# Stereoselective synthesis of highly functionalized (Z)-chloroalkene dipeptide isosteres containing an α,α-disubstituted amino acid



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COMMUNICATION

# Stereoselective synthesis of highly functionalized (*Z*)-chloroalkene dipeptide isosteres containing an α,α-disubstituted amino acid

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**Described here is the first stereoselective synthesis of highly functionalized chloroalkene dipeptide isosteres containing an α,α-disubstituted amino acid (ααAA). This synthesis requires the construction of a quaternary carbon center, and this challenge was achieved by the Aza-Darzens condensation of ketimine with α,α-dichloroenolate, producing 2-chloroaziridines with quaternary carbon centers including spirocyclic motifs, which are valuable for the previously elusive synthesis of various ααAA-containing chloroalkene isosteres.**

Multi-substituted alkenes flanking two stereogenic centers are an attractive motif for peptidomimetics with a functionalized alkene as a peptide bond surrogate (alkene dipeptide isosteres: ADIs).[1] Several methods for their stereoselective synthesis of these structures have been published, but most are limited to ADIs with tertiary chiral centers that correspond to natural α-amino acids. Common synthetic strategies involve the diastereoselective alkylation of dienolates,[2] organocuprate-mediated allylic alkylation of preorganized enoates,[3] or an asymmetric aldol reaction followed by [3,3]-sigmatropic rearrangement leading to the α-alkylated ADIs.[4] Despite these advances, none of the approaches addresses the challenge facing stereoselective synthesis of ADIs with quaternary carbon centers corresponding to α,α-disubstituted amino acids (ααAA). Amino acids of this sort have attracted increasing interest as building blocks of unnatural peptides which are able to promote the formation of secondary structures and can lead to peptides with increased hydrolytic stability.[5]

As part of our program on development of synthetic methodologies for peptidomimetics, we previously reported the diastereoselective allylic alkylation of γ,γ-dichloro-α,β-enoates with organocuprates by 1,4-asymmetric induction, stereo-selectively affording (*Z*)-chloroalkene-type ADIs (CADIs) for peptide bond isosteres (Figure 1B).[6] This approach can provide direct routes to the isosteres with various side chains by modifying the starting aldimines. The use of ketimine substrates instead of aldimines would result in the formation of (*Z*)-CADIs containing ααAAs. A 1,4-asymmetric induction strategy would be difficult to use in the stereoselective

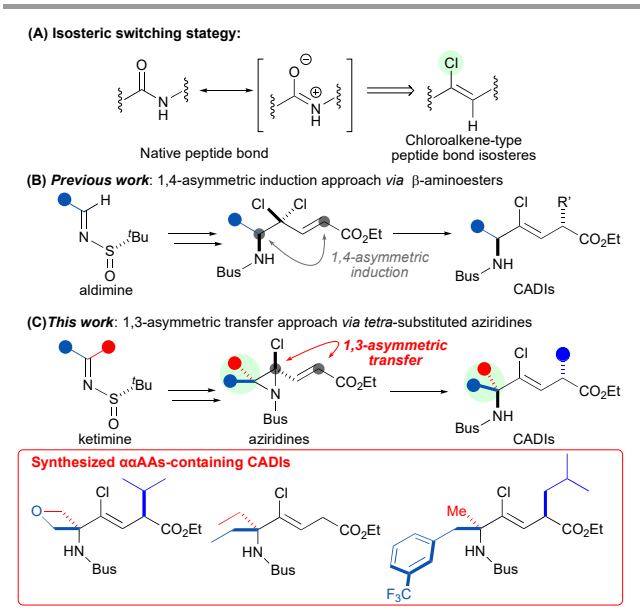


**Figure 1.** (A) Isosteric switching strategy of peptide bond-to-(*Z*)-chloroalkene moiety. Synthetic approaches toward CADIs containing (B) α-amino acids and (C) α,α-disubstituted amino acid.

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synthesis of isosteres containing ααAAs such as aminobutyric acid (Aib) and diethylglycine (Deg) without a chiral center. We also noted that owing to the steric hindrance posed by α,α-disubstituted alkyl groups, elaboration of ααAAs derivatives by conventional carbonyl chemistry is often problematic.[7]

Due to their high ring strain, substituted aziridines are uniquely reactive and are valuable building blocks.[8] Based on the existing publications which describe the ring opening of aziridines as a key step in classical bond-forming methods, we envisaged that a stereoselective ring opening of 2-chloroaziridine derivatives would be highly useful for the synthesis of ααAAs-containing (*Z*)-CADIs. Herein, we report the diastereoselective synthesis of (*Z*)-CADIs containing ααAAs with a strategy that combines multi-substituted aziridine synthesis from chiral sulfinimines[9] with organocuprate-mediated reactions. The method is characterized by the unique reactivity of 2-chloroaziridines containing sterically hindered quaternary carbons, which permits diastereoselective allylic alkylation *via* 1,3-asymmetric transfer through the stereoselective ring-opening of aziridines. The utility of this protocol is demonstrated by the stereoselective synthesis of various ααAA-containing (*Z*)-CADIs that cannot be prepared by 1,4-asymmetric induction strategy (Figure 1C).

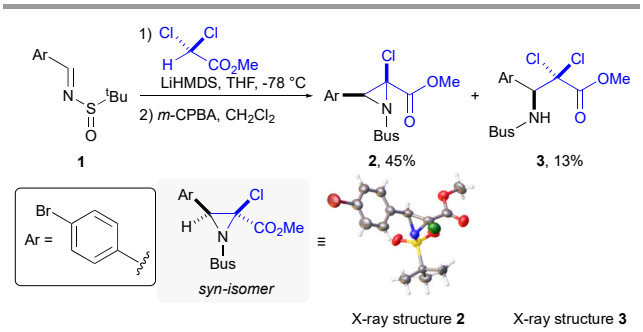



**Figure 2.** Aza-Darzens condensation of *p*-bromophenyl-type aldimine (**1**) and X-ray structures of the reaction products (**2**, **3**).

This ring opening of 2-chloroaziridines is predicated upon our recent discovery of the unexpected formation of methyl 2-chloroaziridine 2-carboxylate (**2**), which was obtained from the reaction of the N-sulfinimine (**1**) with lithium α,α-dichloroenolate and subsequent oxidation of the N-sulfinyl group by *m*-CPBA (Figure 2A). Although the synthesis of similar 2-chloroaziridines requires two steps, including potassium hydride-mediated cyclization of α,α-dichloro-β-amino esters,[9a] the aza-Darzens condensation proceeded to afford the corresponding 2-chloroaziridine (**2**) in 45% yield as the major product together with the α,α-dichloro-β-amino ester (**3**) in 13% yield. The structures of **2** and **3** were established by X-ray crystallography and **2** was found to be the *syn*-isomer. Based on these findings, we wondered if a 2-chloroaziridine with quaternary carbon centers could be synthesized by the aza-Darzens condensation of ketimine, promoted by the Thorpe–Ingold effect.[10] In this strategy, the C-N bond of 2-chloroaziridine would be selectively cleaved in an *anti*-$S_N2'$ manner in the organocuprate-mediated allylic alkylation,

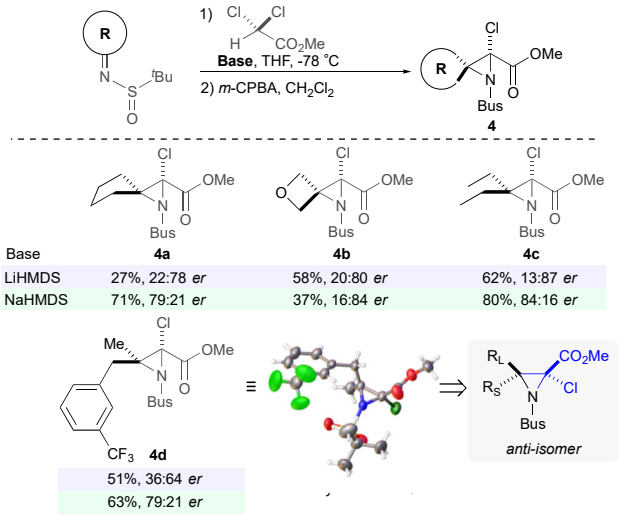



**Figure 3.** Scope of aza-Darzens condensation of chiral ketimines with LiHMDS or NaHMDS. Enantiomer ratios were determined by chiral HPLC analysis after converting to the corresponding enoates (**5**, **7**, **9**) except **4d**.

leading to the selective formation of the corresponding α-alkylated isosteres.

This hypothesis was tested by the aza-Darzens condensation of ketimines, prepared from various ketones and (*S*)-*t*-butylsulfinamide, with 1.5 equiv of α,α-dichloroenolate in THF at -78 °C. An example of the synthesis of 2-chloroaziridines and the yields that were obtained after oxidation of the N-sulfinyl group with *m*-CPBA is shown in Figure 3. Under these conditions, the corresponding chloroaziridines were obtained with moderate levels of enantioselectivity and the formation of the corresponding β-amino esters were not observed. Although the reaction of a ketimine derived from cyclopentanone with lithium α,α-dichloroenolate showed low efficiency, use of sodium α,α-dichloroenolate provided the corresponding

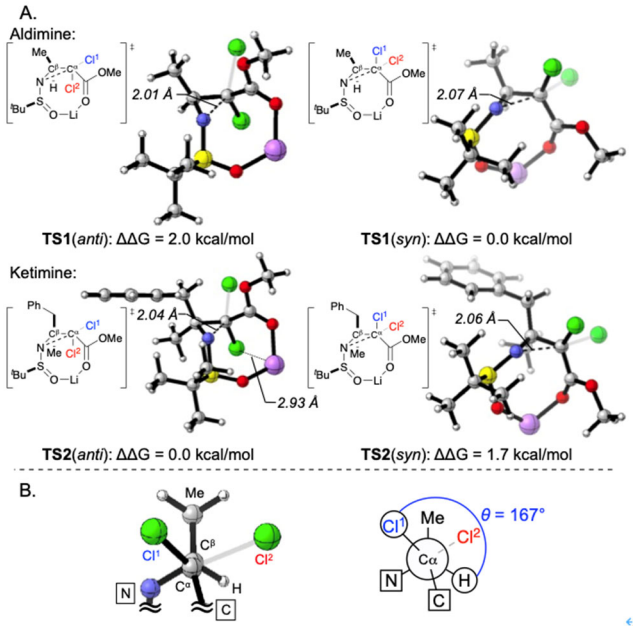



**Figure 4.** (A) Structures and relative Gibbs free energies of transition states of cyclization step in aza-Darzens condensation. (B) Newman projections for **TS1**(syn).

spirocyclic 2-chloroaziridines (**4a**) in 71% yield. Use of NaHMDS instead of LiHMDS led to inversion of the enantioselectivity. This switchover phenomenon in the 1,2-addition of organometallic reagents to imines has been reported previously.[11] This protocol tolerates a structurally strained oxetane ring, affording the corresponding spiro[2.3]-cyclic aziridines (**4b**) with a similar enantioselectivity. In **4b**, the inversion of enantioselectivity was not observed. Use of acyclic ketimines also delivered the expected 2-chloroaziridines (**4c**, **4d**). The ketimine derived from diethylketone afforded the 3,3-diethyl 2-chloroaziridine (**4c**) corresponding to the Deg derivatives. The reaction of the ketimine prepared from 3-(trifluoromethyl)phenylacetone provided the corresponding 2-chloroaziridine (**4d**) in an acceptable yield as single diastereomers. The relative stereochemistry of **4d** was identified by X-ray crystallography as the *anti*-isomer. The observed stereochemical outcome of **4h** was different from the result from the aldimine (**1**), which gave the *syn*-isomer.

To explore the factors controlling diastereoselectivity in the aza-Darzens condensation,[12]we computationally investigated the cyclization steps at the M06/6-311++G(d,p)//B3LYP/6-31+G(d)-PCM(THF) level of theory using truncated models of aldimine and ketimine.[13] The diastereoselectivity in the aza-Darzens condensation is determined by the positions of the α,α-chlorine groups in the intramolecular cyclization after forming the C-C bond through the well-known Li-chelated six-membered transition state.[14] For aldimine, **TS1**(*syn*) is energetically favoured over **TS1**(*anti*). This is consistent with the experimental diastereoselectivity. In **TS1**(*syn*), the dihedral angle between $Cl^1$-$C^\alpha$ and $C^\beta$-H is -167°., as shown in Figure 4B. Here, $C^\beta$-H overlaps with the $Cl^1$-$C^\alpha$ antibonding orbital (σ*) and stabilizes itself by hyperconjugation as shown in a Newman projection. As a result, **TS1**(*syn*) is approximately 2.0 kcal/mol lower in free energy than the corresponding **TS1**(*anti*), which lacks this stabilizing effect. For ketimine, the large difference in

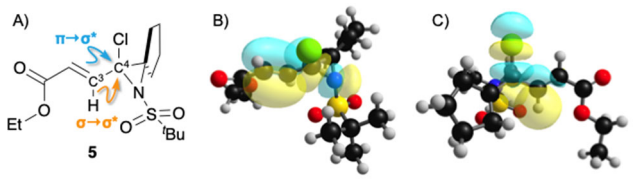



**Figure 6.** (A) Putative orbital interactions. NBO analysis characterized by overlap of (B) the C=C π orbital and C-N σ* orbital, (C) C-H σ orbital and C-Cl σ* orbital.

the stabilization effects from the hyperconjugation is absent. In **TS2**(*anti*), the negative electrostatic potential region of the $Cl^2$ group is proximal to the $Li^+$, as highlighted in Figure 4A, and the electrostatic interaction stabilizes this anti transition state. Thus, **TS2**(*anti*) is 1.7 kcal/mol more stable than **TS2**(*syn*), and the diastereoselectivity is reversed.

The synthesized aziridine (**4a**) was converted to (*Z*)-CADIs containing 1-aminocyclopentane-1-carboxylic acid (Ac5c) by established methods (Figure 5).[6] Reduction of the ester followed by the Horner-Wadsworth-Emmons reaction gave the corresponding enoates (**5**), which can react with various organocuprates diastereoselectively to provide the expected isosteres (**6a-6f**) with α-alkyl groups including methyl, isopropyl, isobutyl, *sec*-butyl, and benzyl groups that corresponding to the side chains of Ala, Val, Leu, Ile, and Phe, respectively. The structure of **6d** was established by X-ray crystallography after hydrolysis followed by recrystallization complexed with dicyclohexylamine.[15]

We performed structural analyses of the enoate (**5**) in order to investigate the mechanism of the selective ring opening of the aziridine (Figure 6). The X-ray crystallographic data revealed that the chlorine substituent eclipses the double bond to avoid the 1,3-allylic strain, resulting in a $C^4$-N bond being parallel to the π-orbital of the double bond. Next, Natural Bonding Orbital

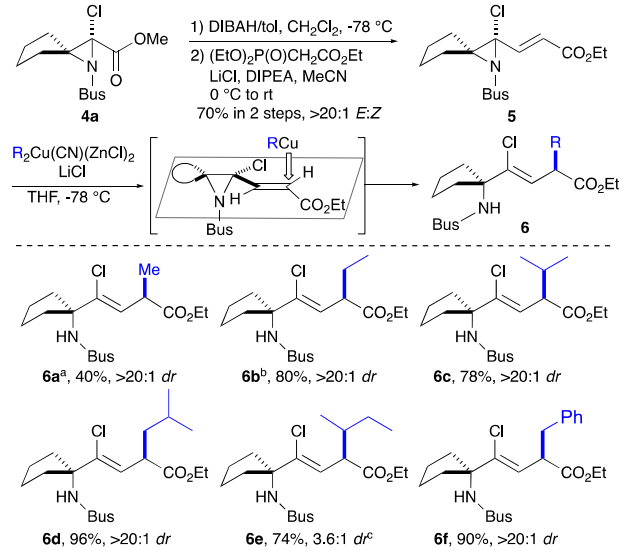
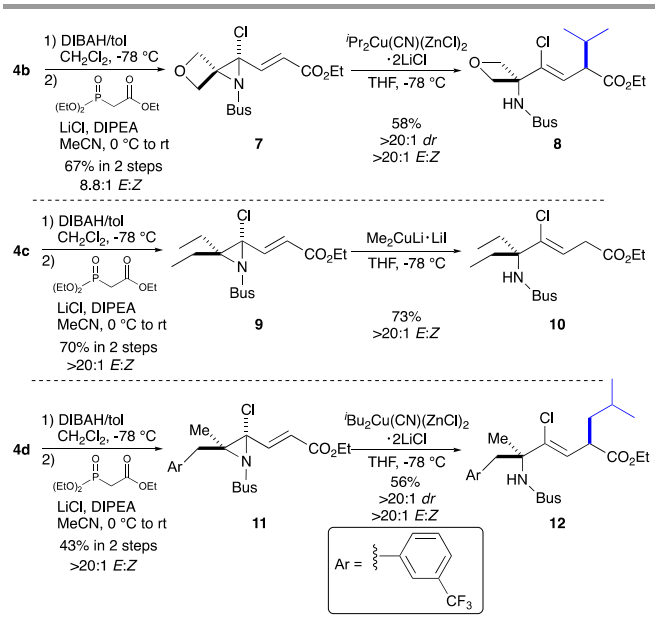
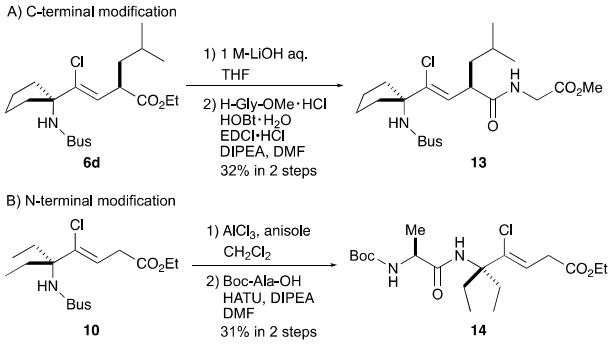



**Figure 5.** Synthesis of ααAAs-containing CADIs. Diastereomer ratio was determined by $^1$H NMR analysis. [a]MeLi was used as alkyl source. [b]$Et_2Zn$ was used as alkyl source. [c]Diastereomer ratio corresponding to the side chain of Ile.




**Scheme 1**. Synthesis of ααAAs-containing CADIs




**Scheme 2.** The N/C-terminus modification of the synthesized isosteres (**6d**, **10**).

(NBO) analysis of the DFT-optimized structure of **5** revealed that the $C^4$-N antibonding orbital ($\sigma^*$) is oriented appropriately for extensive $\pi \rightarrow \sigma^*$ overlap and the allylic system is stabilized by a hyperconjugative interaction between the $C^3$-H bonding orbital ($\sigma$) and the $C^4$-Cl antibonding orbital ($\sigma^*$).[16] As a result, organocuprate-mediated allylic alkylation occurs through the aziridine ring-opening rather than by cleavage of the $C^4$-Cl bond.

The developed protocol was applied to the stereoselective synthesis of $\alpha\alpha$AAs-containing (*Z*)-CADIs from 2-chloroaziridines (**4b-4d**). The structurally unique CADI (**8**) with an oxetane ring and an $\alpha$-isopropyl group corresponding to the side chain of Val can be synthesized diastereoselectively with excellent (*Z*)-selectivity, indicating the utility of this approach. The Deg-Gly-type CADI (**10**) was synthesized using the Gillman reagent as a single electron reductant. Similarly, the product with a trifluoromethyl group (**12**) is also accessible (Scheme 1).

Finally, we explored the modification of the N/C-terminus in the synthesized chloroalkene isosteres. Hydrolysis of Ac5c-Leu-type CADI (**6d**) followed by coupling with H-Gly-OMe provided the chloroalkene-type mimic of the Ala-Deg-Gly tripeptide (**13**). N-terminal modification of the isosteres is also possible by deprotection of the N-Bus group of Deg-Gly-type CADI (**10**) by $AlCl_3$ followed by coupling with Boc-Ala-OH to afford the tripeptide mimic with the sequence of the Ala-Deg-Gly tripeptide (**14**).

## Conclusions

In summary, we have developed a synthetic method for stereoselective synthesis of (*Z*)-CADIs containing $\alpha\alpha$AAs that can serve as an important building block in peptide chemistry. By a combination of appropriate ketimine with organocuprates, this method enables the preparation of chloroalkene isosteres with various types of the side chains including those of natural and unnatural amino acids. The N- and C-termini of the isosteres can be transformed to free forms, leading to the preparation of $\alpha\alpha$AA-containing chloroalkene-type peptidomimetic compounds that were previously unknown.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references


1 For reviews, see: (a) P. Wipf, J. Xiao and C. R. J. Stephenson, *Chimia,* 2009, **63**, 764; (b) A. Choudhary and R. T. Raines, *Chembiochem*, 2011, **12**, 1801.

2 (a) M. T. Cox, D.W. Heaton and J. Horbury, *J. Chem. Soc., Chem. Commun.,* 1980, 799; (b) Y. W. Fu, J. Bieschke and J. W. Kelly, *J. Am. Chem. Soc.,* 2005, **127**, 15366; (c) T. Narumi, K. Niida, K. Tomita, S. Oishi, A. Otaka, H. Ohno and N. Fujii, *Chem. Commun*., 2006, 4720.

3 (a) P. Wipf and P. Fritch, *J. Org. Chem.,* 1994, **59**, 4875; (b) T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, Y. Oguchi, T. Uyehara and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.,* 1990, **29**, 801; (c) T. Ibuka, H. Habashita, A. Otaka, N. Fujii, Y. Oguchi, T. Uyehara and Y. Yamamoto, *J. Org. Chem.,* 1991, **56**, 4370.

4 (a) T. Allmendinger, E. Felder and E. Hungarbühler, *Tetrahedron Lett*., 1990**, 31**, 7301; (b) R. Waelchli, R. Gamse, W. Bauer, E. Lier and J. H. M. Feyen, *Bioorg. Med. Chem. Lett.,* 1996, **6**, 1151; (c) T. Kobayakawa, C. Azuma, Y. Watanabe, S. Sawamura, A. Taniguchi, Y. Hayashi, K. Tsuji and H. Tamamura, *J. Org. Chem.,* 2021, **86**, 5091.

5 (a) H. Yamaguchi, H. Kodama, S. Osada, F. Kato, M. J. Niaraki and M. Kondo, *Biosci. Biotechnol. Biochem.,* 2003, **67**, 2269; (b) M. Tanaka, *Chem. Pharm. Bull.*, 2007, **55**, 349.

6 T. Kobayakawa, T. Narumi and H. Tamamura, *Org. Lett.,* 2015, **17**, 2302.

7 M. Jo, S. W. Won, D. G. Lee, J. K. Jung, S. Kim and Y. S. Kwak, *Arch. Pharm. Res.,* 2018, **41**, 259.

8 (a) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (b) J. B. Sweeney, *Chem. Soc. Rev*., 2002, **31**, 247; (c) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (d) P. Zhou, B. -C. Chen, F. A. Davis, *In Aziridines and Epoxides in Organic Synthesis; Yudin, A. K., Ed.; Wiley-VCH: Weinheim*, 2006, p73; (e) T. Ishikawa, *Heterocycles*, 2012, **85**, 2837.

9 For selected examples of multi-substituted aziridine synthesis from chiral sulfinimines, see: (a) F. A. Davis and J. Deng, *Org. Lett*., 2007, **9**, 1707; (b) T. Moragas, I. Churcher, W. Lewis and R. A. Stockman, *Org. Lett.*, 2014, **16**, 6290; (c) M. A. Marsini, J. T. Reeves, J. N. Desrosiers, M. A. Herbage, J. Savoie, Z. Li, K. R. Fandrick, C. A. Sader, B. McKibben, D. A. Gao, J. Cui, N. C. Gonnella, H. Lee, X. Wei, F. Roschangar, B. Z. Lu and C. H. Senanayake, *Org. Lett.*, 2015, **17**, 5614.

10 (a) R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, 1915, **107**, 1080; (b) C. K. Ingold, *J. Chem. Soc.*, 1921, **119**, 305; (c) C. K. Ingold, S. Sako and J. F. Thorpe, *J. Chem. Soc*., 1922, 1117; (d) F.C. Lightstone and T.C. Bruice, *J. Am. Chem. Soc.*, 1994, **116**, 10789; (e) M.E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735.

11 For selected examples, see: (a) D. A. Cogan, G. Liu and J. Ellman, *Tetrahedron*, 1999, **55**, 8883; (b) T. Fujisawa, Y. Kooriyama, M. Shimizu, *Tetrahedron Lett.*, 1996, **37**, 3881; (c) J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, P. G. Nantermet, *Tetrahedron Lett., 2001*, **42**, 2051; (d) N. Plobeck and D. Powell, *Tetrahedron Asymmetry*, 2002, **13**, 303.

12 For selected examples of diastereoselective Darzens condensation with methyl dichloroacetate: (a) I. Nishiguchi, S. Goda, T. Kikkawa, Y. Ishino and H. Maekawa, *J. Electroanal. Chem*., 2001, **507**, 185; (b) V.A. Mamedov, E. A. Bernikov, S. Tsuboi, H. Hamamoto, T. Komiyama, E. A. Gorbunova, A. T. Gubaidullin and I. A. Livinov, *Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1455.

13 See Supporting Information for the details.

14 (a) T. P. Tang and J. A. Ellman, *J. Org. Chem*., 2002, **67**, 7819; (b) N. Plobeck and D. Powell, *Tetrahedron Asymmetry*, 2002, **13**, 303.

15 See Supporting Information for the details.

16 See Supporting Information for the details.