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Enantioselective α-Alkylation of Benzylideneamino *tert*-Butyl Malonates by Phase-Transfer Catalysis

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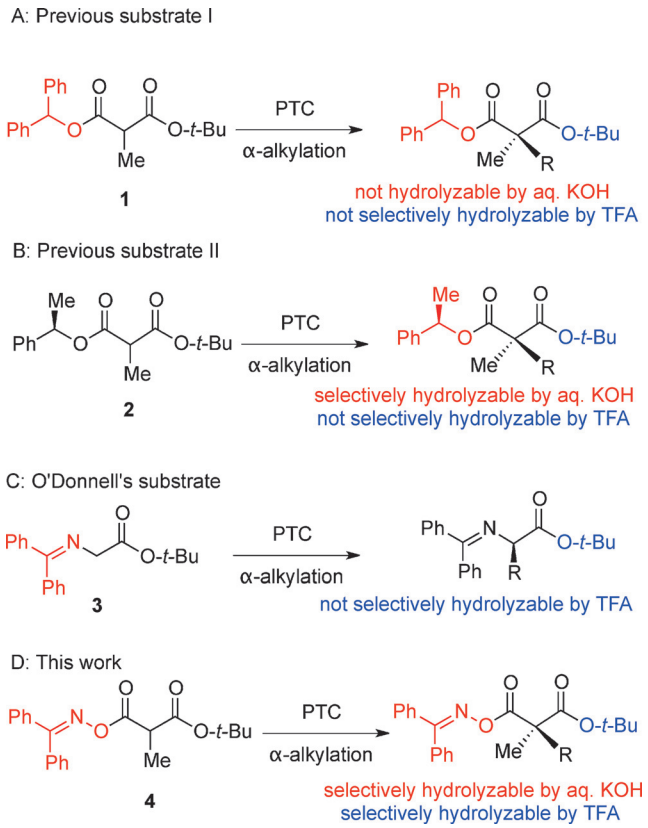
Abstract: A new enantioselective synthetic method for the synthesis of α,α-dialkylmalonates with a quaternary carbon center was developed *via* α-alkylation of prochiral malonates by phase-transfer catalysis (PTC). Asymmetric α-alkylation of benzylideneamino *tert*-butyl α-methylmalonates under phase-transfer catalytic conditions in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide afforded the corresponding α,α-dialkylmalonates in high yields (up to 97%) with excellent enantioselectivities (up to 98% *ee*). The products were then selectively hydrolyzed to chiral malonic monoacids under basic, acidic, or catalytic hydrogenation conditions.

Keywords: asymmetric synthesis; α,α-dialkylmalonates; enantioselectivity; phase-transfer catalysis; PTC

Introduction

The construction of the carbon skeletons of organic molecules is one of the most important processes in organic synthesis. 1,3-Dicarbonyl compounds have been regarded as the most fundamental synthetic starting materials for C–C bond formation by coupling themselves with electrophilic carbon resources, such as alkyl halides, imines, and carbonyl compounds including α,β-unsaturated carbonyls.[1] Among the 1,3-dicarbonyl compounds,[2,3] chiral malonates have been quite popularly employed for the construction of chiral quaternary carbon centers of biologically active organic molecules *via* the selective chemical conversion of two esters.[4] Chiral α,α-dialkylmalonates have been mostly obtained by the enzymatic resolution of (±)-α,α-dialkylmalonates or (±)-α,α-dialkylmalonic acids as well as by chiral HPLC resolution.[5] The chemical synthesis of chiral quaternary carbon centers from malonates has been challenging and only a few examples are reported *via* asymmetric α-alkylation in combination with chiral auxiliary groups or α-fluorination using organometallic catalysis.[6] In addition, the enantioselective direct catalytic α-alkylation of malonates has not been well studied to date.[7]

Recently, we reported a new synthetic method for chiral α,α-dialkylmalonates through phase-transfer catalytic α-alkylation of diphenylmethyl *tert*-butyl α-alkylmalonate (**1**), which represents the first reported enantioselective direct catalytic α-alkylation of malonates (Scheme 1, A).[8] The resulting diphenylmethyl *tert*-butyl α,α-dialkylmalonates could be converted to various versatile chiral intermediates, and they also could be successfully applied for the total synthesis of (−)-horsfiline *via* the selective deprotection of the diphenylmethyl group by catalytic hydrogenation.[9] However, selective removal of the *tert*-butyl group under acidic conditions was not successful due to partial hydrolysis of the diphenylmethyl group. In alkali basic conditions, the diphenylmethyl ester was not selectively hydrolyzed due to steric hindrance from the diphenyl group. In order to extend the usefulness for the versatile derivatization of our synthetic method to chiral α,α-dialkylmalonates, especially in the case of reducible electrophiles by catalytic hydrogenation, we have developed a new selective hydrolyzable malonate substrate (**2**) in alkali basic conditions by replac-

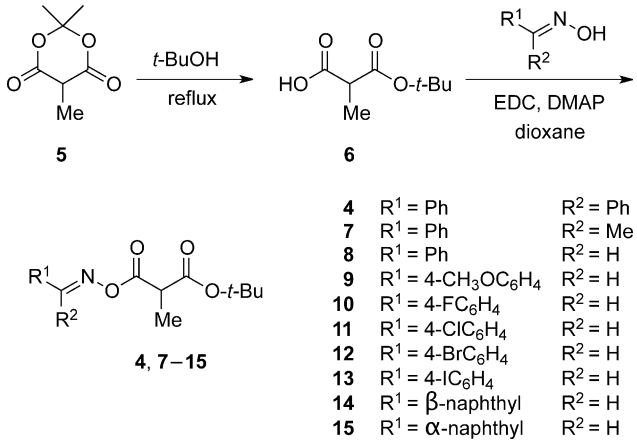


Scheme 1. Enantioselective PTC α-alkylation from various substrates.

ing one of the phenyl groups with a methyl group, and it was successfully applied for enantioselective PTC α-alkylations (Scheme 1, B).[10] However, the reaction rate of **2** (α-benzylation: 90% *ee*, 7 days, −40 °C) under the best conditions for enantioselectivity was too slow, and the enantioselectivity was also relatively lower than that of **1** (α-benzylation: 95% *ee*, 16 h, 0 °C). In this paper, we report a highly enantioselective phase-transfer catalytic α-alkylation of the new malonate substrates whose two ester groups can be selectively hydrolyzed under either acidic or basic conditions.[11]

Results and Discussion

First, we needed to design new malonate substrates possessing an efficient hydrolyzable ester group while preserving both a faster reaction rate and a higher enantioselectivity than those of **2**. We speculated that the slow catalytic turnover rate of **2** might come from the reduced π–π stacking interactions in the ionic complex between quaternary ammonium catalysts and the enolate of malonate **2**, due to the removal of one phenyl group of **1**, which is ultimately responsible for the relatively lower enantioselectivity. Therefore, we decided to restore the diphenyl group and reduce



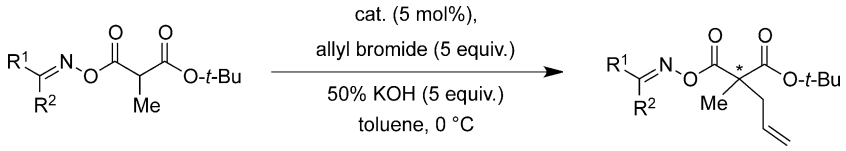
4	R^1 = Ph	R^2 = Ph
7	R^1 = Ph	R^2 = Me
8	R^1 = Ph	R^2 = H
9	R^1 = 4-$CH_3OC_6H_4$	R^2 = H
10	R^1 = 4-FC_6H_4	R^2 = H
11	R^1 = 4-ClC_6H_4	R^2 = H
12	R^1 = 4-BrC_6H_4	R^2 = H
13	R^1 = 4-IC_6H_4	R^2 = H
14	R^1 = β-naphthyl	R^2 = H
15	R^1 = α-naphthyl	R^2 = H

Scheme 2. Preparation of benzylideneamino *tert*-butyl α-methylmalonates (**4**, **7**–**15**).

the steric hindrance of the diphenyl group by leaving a space between it and the carbonyl group in the design of the new substrate. Finally, we chose diphenylmethyleneamino malonate (**4**) (Scheme 1, D) as the new substrate by combining the substrate **3**[12] for the asymmetric synthesis of α-amino acids (Scheme 1, C) and our previous malonate substrate **1** (Scheme 1, A).

For the preliminary study, diphenylmethyleneamino *tert*-butyl α-methylmalonate (**4**) was successfully prepared in two steps from α-methyl-Meldrum's acid (**5**) (Scheme 2). The *tert*-butanolysis of α-methyl-Meldrum's acid, followed by esterification with benzophenone oxime using EDC in the presence of DMAP afforded **4** (95% from **5**). Because the enantioselectivity of α-allylation is generally and significantly lower than that of benzylation in PTC alkylation, we thought that allylation is more suitable to accurately evaluate the efficiency of the substrate and catalyst. Thus, the prepared malonate **4** was examined for its efficiency as a substrate by α-allylation under typical PTC conditions based on our previous report (Table 1).[8] Enantioselective PTC allylation was performed using the representative PTC catalysts (**16**–**21**)(Figure 1),[13] along with allyl bromide (5.0 equiv.) and 50% KOH (aqueous, 5.0 equiv.) at 0 °C in toluene. As shown in Table 1, catalyst **16** successfully afforded the corresponding α-allylated product with 71% *ee* and 86% chemical yield in 5 h (entry 1). The allylation of **2** in the presence of catalyst **7** under the same PTC conditions gave the corresponding allylated products with 57% *ee* and 80% chemical yield in 5 days. The diphenylmethyleneamino malonate substrate (**4**) showed a much faster reaction rate than that of 2-methylbenzyl malonate (**3**) with a significantly higher enantioselectivity. Unfortunately, catalyst **17** and the *Cinchona*-derived catalysts (**18**–**21**) afforded lower enantioselectivities with similar chemical yields compared to those of catalyst **16**.

Table 1. Enantioselective PTC α-allylation of benzylideneamino *tert*-butyl α-methylmalonates (**16**–**21**).[a]



Entry	R^1	R^2	Cat	Time [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**16**	5	86	71
2	Ph	Ph	**17**	2	78	13
3	Ph	Ph	**18**	3	67	33
4	Ph	Ph	**19**	2	80	5
5	Ph	Ph	**20**	1	93	25
6	Ph	Ph	**21**	2	81	45
7	Ph	Me	**16**	5	73	63
8	Ph	H	**16**	5	81	71
9	4-$MeOC_6H_4$	H	**16**	7	74	71
10	4-FC_6H_4	H	**16**	5	74	78
11	4-ClC_6H_4	H	**16**	6	76	80
12	4-BrC_6H_4	H	**16**	5	80	82
13	4-IC_6H_4	H	**16**	5	74	80
14	β-naphthyl	H	**16**	7	77	75
15	α-naphthyl	H	**16**	2	50	69

[a] Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of 50% KOH (aqueous) under the given conditions.
[b] Isolated yields.
[c] Enantioselectivity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H, and AS-H, Chiralcel OD-H, and OJ-H).

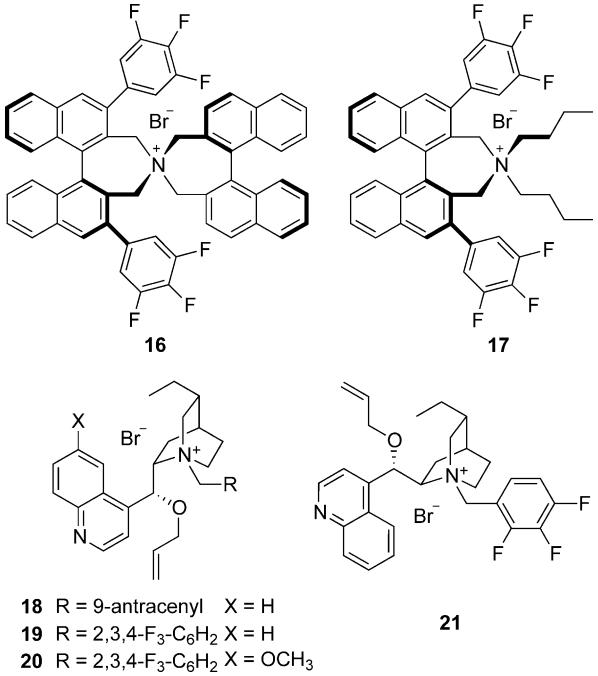
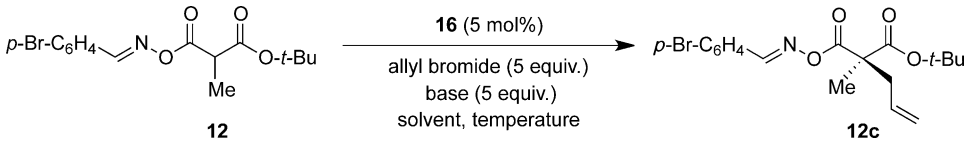


Figure 1. Chiral phase transfer catalysts.

The promising results prompted us to optimize the structure of the oxime malonate substrate to increase the enantioselectivity. Nine additional *tert*-butyl oxime α-methylmalonates (entries 7–15) were prepared using various oximes, and their substrate efficiencies were evaluated by PTC allylation in the presence of the best catalyst **16** (5 mol%) at 0 °C. As shown in Table 1, the enantioselectivity varied depending on the oxime group. An acetophenone oxime group (entry 7, 63% *ee*) gave an enantioselectivity that was approximately 10% *ee* lower compared to the benzophenone oxime group (entry 1, 71% *ee*). However, surprisingly, the benzaldehyde oxime group (entry 8, 71% *ee*) showed a comparable enantioselectivity to that of the benzophenone oxime group (entry 1), which contradicts our initial assumption involving the π–π stacking interactions *via* phenyl groups in substrate **1**. We speculate that the *cis*-phenyl group of the oxime in substrate **4** might not participate the π–π stacking interaction between the substrate and PTC catalyst **16** due to its sp^2 geometrical conformation in comparison to the sp^3 geometrical conformation of **1**. It is notable that there was a significant electronic effect, especially, *p*-halogen substituents increased the enantioselectivity according to the following order: Br (entry 12, 82% *ee*) > Cl (entry 11, 80% *ee*) ~ I (entry 13, 80% *ee*) > F (entry 10, 78% *ee*). The electron donating *p*-methoxy group (entry 9, 71% *ee*) did not increase the enantioselectivity. In the case of bulky groups, the β-napthyl aldehyde oxime group (entry 14, 75% *ee*) showed a slightly higher enantiose-

Table 2. Optimization of the reaction conditions.[a]



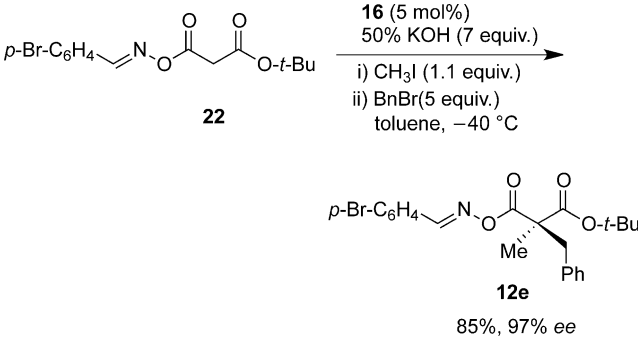
Entry	Base	Temp. [°C]	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	50% NaOH	0	toluene	8	75	82
2	50% KOH	0	toluene	5	80	82
3	50% CsOH	0	toluene	4	55	82
4	KOH	0	toluene	1	45	79
5	CsOH	0	toluene	0.5	38	80
6	K_2CO_3	0	toluene	120	85	79
7	50% KOH	0	CH_2Cl_2	24	62	34
8	50% KOH	0	THF	4	48	54
9	50% KOH	−20	toluene	6	83	88
10	50% KOH	−40	toluene	9	91	90
11	50% KOH	−60	toluene	24	21	87

[a] Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of 50% KOH (aqueous) under the given conditions.
[b] Isolated yields.
[c] Enantioselectivity was determined by HPLC analysis of the corresponding allylated products **12c** using a chiral column (DAICEL Chiralpak AS-H).

lectivity than the benzaldehyde oxime group (entry 8).

Next, optimization of the base and temperature conditions was performed using the best substrate **12** in the presence of catalyst **16**. As shown in Table 2, generally, the chemical yield and enantioselectivity did not have a significant dependence on the base at 0 °C, however, the weak base, K_2CO_3 showed a longer reaction time (entry 6, 120 h). A significant decrease in the enantioselectivity was observed in CH_2Cl_2 (entry 7, 34% *ee*). As for the temperature, a lower reaction temperature gave a higher enantioselectivity (entries 2, 9–10). However, a significantly longer reaction time was observed at −60 °C (entry 11). We finally chose the reaction conditions (50% KOH, toluene, −40 °C) of entry 10 in Table 2 as the optimized reaction conditions according to the enantioselectivity, chemical yield and reaction time (entry 10; 91%, 90% *ee*, 9 h).

Further investigation into the scope and limitations of the alkylating agents was performed under the optimized PTC conditions (Table 2, entry 10). Very high enantioselectivities in allylic, propargylic and benzylic halides were observed. However, an unactivated alkyl halide such as hexyl iodide provided a poor chemical yield (24 h, 0 °C, 43%, 79% *ee*). The successive α-methylation and α-benzylation of malonate, **22**, also could afford the corresponding α-methyl-α-benzylmalonate (**12e**) without loss of enantioselectivity with a high chemical yield (Scheme 3). The high enantioselectivities (up to 98% *ee*) in Table 3 indicate that this reaction method is an efficient enantioselective synthetic method for α,α-dialkylmalonates.

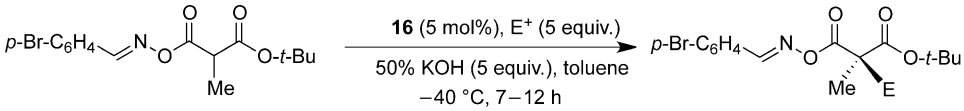


Scheme 3. Double PTC α-alkylations of malonate **12**.

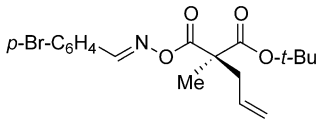
A plausible transition state model was proposed to account for the observed absolute configuration of the *p*-bromobenzylation adduct **12i** based on the previously reported DFT-based conformational analysis (Figure 2).[15] The malonate enolate anion forms an ionic complex with catalyst (*S*,*S*)-**16** and then, *p*-bromobenzyl bromide might approach from the sterically less hindered upper side leading to the alkylated adduct **12i** with the observed absolute configuration, which was determined by X-ray analysis (Figure 3).

We confirmed the selective hydrolysis in alkali basic and TFA acidic conditions. The selective hydrolysis of *p*-bromobenzyloxime ester of α-methyl-α-benzylmalonate (**12e**) was successfully accomplished to afford the corresponding acid **23** in a 98% yield by 1 N KOH (Scheme 4). Fortunately, we found that the

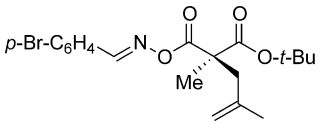
Table 3. Enantioselective synthesis of α,α-dialkylmalonates *via* the PTC α-alkylation of **12**.[a]



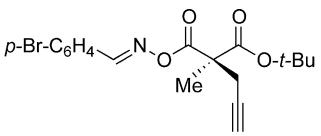
12 **12a–l**



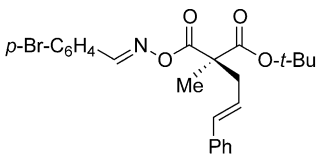
12a 92%,[b] 90% *ee*[c]



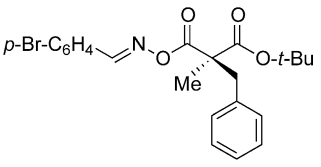
12b 92%, 94% *ee*



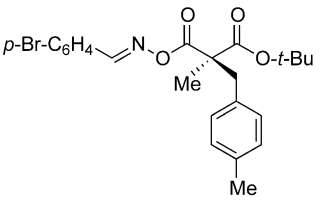
12c 95%, 85% *ee*



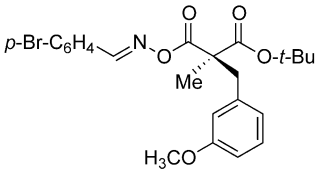
12d 96%, 95% *ee*



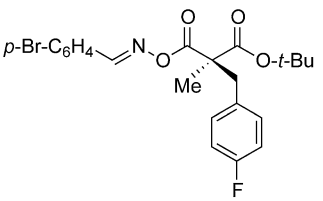
12e 94%, 97% *ee* (*R*)[d]



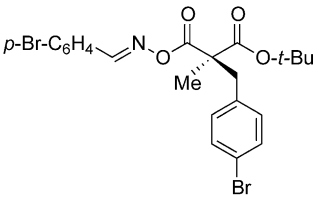
12f 97%, 98% *ee*



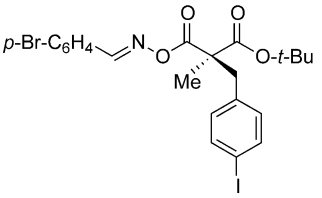
12g 90%, 94% *ee*



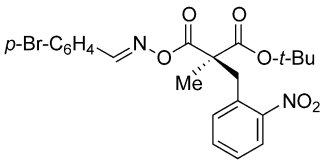
12h 91%, 97% *ee*



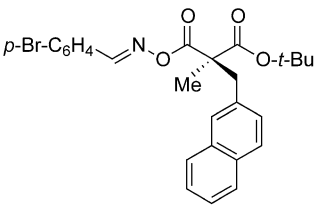
12i 90%, 98% *ee* (*R*)[e]



12j 95%, 94% *ee*



12k 90%, 95% *ee*



12l 94%, 95% *ee*

[a] Reactions were performed with 5.0 equiv. of allyl bromide and 5.0 equiv. of 50% KOH (aqueous) under the given conditions.
[b] Isolated yields.
[c] Enantioselectivity was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H, and AS-H, Chiralcel OD-H, and OJ-H).
[d] Absolute stereochemistry was determined by comparison of the optical rotation value of the diphenylmethyl ester derivative prepared from benzylated products **12e** with the reported value.[8]
[e] Absolute stereochemistry was determined by X-ray crystallographic analysis of **12i**.[14]

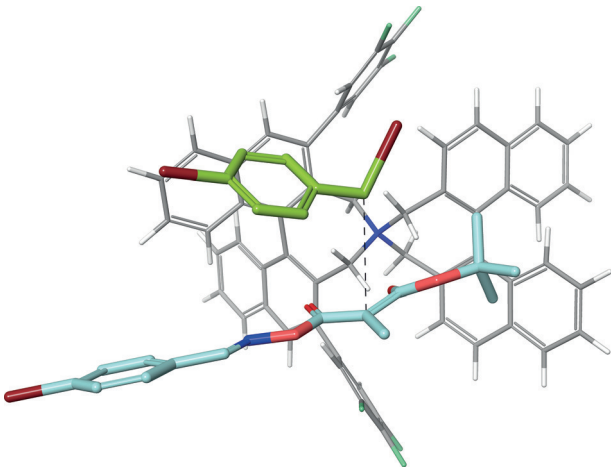


Figure 2. Plausible transition state model for the *p*-bromobenzylation of **12**.

tert-butyl ester was selectively hydrolyzed to the corresponding acid (**24**) in the presence of trifluoroacetic acid in dichloromethane at 0 °C, which was not possi-

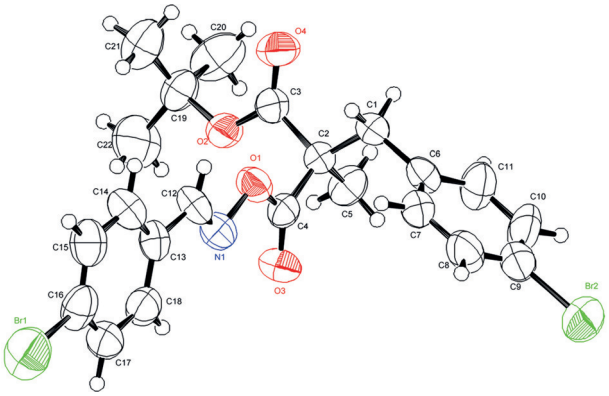
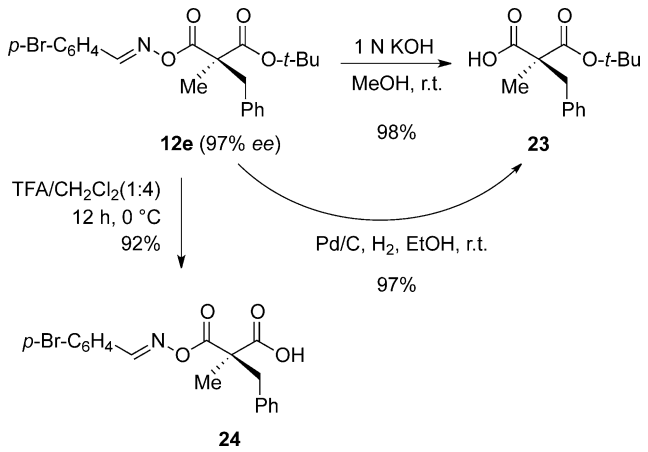
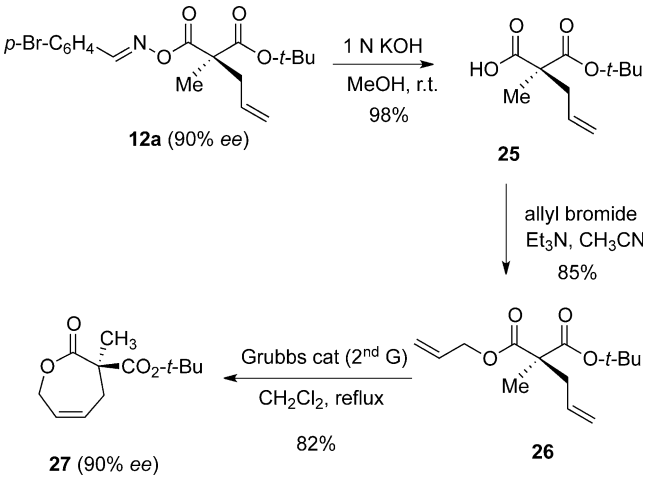


Figure 3. X-ray crystallographic structure of (*R*)-**12i**.[14]



Scheme 4. Selective hydrolysis of **12e** under basic, acidic and catalytic hydrogenation conditions.



Scheme 5. Conversion of **12a** to lactone **27**.

ble in the case of the previous substrates (**1**–**3**) (Scheme 1, A–C). Monoacid (**23**) could be also obtained by catalytic hydrogenation in the presence of Pd/C under 1 atm of H_2.

The synthetic potential of this method has been demonstrated *via* the synthesis of chiral α-carboxylactone from **12a** as outlined in Scheme 5. Optically enriched α-methyl-α-allylmalonate (**12a**) was hydrolyzed to the corresponding acid **25** in a 98% yield by 1 N KOH. Allyl ester formation from **25** using allyl bromide in the presence of triethylamine in acetonitrile, followed by ring metathesis successfully afforded the corresponding chiral 7-membered lactone **27** that is normally hard to obtain by the direct PTC methylation of the corresponding α-carboxylactones.[16]

Conclusions

A novel enantioselective PTC α-alkylation of benzylideneamino *tert*-butyl malonates has been developed. Asymmetric PTC α-alkylation of *p*-bromobenzylideneamino *tert*-butyl α-methylmalonate afforded the corresponding α,α-dialkylmalonates in high chemical (up to 97%) and optical (up to 98% *ee*) yields. It is notable that the selective hydrolysis under alkali basic conditions and TFA acidic conditions as well as catalytic hydrogenation extended the usefulness of the enantioselective PTC alkylation of the malonate system, which was confirmed by its application to the synthesis of chiral α-alkyl-α-carboxylactone. Our new catalytic system provides an attractive synthetic method for various chiral building blocks that could be readily converted en route to the synthesis of versatile chiral target molecules with the involvement of quaternary carbon centers.

Experimental Section

Typical Experimental Procedure for the Preparation of Benzylideneamino *tert*-Butyl Malonates (12)

EDC hydrochloride (660 mg, 3.4 mmol) and DMAP (21 mg, 0.2 mmol) were added to a solution of *tert*-butyl α-methylmalonic acid **6** (300 mg, 1.7 mmol) in dioxane (6 mL). (*E*)-4-bromobenzaldehyde oxime (1.7 mmol) was added to the solution. After being stirred for 24 h, the mixture was diluted with ethyl acetate (50 mL) and washed with water (10 mL × 2). The organic extract was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (230–400 mesh silica gel, hexane:acetone = 15:1) to give **12** as a white solid; yield: 530 mg (87%); mp 62.5 °C. ^{1}H NMR(300 MHz, $CDCl_3$): $\delta = 8.30$ (s, 1H), 7.57 (dd, $J_1 = 8.70$ Hz, $J_2 = 3.48$ Hz, 4H), 3.53 (q, $J = 7.32$ Hz, 1H), 1.47 (d, $J = 7.32$ Hz, 3H), 1.44 (s, 9H); ^{13}C NMR(300 MHz, $CDCl_3$): $\delta = 170.2$, 169.3, 155.2, 132.3, 129.8, 128.9, 126.5, 119.4, 82.0, 40.1, 27.9, 19.8; IR (KBr): $\nu = 3565$, 2980, 2310, 1776, 1732, 1591, 1508, 1488, 1456, 1397, 1370, 1338, 1162, 1071, 1010, 952, 914, 877, 822 cm^{-1}; HR-MS (FAB): $m/z = 356.0498$, calcd. for $[C_{15}H_{18}BrNO_4]^+$: 355.0419.

General Procedure for Enantioselective Phase-Transfer Catalytic Alkylation (Benzylation of 12)

Benzyl bromide (120 μL, 1.0 mmol) was added to a solution of **12** (75 mg, 0.2 mmol) and PTC catalyst **16** (0.01 mmol) in toluene (2.0 mL). At −40 °C, 50% KOH (1.0 mmol) was added to the reaction mixture and stirred until the starting material had disappeared. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (10 mL), washed with brine (5 mL × 2), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (silica gel 230 ~ 400 mesh, hexane:EtOAc = 20:1) to afford **12e** as a white solid; yield: 84 mg (94%); mp: 83–85 °C. ^{1}H NMR(300 MHz,

$CDCl_3$): $\delta = 8.23$ (s, 1H), 7.59 (q, $J = 7.75$ Hz, 4H), 7.25–7.15 (m, 5H), 3.26 (q, $J = 12.63$ Hz, 2H), 1.44 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (600 MHz, $CDCl_3$): $\delta = 170.2$, 169.2, 155.2, 135.9, 132.2, 130.3, 129.8, 128.8, 128.2, 126.9, 126.4, 82.1, 54.8, 41.0, 27.8, 19.9; IR (KBr): $\nu = 3839$, 2980, 1776, 1734, 1590, 1488, 1455, 1369, 1253, 1151, 1113, 1083, 1011, 925, 847, 821, 735, 701 cm^{-1}; HR-MS(FAB): $m/z = 446.0952$, calcd. for $[C_{22}H_{24}BrNO_4]^+$: 445.0889. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralpak AS-H, hexane:2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, 23 °C, $\lambda = 256$ nm): retention times *S* isomer (minor) 11.1 min, *R* isomer (major) 12.1 min; 97% *ee*; $[\alpha]_D^{25}$: +60.70 (*c* 1.0, $CHCl_3$).

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