Stereoselective Carbon–Carbon Bond Forming Reactions between Various Chiral Alkyl Aryl Carbinols and Triethyl Methanetricarboxylate by Oxidation–Reduction Condensation Using Alkyl Diphenylphosphinites

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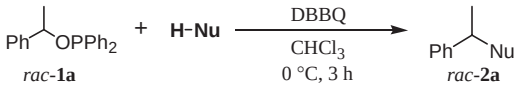
Oxidation–reduction condensation reactions between alkyl diphenylphosphinites derived from chiral alkyl aryl carbinols and triethyl methanetricarboxylate proceeded smoothly to afford the corresponding condensation products in good yields with inversion of stereochemistries.

To develop carbon–carbon bond forming reactions by controlling the absolute stereochemistry is a fundamental challenge in synthetic organic chemistry. Bimolecular nucleophilic substitution (S_N2) reactions using carbon nucleophiles and chiral secondary alcohols as alkylating agents are simple and effective methods to construct inverted chiral tertiary stereogenic centers.[1] Recently, Tsunoda et al. reported C-alkylation of active methylene compounds with primary and secondary alcohols using phosphorane reagents such as cyanomethylenetrimethylphosphorane (CMMP).[2] It was also reported from our laboratory that C-alkylation of (phenylsulfonyl)acetonitrile proceeded smoothly under mild and neutral conditions by oxidation–reduction condensation using alkyl diphenylphosphinites and 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ).[3] When chiral secondary alkyl diphenylphosphinite **1h** derived from (*R*)-4-phenyl-2-butanol was employed in the above condensation, the corresponding alkylated product was formed in a good yield with complete stereo-inversion. However, the above combination using (phenylsulfonyl)acetonitrile and DBBQ was less effective when benzylic phosphinites derived from alkyl aryl carbinols such as **1a** was employed owing to their high reactivities which caused undesired side reactions[3] (see Table 1, Entry 1). Then, the use of alkyl aryl carbinols in C-alkylation was continuously studied. We would like here to report stereoselective C–C bond formation from chiral alkyl aryl carbinols via oxidation–reduction condensation between alkyl diphenylphosphinites and triethyl methanetricarboxylate (TEMT) using dialkyl azodicarboxylates.

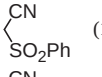
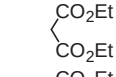
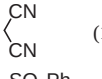
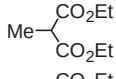
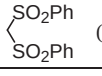
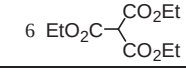
In the first place, C-alkylation of various carbon nucleophiles with racemic phosphinite **1a** and DBBQ was examined in order to find a suitable reagent (Table 1). In spite of their similar pK_a values, (phenylsulfonyl)acetonitrile gave the desired product only in 45% yield (Entry 1), and the result of using malononitirile and bis(phenylsulfonyl)methane were also unsatisfactory (Entries 2 and 3). At the same time, the use of diethyl malonate and the corresponding methine derivative did not afford the desired product either, which was probably due to their low acidities (Entries 4 and 5). Based on the above results, the use of triethyl methanetricarboxylate (pK_a 7.5 in DMSO) was then tried and the C-alkylated product was afforded in 60% yield (Entry 6).

Next, optimization of the reaction conditions of using chiral phosphinite (*R*)-**1a** (99% ee) and TEMT was tried (see Table 2). When 1,4-benzoquinone derivatives were employed, the yield of **2a** was significantly influenced by the substituents located at 2- and 6-positions of 1,4-benzoquinone (Entries 1–3) and the

Table 1. Screening of carbon nucleophiles[a]

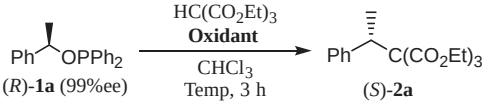


rac-**1a** *rac*-**2a**

Entry	H-Nu	(pK_a)[b]	Yield/%	Entry	H-Nu	(pK_a)[b]	Yield/%
1		(12.0)	45	4		(13.3)	ND
2		(11.1)	27	5		(–)	ND
3		(12.2)	ND	6		(7.5)	60

[a]The reactions were carried out by using *rac*-**1a** (1.0 equiv.), DBBQ (1.2 equiv.), and nucleophiles (1.2 equiv.). [b]pK_a values in DMSO.

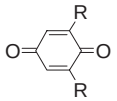
Table 2. Optimization of reaction conditions[a]



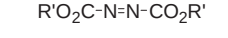
(*R*)-**1a** (99%ee) (*S*)-**2a**

Entry	Oxidant	Temp/°C	Yield/%	Ee/%
1	1,4-Benzoquinone	0	ND	—
2	DMBQ	0	36	97
3	DBBQ	0	60	97
4	DEAD	0	72	97
5	DIAD	0	67	97
6	DTBAD	0	72	96
7	ADDP	0	ND	—
8	DEAD	−63	73	98
9	DIAD	−63	69	97
10	DTBAD	−63	74	97

[a]The reactions were carried out by using **1a** (1.0 equiv.), oxidant (1.2 equiv.), and TEMT (1.2 equiv.).

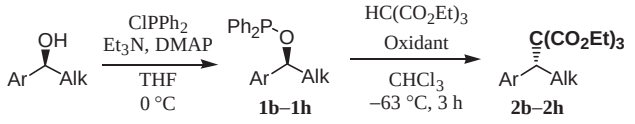


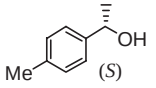
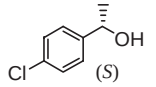
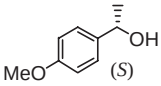
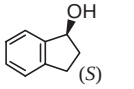
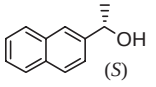
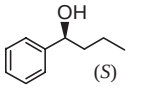
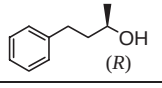
DMBQ (R = Me)
DBBQ (R = *t*-Bu)



DEAD (R′ = Et)
DIAD (R′ = *i*-Pr)
DTBAD (R′ = *t*-Bu)

Table 3. Condensation reactions using various chiral alcohols[a]



Alcohol	Ee/%	Phosphinite**1** Yield/%	Oxidant	Tricarboxylate **2** Yield/%	Ee/%[b]	
	93	**1b** (93)	DEAD DIAD DTBAD	79 81 80	88 88 88	(*R*)-**2b**
	77	**1c** (95)	DEAD DIAD DTBAD	58 56 59	75 75 75	(*R*)-**2c**
	81	**1d** (91)	DEAD DIAD DTBAD	87 89 89	38 42 49	(*R*)-**2d**
	99	**1e** (quant.)	DEAD DIAD DTBAD	71 63 56	96 96 96	(*R*)-**2e**
	99	**1f** (quant.)	DEAD DIAD DTBAD	78 57 48	97 79 73	(*R*)-**2f**
	81	**1g** (quant.)	DEAD DIAD DTBAD	54 56 62	81 81 81	(*R*)-**2g**
	99	**1h** (95)	DEAD DTBAD	8 13	99 99	(*S*)-**2h**

[a]The reactions were carried out by using **1b**–**1h** (1.0 equiv.), oxidant (1.2 equiv.), and TEMT (1.2 equiv.). [b]Ee values were determined by chiral HPLC analysis.

reaction with DBBQ afforded **2a** in 60% yield with 97% ee. After screening various oxidants, it was found that diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and di-*tert*-butyl azodicarboxylate (DTBAD) gave the desired product in 67–72% yields with 96–97% ees (Entries 4–6), whereas 1,1′-(azodicarbonyl)dipiperidine (ADDP) did not afford the desired product at all (Entry 7). When the reaction was carried out by using DEAD at −63 °C, the inverted (*S*)-**2a** was obtained in 73% yield with 98% ee.

With the optimal reaction conditions in hand, the scope of the reaction was investigated by using various chiral alkyl aryl carbinols (Table 3). First, chiral alcohols were transformed into the corresponding phosphinites in excellent yields according to the previously reported procedure of using chlorodiphenylphosphine.[4] Subsequent condensation reactions were then carried out by using dialkyl azodicarboxylates under the above-mentioned conditions ($CHCl_3$, −63 °C) and the corresponding triester-products **2** were successfully afforded in good yields with complete or almost complete inversion of stereochemistries when benzylic diphenylphosphinites **1b**, **1c**, and **1e**–**1g** were employed. Significant loss of enantiomeric excess was observed in the alkylation using phosphinite **1d** bearing a *para*-methoxy moiety because the reaction proceeded via S_N1 and S_N2 pathways competitively. C-Alkylation of TEMT with the unreactive non-benzylic phosphinite **1h** gave the desired product **2h** in poor yields.[1f] Interestingly, bulkiness of the ester moieties of azo-oxidants affected inversion ratios only when **1e** and **1f** were used. These triester products **2** can be transformed to the corresponding chiral 3-aryl-3-alkyl propanoic acids by the reported saponification–decarboxylation procedure.[1e–1g]

General procedures are as follows. (1) Preparation of phosphinites **1a**–**1h**: To a stirred solution of an alcohol (10 mmol) and 4-(dimethylamino)pyridine (3 mmol) in anhydrous THF (20 mL) were added successively triethylamine (12 mmol) and chlorodiphenylphosphine (11 mmol) at 0 °C (the reaction was carried out at −78 °C only in the case of **1d**). After stiring at 0 °C (−78 °C for **1d**) for 1 h, the white slurry was concentrated in vacuo at rt, and the residue was then diluted with hexane–ethyl acetate (100 mL, v/v = 8/1). Insoluble triethylamine salts were filtered off through an alumina–celite bed. After concentration, the corresponding phosphinite was obtained as analytically pure form. (2) Oxidation–reduction condensation between **1a**–**1h** and TEMT: At −63 °C, to a solution of **1** (0.5 mmol) and TEMT (0.6 mmol) in 2 mL of anhydrous THF was added dropwise a 2 M toluene solution of a dialkyl azodicarboxylate (0.6 mmol). After 3 h, the mixture was allowed to warm to rt and then concentrated in vacuo. The residue was dissolved in diethyl ether, washed with 4 M NaOH and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude was purified by preparative TLC on silica gel (eluent, hexane/EtOAc) to yield the desired triester-product **2a**–**2h**.

It is noted that an efficient method for C–C bond formation using chiral alkyl aryl carbinols as chiral alkylating agents was developed by oxidation–reduction condensation using alkyl diphenylphosphinites. The new combination of phosphinites, dialkyl azodicarboxylates and TEMT worked effectively to produce the desired triesters **2** in good yields with a highly inverted fashion.

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