ACS Catalysis

RESEARCH ARTICLE

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Asymmetric Alkylation of Malonic Diester Under Phase-Transfer Conditions

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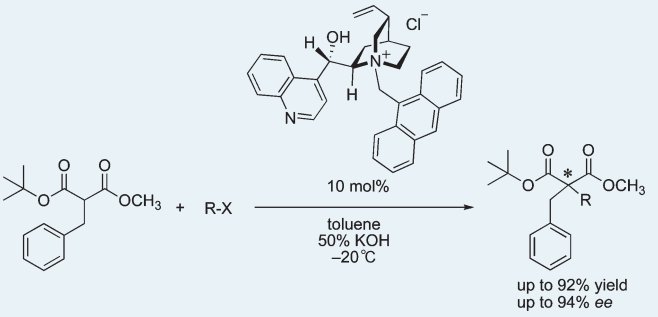
Supporting Information

ABSTRACT: An enantioselective phase-transfer catalytic alkylation of α-monosubstituted malonic diester has been developed. The alkylation of α-monosubstituted *tert*-butyl methyl malonate in the presence of *N*-(9-anthracenylmethyl)cinchoninium chloride afforded α,α-disubstituted products in high yields and with high enantioselectivities. Moreover, a successful gram-scale (10 mmol) experiment using the cinchona catalyst indicates the potential for practical applications of this methodology. To demonstrate the utility of this method, product with a quaternary chiral carbon was converted to both (*R*)- and (*S*)-α,α-dialkylated amino acids through alternative chemoselective transformation of the two ester groups.



KEYWORDS: organocatalysis, asymmetric synthesis, phase-transfer catalysis, quaternary stereocenter, malonic ester

INTRODUCTION

The construction of all-carbon substituted quaternary carbon centers is difficult due to steric repulsion between the substituents. In particular, the enantioselective synthesis of chiral quaternary centers has been quite challenging. In this context, the catalytic α-alkylation of carbonyl compounds has been extensively studied, and several powerful methods have been developed.[1−6] Our laboratory is interested in the construction of α,α-dialkyl malonic diesters containing a chiral center with four carbon substituents. Chiral α,α-disubstituted malonyl derivatives are important intermediates in the synthesis of biologically active compounds. However, there have been few reports of enantioselective catalytic additions at the α-position of malonyl derivatives, and few synthetic methods have been disclosed.[7−9] This is despite the fact that chiral α,α-dialkyl malonic diesters are quite attractive synthetic units for various chiral syntheses as a result of their readiness to undergo chemoselective transformations. Recently, Park and co-workers reported an enantioselective catalytic alkylation using (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide as a phase-transfer catalyst (PTC) for the construction of all-carbon substituted quaternary carbon centers of diphenylmethyl *tert*-butyl malonate;[10] however, to our knowledge, this is the only such synthesis reported to date. Although the diphenylmethyl group can be efficiently cleaved by catalytic hydrogenation, the substrates cannot contain substituents sensitive to hydrogenolysis.

To develop a new and convenient method for synthesizing quaternary carbon centers, we investigated an alkylation reaction of *tert*-butyl methyl α-monoalkylated malonate under phase-transfer conditions using a cinchona alkaloid derivative. *tert*-Butyl and methyl ester are simple protecting groups that are readily cleaved chemoselectively under acidic or alkaline conditions. Phase-transfer catalytic reactions are regarded as one of the most efficient synthetic methods, from the viewpoint of being both inexpensive and relatively environmentally benign.[11−14] We previously reported the asymmetric alkylation of α-cyanocarboxylates and acetoacetates under phase-transfer conditions.[15,16]

In this paper, we report a highly efficient enantioselective α-alkylation of *tert*-butyl methyl α-monoalkylated malonate using cinchona alkaloid derivatives as inexpensive PTCs and use this approach to synthesize α,α-disubstituted amino acids from the chiral α,α-disubstituted malonic diester. In this transformation, both (*S*)- and (*R*)-α,α-disubstituted amino acids could be prepared via similar procedures from the same stereoisomer.

To explore the effect of the phase-transfer catalytic alkylation of malonic diester, we screened various PTCs (Figure 1) previously used as catalysts for asymmetric reactions.[17−21] α-Benzylated *tert*-butyl methyl malonate **8**, prepared from Meldrum's acid through solvolysis followed by esterification with hafnium(IV) salt,[22] was used in the allylation reaction to evaluate the catalysts. Using conditions previously reported,[23−26] the reaction was carried out with the representative chiral PTCs **1**−**7**, 1.2 equiv of allyl iodide (**9**), and KOH solid at room temperature in toluene (Table 1). Cinchona catalysts **1**−**4** afforded moderate to high chemical yields and enantioselectivities. Catalyst **4**, which has a bulky anthracenylmethyl group at the tertiary amine of cinchonine, provided the best chemical yield and enantioselectivity (Table 1, entry 4). (*R*,*R*)-3,4,5-Trifluorophenyl-NAS bromide (**5**) and (*R*,*R*)-3,5-bis(trifluoromethyl)phenyl-NAS bromide (**6**) afforded

Received: June 14, 2011
Revised: August 5, 2011
Published: August 17, 2011

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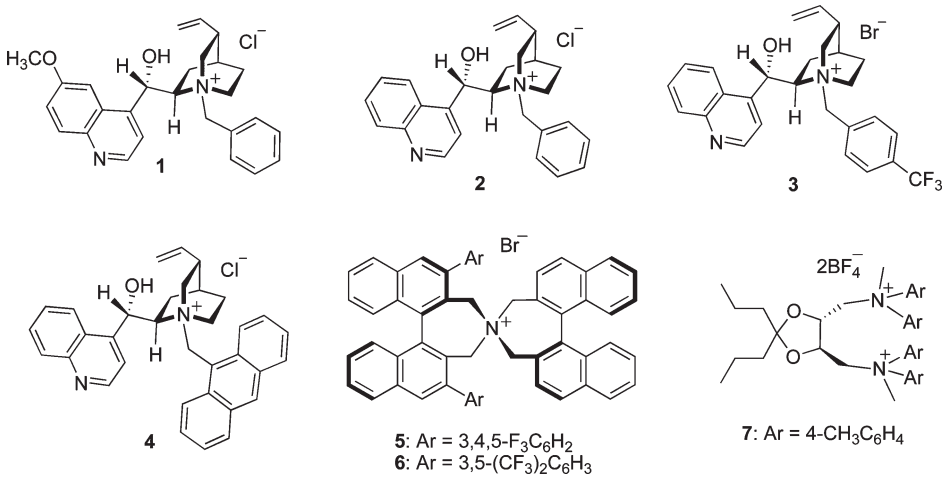
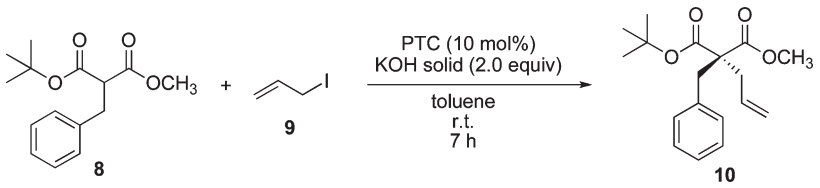


Figure 1. Structures of the phase-transfer catalysts.

Table 1. Catalyst Screening for the Alkylation of α-Benzyl *tert*-Butyl Methyl Malonate 8



entry	PTC	yield (%)[a]	ee (%)[b]
1	**1**	52	34
2	**2**	79	48
3	**3**	57	44
4	**4**	93	60
5	**5**	52	16
6	**6**	46	45
7	7	35	11

[a] Isolated yields. [b] Determined by chiral HPLC.

moderate chemical yields but unsatisfactory enantioselectivities (Table 1, entries 5 and 6). TaDiAs-[(4*R*,5*R*)-2,2-dipropyl-*N*,*N*,*N*′,*N*′-tetrakis(4-methylbenzyl)]bis(tetrafluoroborate) (**7**) gave both low chemical yield and poor enantioselectivity (Table 1, entry 7). On the basis of these results, the reaction conditions were then optimized using catalyst **4**.

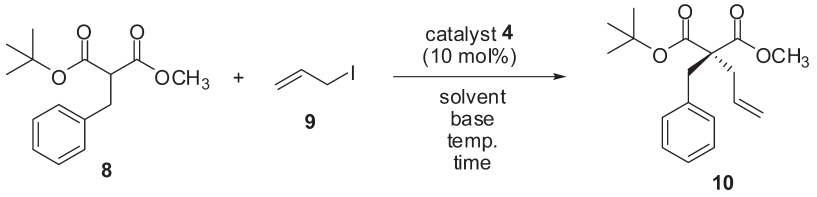
The optimization studies, summarized in Table 2, showed that the reaction medium significantly influences the rate of the reaction (Table 2, entries 1−7). In ether solvents, such as diethyl ether, *tert*-butyl methyl ether, and tetrahydrofuran, the products were afforded in unsatisfactory enantioselectivities (Table 2, entries 1−3). Dichloromethane gave slightly better selectivity, but the yield was very low (Table 2, entry 4). Acetonitrile also provided poor enantioselectivity (Table 2, entry 5). In contrast, reactions carried out in toluene and xylene gave higher enantioselectivities (Table 2, entries 6 and 7). Notably, reaction in toluene afforded the highest chemical yield, so toluene was selected as the reaction solvent of choice.

To further improve the reaction, we next screened several bases in toluene in the presence of catalyst **4** (Table 2, entries 7−12). KOH solid and CsOH solid gave similar performances (Table 2, entries 7 and 8), whereas NaOH solid provided lower yield and selectivity (Table 2, entry 9) and LiOH and K_2CO_3 solid were completely ineffective (Table 2, entries 10 and 11). The use of KOH aqueous solution (50%, w/w) provided higher enantioselectivity compared to KOH solid (Table 2, entry 12). Moreover, an increase in enantioselectivity was obtained by gradually decreasing the reaction temperature to −20 °C (Table 2, entries 13−15), although at −30 and −40 °C, significant decreases in both chemical yield and enantioselectivity were observed (Table 2, entries 16 and 17).

Using the reaction conditions optimized so far, we then examined a variety of alkyl halides and malonic diester **8** to prove the general utility of cinchona catalyst **4** in the catalytic asymmetric alkylation reaction. The results are summarized in Table 3. The alkylation of α-benzylated *tert*-butyl methyl malonate **8** with alkyl halides was carried out in toluene and aqueous 50% KOH at −20 °C using PTC **4**. Significantly, all alkyl halides exhibited high enantioselectivities. Compared with allyl iodide, allyl bromide provided lower yield (77%) and enantioselectivity (86% ee) to give the corresponding α-allyl α-benzyl product **10** (Table 3, entry 2). The reaction with prenyl bromide was faster and afforded product **11** in high yield with high enantioselectivity (Table 3, entry 3). The alkylation reaction with methyl iodide

dx.doi.org/10.1021/cs200304g |*ACS Catal.* 2011, 1, 1331–1335

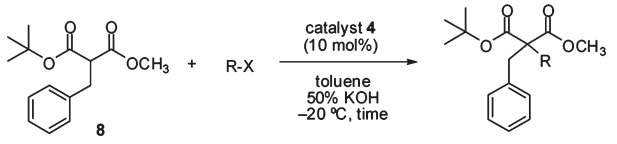
Table 2. Optimization Studies of the Alkylation Reaction

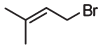
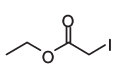
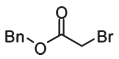


entry	solvent	base	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Et_2O	KOH solid	r.t.	7	79	35
2	TBME	KOH solid	r.t.	7	36	36
3	THF	KOH solid	r.t.	7	59	16
4	CH_2Cl_2	KOH solid	r.t.	7	20	41
5	CH_3CN	KOH solid	r.t.	7	36	7
6	xylene	KOH solid	r.t.	7	44	74
7	toluene	KOH solid	r.t.	7	93	60
8	toluene	CsOH solid	r.t.	7	89	61
9	toluene	NaOH solid	r.t.	7	67	7
10	toluene	LiOH-H_2O solid	r.t.	7	NR[c]	
11	toluene	K_2CO_3 solid	r.t.	7	NR[c]	
12	toluene	50% KOH aq	r.t.	7	86	76
13	toluene	50% KOH aq	0	72	87	85
14	toluene	50% KOH aq	−10	72	86	85
15	toluene	50% KOH aq	−20	72	92	94
16	toluene	50% KOH aq	−30	96	24	84
17	toluene	50% KOH aq	−40	168	43	75

[a] Isolated yields. [b] Determined by chiral HPLC. [c] No reaction.

Table 3. Asymmetric Alkylation of *tert*-Butyl Methyl Malonate 8 with Various Alkylation Reagents



entry	R-X	product	time (h)	yield (%)[a]	ee (%)[b]
1		**10**	72	92	94
2		**10**	72	77	86
3		**11**	48	90	88
4[c]	CH_3-I	**12**	96	70	84
5[c]	CH_3CH_2-I	**13**	96	52	83
6		**14**	96	89	94
7		**15**	96	81	94

[a] Isolated yields. [b] Determined by chiral HPLC. [c] 4.0 equiv of alkylating agent was used.

and ethyl iodide proceeded with good enantioselectivity to give products **12** and **13** in 70% and 52% yield, respectively (Table 3, entries 4 and 5). In the case of ethyl iodoacetate, the reaction provided both high yield and excellent enantioselectivity (Table 3, entry 6). Benzyl bromoacetate provided similar enantioselectivity, albeit with slightly lower yield (Table 3, entry 7).

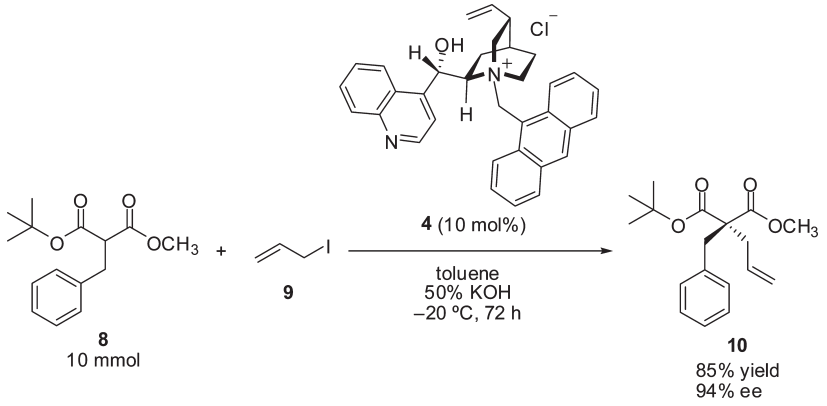
Next, to show the utility of the reaction using cinchona catalyst **4**, a gram-scale (10 mmol) experiment was carried out (Scheme 1). The catalytic reaction proceeded smoothly, and excellent enantioselectivity was maintained to provide **10** in high yield. This result indicates that this economical cinchona-catalyzed asymmetric reaction is practical, since catalyst **4** is 100 times less expensive than NAS.

As anticipated, cinchonidine-derived PTC **16**, a pseudoenantiomer of cinchonine-derived PTC **4**, led to the formation of enantiomer of **10** in excess.[27] As a result, the catalyst **16** afforded (*S*)-**10** in 72% yield with 42% ee (Scheme 2). This low enantioselectivity suggested that the vinyl group in catalyst **16** has an effect on the transition state of the reaction intermediate.

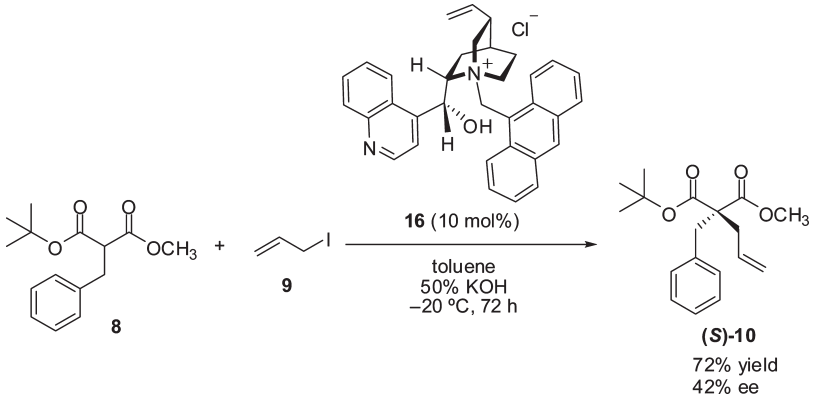
The utility of the present reaction was further demonstrated by the synthesis of α,α-disubstituted amino acids (Scheme 3). These compounds are of interest because they belong to the broad class of nonproteinogenic amino acids.[28−31] Due to the quaternary stereocenter, the replacement of natural amino acids by α,α-disubstituted amino acids in peptides might result in conformationally rigid and proteolytically stable peptides.[32−35] The *tert*-butyl or methyl ester of an α,α-disubstituted malonic diester can be chemoselectively deprotected. Thus, the asymmetric reaction product **10** can be selectively converted into carboxylic acid **17** or **20**, respectively, in quantitative yield. Carboxylic acids **17** and **20** were converted into amines **18** and **21** through Curtius rearrangement with diphenylphosphoryl

dx.doi.org/10.1021/cs200304g |*ACS Catal.* 2011, 1, 1331–1335

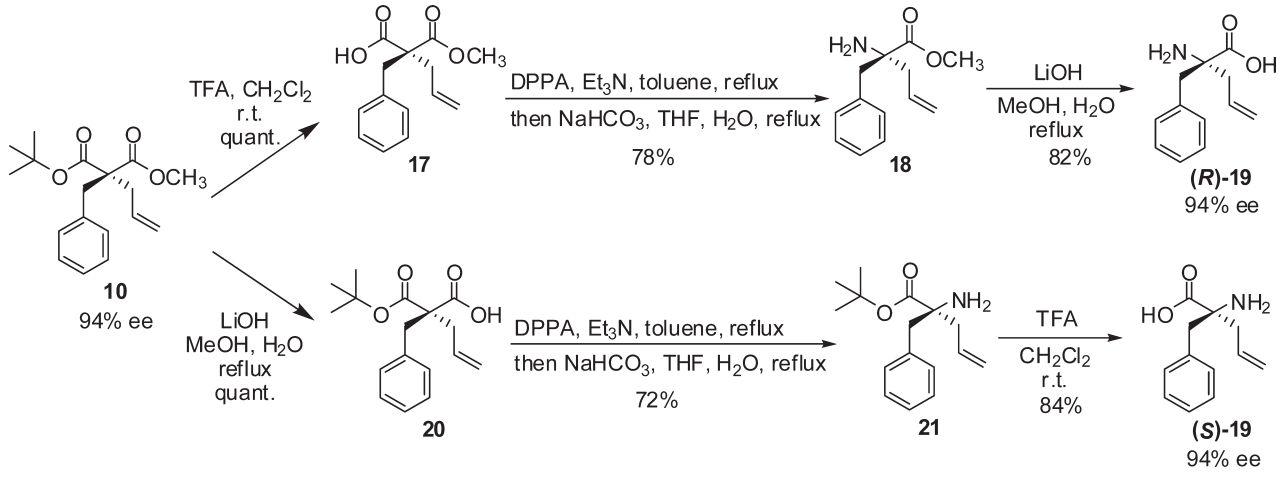
Scheme 1. Gram-Scale Asymmetric Alkylation of *tert*-Butyl Methyl Malonate 8 with PTC 4



Scheme 2. Asymmetric Alkylation of *tert*-Butyl Methyl Malonate 8 with PTC 16



Scheme 3. Synthesis of (*R*)- and (*S*)-α-Allylphenylalanine



azide[36,37] in the presence of triethylamine, followed by hydrolysis. Deprotection of methyl ester **18** by hydrolysis under alkaline conditions provided (*R*)-α-allylphenylalanine ((***R***)-**19**). On the other hand, *tert*-butyl ester **21** was treated with TFA to obtain (*S*)-α-allylphenylalanine ((***S***)-**19**). Both (***R***)- and (***S***)-**19** exhibited full optical activity. The stereochemistry of (***R***)- and (***S***)-**19** was determined on the basis of the measured optical rotation compared with literature values.[38−41] Thus, the synthesis of α-allylphenylalanine (**19**) defined the absolute configuration of the **10** as *R* form.

dx.doi.org/10.1021/cs200304g |*ACS Catal.* 2011, 1, 1331–1335

CONCLUSION

In conclusion, we have described the highly enantioselective alkylation of malonic diesters catalyzed by *N*-(9-anthracenylmethyl)cinchoninium chloride and demonstrated the utility of the inexpensive cinchona catalyst in a gram-scale reaction. This method provides access to α,α-disubstituted malonic diesters containing an all-carbon substituted quaternary stereocenter. Through chemoselective transformation of the simple *tert*-butyl or methyl ester, the α,α-disubstituted malonic diesters were readily converted into chiral amino acid of both enantiomers. The utility of this method was demonstrated by the successful synthesis of (*R*)- and (*S*)-α-allylphenylalanine. In addition to α-benzylated malonate, we are currently investigating the alkylation reaction with other α-substituted malonates. The results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data of the products, and copies of the ^{1}H and ^{13}C spectra and the HPLC traces. This information is available free of charge via the Internet at http://pubs.acs.org/.

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ACKNOWLEDGMENT

This work was supported in part by a Grant for the High-Tech Research Center Project from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES

(1) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367.
(2) Christoffers, J.; Baro, A. *Quaternary Stereocenters*; Wiley-VCH: Weinheim, 2005.
(3) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396.
(4) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994.
(5) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583–1614.
(6) Prakash, J.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623.
(7) Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 164–168.
(8) Kim, M.-h.; Choi, S.-h.; Lee, Y.-J.; Lee, J.; Nahm, K.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Chem. Commun.* **2009**, 782–784.
(9) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 14990–14999.
(10) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.-h.; Jew, S.-s.; Park, H.-g. *J. Am. Chem. Soc.* **2011**, *133*, 4924–4929.
(11) O'Donnell, M. *Acc. Chem. Res.* **2004**, *37*, 506–517.
(12) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.
(13) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682.
(14) Jew, S.-s.; Park, H.-g. *Chem. Commun.* **2009**, 7090–7103.
(15) Nagata, K.; Sano, D.; Itoh, T. *Synlett* **2007**, 547–550.
(16) Nagata, K.; Sano, D.; Shimizu, Y.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2530–2536.
(17) Adam, W.; Rao, P. B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Möller, C. R. *J. Org. Chem.* **2002**, *67*, 259–264.
(18) Matsushita, M.; Yoshida, K.; Yamamoto, N.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5984–5987.
(19) Chinchilla, R.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2006**, *17*, 3423–3429.
(20) Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S.; Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394–6395.
(21) Bandini, M.; Eichhoizer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241.
(22) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140–1142.
(23) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382–2385.
(24) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897–6899.
(25) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557–1560.
(26) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *J. Org. Chem.* **2006**, *71*, 8276–8278.
(27) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391–2402.
(28) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430.
(29) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623.
(30) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349–358.
(31) Soloshonok, V. A.; Sorochinsky, A. E. *Synthesis* **2010**, 2319–2344.
(32) Toniolo, C.; Crisma, M.; Formaggio, F.; Valle, C.; Cavicchioni, G.; Precigoux, G.; Aubry, A.; Kamphuis, J. *Biopolymers* **1993**, *33*, 1061–1072.
(33) Formaggio, F.; Barazza, A.; Bertocco, A.; Toniolo, C.; Broxterman, Q. B.; Kaptein, B.; Brasola, E.; Pengo, P.; Pasquato, L.; Scrimin, P. *J. Org. Chem.* **2004**, *69*, 3849–3856.
(34) Crisma, M.; Saviano, M.; Moretto, A.; Broxterman, Q. B.; Kaptein, B.; Toniolo, C. *J. Am. Chem. Soc.* **2007**, *82*, 15471–15473.
(35) Demizu, Y.; Doi, M.; Kurihara, M.; Okuda, H.; Nagano, M.; Suemune, H.; Tanaka, M. *Org. Biomol. Chem.* **2011**, *9*, 3303–3312.
(36) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.
(37) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
(38) Zydowsky, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5439–5442.
(39) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470.
(40) Achatz, O.; Grandl, A.; Wanner, K. T. *Eur. J. Org. Chem.* **1999**, 1967–1978.
(41) Uraguchi, D.; Asai, Y.; Seto, Y.; Ooi, T. *Synlett* **2009**, 658–660.