph reagent **4a** with aromatic aldehydes, benzaldehyde and *p*-methoxybenzaldehyde using *t*-BuOK in the presence of 1 equiv of 18-crown-6 at −78 °C gave **6** in 98:2 and 97:3 selectivity in high yields (entries 1 and 3). The reaction of the *o*-*t*-BuPh reagent **4d** with benzaldehyde and *p*-chlorobenzaldehyde gave **6** with 99:1 selectivity by just using *t*-BuOK (entries 2 and 4). Since the reaction of **4d** with the aliphatic aldehydes hardly proceeded at −78 °C, the reaction mixture was gradually warmed to 0 °C over about 2 h after the addition of the aldehydes. 92% cis selectivity was obtained in the reaction with *n*-octanal by using *t*-BuOK (entry 5). The selectivity was improved by using *t*-BuONa and **6** was obtained with 96% selectivity (entry 6). The reaction with cyclohexanecarboxaldehyde and pivalaldehyde gave 94 and 96% selectivity, respectively, using either *t*-BuOK or *t*-BuONa as a base (entries 7–10). For the α,β-unsaturated aldehyde, 2-trans-hexenal, the reaction also gave **6** with high selectivity (94:6) in 98% yield. These results clearly show that the new reagent **4d** is applicable to a diverse range of aldehydes for the synthesis of cis-α,β-unsaturated morpholine amides with high selectivity. Thus, *t*-BuONa is the best base for the reaction of **4d** with saturated aliphatic aldehydes and *t*-BuOK is the best one for aromatic and α,β-unsaturated aldehydes. These base preferences are similar to the results from the HWE reaction of (diarylphosphono)acetate **1**.[7a–c]

Encouraged by the results of the morpholine amide reagent **4d**, we also prepared the Weinreb amide reagent **7** (Scheme 3). *N*-Methoxy-*N*-methybromoacetamide **8**[13] was prepared in 81% yield

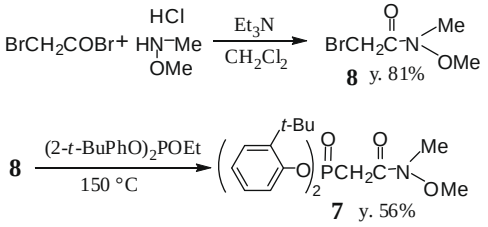
Table 1
The HWE reaction of **4a–d** with 2-ethylhexanal



4a-d **6a**

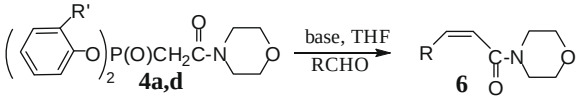
Entry	R′	Base	Temperature	Yield (%)	cis:trans
1	H **4a**	NaH	−78 to 0 °C	35	68:32
2	Me **4b**	NaH	0 °C	32	81:19
3	Me **4b**	NaH[a]	0 °C	94	83:17
4	*i*-Pr **4c**	NaH[a]	0 °C	99	82:18
5	Me **4b**	NaH	−78 to 0 °C	92	89:11
6	*t*-Bu **4d**	NaH[a]	0 °C	78	94:6
7	*t*-Bu **4d**	NaH	−78 to 0 °C	87	95:5
8	*t*-Bu **4d**	*t*-BuOK	−78 to 0 °C	91	95:5
9	*t*-Bu **4d**	*t*-BuONa	−78 to 0 °C	98	97:3

[a] Base was added in the presence of RCHO.



Scheme 3.

Table 2
The HWE reaction of **4** with aldehydes

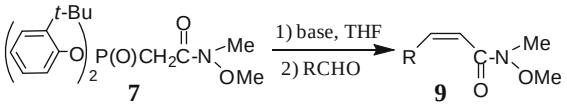


4a,d **6**

Entry	R′	RCHO	Base	Temperature	Yield (%)	cis:trans
1	H	PhCHO	*t*-BuOK[a]	−78 °C, 3 h	97	98:2
2	*t*-Bu	PhCHO	*t*-BuOK	−78 °C, 2 h[b]	94	99:1
3	H	*p*-MeOPhCHO	*t*-BuOK	−78 °C, 3 h	78	97:3
4	*t*-Bu	p-ClPhCHO	*t*-BuOK	−78 °C, 2 h	96	99:1
5	*t*-Bu	*n*-Octanal	*t*-BuOK	−78 to 0 °C	95	92:8
6	*t*-Bu	*n*-Octanal	*t*-BuONa	−78 to 0 °C	87	96:4
7	*t*-Bu	*c*-HexylCHO	*t*-BuOK	−78 to 0 °C	97	94:6
8	*t*-Bu	*c*-HexylCHO	*t*-BuONa	−78 to 0 °C	96	94:6
9	*t*-Bu	*t*-BuCHO	*t*-BuOK	−78 to 0 °C	87	96:4
10	*t*-Bu	*t*-BuCHO	*t*-BuONa	−78 to 0 °C	99	96:4
11	H	2*E*-Hexenal	*t*-BuOK[a]	−78 to 0 °C	95	80:20
12	*t*-Bu	2*E*-Hexenal	*t*-BuOK	−78 to 0 °C	98	94:6

[a] 18-crown-6 (1 equiv).
[b] After the specified time, the reaction mixture was gradually warmed to −30 °C.

Table 3
The HWE reaction of **7** with aldehydes



7 **9**

Entry	RCHO	Base	Temperature	Yield (%)	cis:trans
1	PhCHO	*t*-BuOK	−78 °C, 4 h[a]	94	96:4
2	PhCHO	*t*-BuOK[b]	−78 °C, 4 h[a]	97	98:2
3	p-ClPhCHO	*t*-BuOK	−78 °C, 2 h	95	97:3
4	*n*-Octanal	*t*-BuOK	−78 to 0 °C	92	90:10
5	*n*-Octanal	*t*-BuONa	−78 to 0 °C	95	92:8
6	*c*-HexylCHO	*t*-BuOK	−78 to 0 °C	95	89:119
7	*c*-HexylCHO	*t*-BuONa	−78 to 0 °C	91	91:9
8	2-Et-hexanal	*t*-BuOK	−78 to 0 °C	96	94:6
9	2-Et-hexanal	*t*-BuONa	−78 to 0 °C	89(11)[c]	93:7
10	*t*-BuCHO	*t*-BuOK	−40 to 25 °C	91	95:5
11	*t*-BuCHO	*t*-BuONa	−78 to 0 °C	86	92:8
12	2*E*-Hexenal	*t*-BuOK[b]	−78 to 0 °C	75(16)[c]	89:11

[a] After the specified time, the reaction mixture was gradually warmed to 0 °C.
[b] 18-crown-6 (1 equiv).
[c] The number in parentheses is the recovered yield of **7** (%).

from bromoacetyl bromide and *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of triethylamine in 81% yield. The *o*-*t*-BuPh reagent **7** was prepared by heating (2-*t*-BuPhO)$_2$POEt and **8** in 56% yield.[14]

The results of the HWE reaction of **7** are summarized in Table 3.[15] The *o*-*t*-BuPh reagent **7** was treated with *t*-BuOK at −78 °C for 15 min and reacted with benzaldehyde. Since a trace of the reagent **7** was left after 4 h, the mixture was allowed to warm up to 0 °C. The α,β-unsaturated amide **9** was obtained with 96% cis selectivity in 94% yield (entry 1). Adding 1 equiv of 18-crown-6 improved the selectivity to 98% (entry 2). *p*-Chlorobenzaldehyde is more reactive than benzaldehyde and the reaction took only two hours at −78 °C to complete. 97% cis selectivity was obtained in 95% yield (entry 3). For the aliphatic aldehydes, the reaction also hardly proceeded at −78 °C, thus the reaction mixture was gradually warmed to 0 °C over about 2 h after the addition of the aldehydes. The reaction with *n*-octanal gave **9** in 90% selectivity using *t*-BuOK. This selectivity was improved to 92% by using *t*-BuONa as in the case of the morpholine amide reagent **4d** (entries 4 and 5). Also, *t*-BuONa gave a higher selectivity for the reaction with cyclohexanecarboxaldehyde (entries 6 and 7). However, *t*-BuOK gave higher 95 and 94% selectivity for the reactions with 2-ethylhexanal and pivalaldehyde (entries 8–11). The reaction with 2-trans-hexenal also gave **9** selectively (entry 12). These results can be favorably compared with the results of the phenyl reagent **2c**.[3]

The methods described here provide simple routes to a wide range of cis-α,β-unsaturated morpholine and Weinreb amides in almost quantitative yields. These amides are believed to be transformable to ketones and aldehydes with ease. In fact, cis-α,β-unsaturated *N*-methoxy-*N*-methylamides were efficiently transformed to cis-α,β-unsaturated ketones by using organocerium reagents.[5b] Since it is easy to make the HWE reagents containing other amide moieties, this method should give a variety of cis-α,β-unsaturated amides with high selectivity. We have already made both the dimethylamide reagent and the reagent bearing a methyl glycinate. Both can serve as reagents for the synthesis of bioactive natural products. The results will be reported in the near future.

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12. All the HWE products and the reagents described in this Letter were characterized by 400 MHz ^{1}H NMR spectra and mass spectroscopy. The cis:trans ratios were determined by integration of the vinyl proton signals.
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14. *Preparation of* **7**: A mixture of (*o*-*t*-BuPhO)$_2$POEt (6.890 g, 18.4 mmol) and **8** (3.351 g, 18.4 mmol) was heated at 150 °C under Ar atmosphere for 8 h. Column chromatography (silica gel/33% AcOEt in hexane) gave 7 (4.573 g, 56%) as a colorless powder (mp 62.7–63.5 °C). The reagents **4b**–**d** were prepared in the same way.
15. A typical procedure of the HWE reaction of **7** with *p*-ClPhCHO (entry 3 in Table 3): A solution of **7** (0.30 mmol) in THF (6 mL) was treated with *t*-BuOK (0.39 mmol) at −78 °C for 15 min. Then, *p*-ClPhCHO (0.32 mmol) was added. After 2 h, the reaction was quenched with aqueous NH_4Cl, extracted with AcOEt, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (50% AcOEt in hexane) to give amide **9** (0.0729 g, 96%) as a colorless oil.