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Facile Approach to Optically Active α-Alkylidene-β-amino Esters by Thermal Overman Rearrangement

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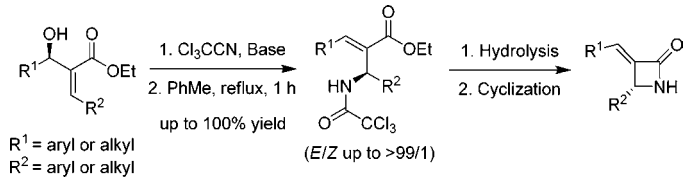
ABSTRACT



A convenient synthetic method for enantioenriched (*E*)-α-alkylidene-β-amino esters has been developed through thermal Overman rearrangement. Readily accessible (*Z*)-β-branched Morita−Baylis−Hillman esters serve as chiral pool precursors. Thermal rearrangement proceeded through a concerted pseudopericyclic transition state to produce (*E*)-stereoselective products. We expanded the synthetic utilities of α-alkylidene-β-amino esters via preparation of α-alkylidene-β-lactam derivatives.

The transformation of readily available allylic alcohols to relatively inaccessible allylic amines through [3,3]-sigmatropic rearrangement has been the focus of numerous investigations over the past few decades, beginning with the first report by Overman.[1,2] This reaction can be accomplished at either elevated temperature or at room temperature catalyzed by Hg(II) or Pd(II) complexes. [3,3]-Sigmatropic rearrangement has been employed as a pivotal step in the syntheses of alkaloids, antibiotics, unnatural amino acids, and other complex natural products.[3] Among these targets, preparation of β-amino acids is of particular interest to medicinal and bioorganic chemists, as various β-amino acid moieties can be found in HIV-protease inhibitors, β-lactam antibiotics, and peptidomimetics.[4]

Recently, we reported a highly enantioselective and (*Z*)-stereocontrolled three-component coupling reaction of α,β-acetylenic esters, aldehydes, and trimethylsilyl iodide (TMSI) using chiral cationic oxazaborolidinium catalysts.[5] The reaction provides optically active (*Z*)-β-iodo Morita−Baylis−Hillman (MBH) esters with good to excellent yield and enantioselectivity in a straightforward manner.[6,7] In addition, the subsequent metal-catalyzed cross-coupling of these esters are performed directly to access the β-branched MBH esters in a single step (Scheme 1).[8]

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(1) (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (c) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579. (d) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188. (e) Galeazzi, R.; Martelli, G.; Orena, M.; Rinaldi, S. *Synthesis* **2004**, *15*, 2560. (f) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 6712. (g) Lee, E. E.; Batey, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 14887.

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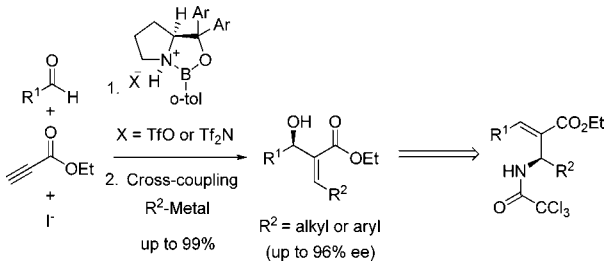
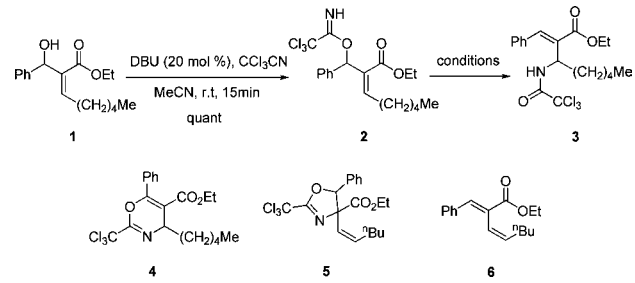
Scheme 1. Asymmetric Synthesis of (*Z*)-*β*-Iodo Morita−Baylis−Hillman Esters



Scheme 2. Overman Rearrangement of Allylic Trichloroacetimidate



We anticipated that the optically active (*Z*)-*β*-branched MBH ester could be useful for producing chiral α-alkylidene-*β*-amino esters through an Overman rearrangement. In this paper, we demonstrate that a series of (*Z*)-*β*-branched MBH esters can be an excellent precursor for enantioenriched (*E*)-α-alkylidene-*β*-amino esters.[9]

The *β*-phenyl-*β*′-pentyl substituted substrate **1** was selected for our initial optimization (Scheme 2). The allylic trichloroacetimidate **2** of this substrate was prepared in quantitative yields using the DBU-catalyzed addition of allylic alcohol to trichloroacetonitrile (5.0 equiv)[1e] in MeCN media.

Initial attempts with mercury(II) and palladium(II) catalyst were unsatisfactory. Specifically, although the mercury(II)-catalyzed reaction provided the desired [3,3]-rearranged compound, undesired mixtures of five- and six-membered cyclized compounds and a *γ*-proton eliminated compound (**4**, **5**, and **6**, respectively; Scheme 2) were also present. Screening a variety of Pd(II) complexes for the desired Overman rearrangement proved to be similarly unsuccessful.

We next changed our focus to thermal [3,3]-sigmatropic rearrangement. At the outset, crude trichloroacetimidate **2** was refluxed under various solvents. As a result, formations of five- and six-membered cyclized products were avoided; however, the remaining DBU and polar basic solvent induced *γ*-proton elimination. Trichloroacetimidate **2** cannot be purified through chromatography on silica gel in either acidic or basic conditions. Further, acidic workup cannot completely remove DBU. Fortunately, short path silica gel filtration was successful. Crude trichloroacetimidate **2** was promptly passed through the minimum amount of silica gel to produce base-free pure trichloroacetimidate **2** in a quantitative yield. Heating of **2** for 1 h in toluene furnished allylic trichloroacetamide **3** in an 84% yield and a 9/1 (*E*)-stereoselectivity. To evaluate the substrate scope of this methodology, we investigated the thermal Overman rearrangements of various R^1 and R^2 under optimized conditions (Tables 1 and 2).

For aromatic aldehydes, substitution by an electron-withdrawing group in the *para* position increased either the chemical yield or the (*E*)-stereoselectivity (Table 1, entries 2−6 and Table 2, entries 2, 6, 7, and 9). Moreover, a more sterically hindered R^1 enhanced (*E*)-selectivity (Table 1, entries 10 and 11).

The DBU-catalyzed preparation of trichloroacetimidate was good for the *β*-MBH esters derived from aromatic aldehydes (R^1 = Ar, **7a**−**7k**, **7n**−**7q**, and **7s**−**7y**). To our surprise, the same conditions did not provide the desired products with aliphatic aldehydes (**7l**, **7m**, and **7r**).

To produce the desired trichlroacetimidate, DBU was exchanged with the stronger base NaH in order to generate the allylic alkoxide. The reaction of alkyl chained MBH esters (R^1 = alkyl) with 2.0 equiv of NaH in dichloromethane provided a corresponding imidate, and sequential rearrangement afforded **8l**, **8m**, and **8r** in excellent yield with moderate *E*/*Z* selectivity (Table 1, entries 12, 13 and Table 2, entry 5).

Transposition of the enantioenriched (*R*)-*β*-branched MBH ester **7a** produced (*R*)-trichloroacetamide **8a** with clean transfer of chirality. Similarly, **7c**, **7o**, and **7s** were rearranged in excellent yields to furnish only the corresponding (*R*)-enantiomers **8c**, **8o**, and **8s**, respectively (Table 3).

The rearrangement of trichloroacetimidate proceeded in a highly (*E*)-stereoselective manner. The (*E*)-stereochemistry of the resulting α-alkylidene-*β*-amino esters were assigned

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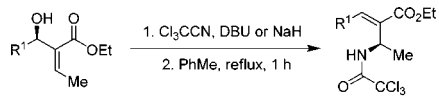
Table 1. Result of Synthesis of Various α-Alkylidene-β-amino Esters from Racemic (*Z*)-β-Branched MBH Esters



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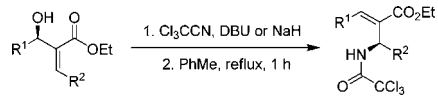
entry		R^1	*E*/*Z*[b]	yield[a] (%)
1	**a**	Ph	92/8	86
2	**b**	(4-F)C_6H_4	>99/1	80
3	**c**	(4-CN)C_6H_4	>99/1	87
4	**d**	(4-CF_3)C_6H_4	91/9	97
5	**e**	(4-Br)C_6H_4	92/8	100
6	**f**	(4-Cl)C_6H_4	92/8	78
7	**g**	(2-F)C_6H_4	77/23	99
8	**h**	*o*-tol	89/11	72
9	**i**	*p*-tol	79/21	50
10[c]	**j**	1-Naph	93/7	70
11	**k**	2-Naph	>99/1	72
12	**l**	Et	61/39	100
13	**m**	^{i}Pr	70/30	86

[a] Combined yield of *E*/*Z* isomers. [b] Determined by column chromatography separation. [c] Reaction time is 2 h.

Table 2. Result of Synthesis of Various α-Alkylidene-β-amino Esters from Racemic (*Z*)-β-Branched MBH Esters



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entry		R^1	R^2	*E*/*Z*[b]	yield[a] (%)
1	**n**	Ph	*n*-C_5H_{13}	90/10	84
2	**o**	(4-F)C_6H_4	*n*-C_5H_{13}	90/10	96
3[c]	**p**	(2-Br)C_6H_4	*n*-C_5H_{13}	82/18	97
4	**q**	*o*-tol	*n*-C_5H_{13}	92/8	82
5	**r**	^{i}Pr	*n*-C_5H_{13}	74/26	94
6	**s**	(4-F)C_6H_4	Et	93/7	70
7	**t**	(4-CF_3)C_6H_4	Et	93/7	96
8	**u**	Ph	^{i}Pr	90/10	88
9	**v**	(4-F)C_6H_4	^{i}Pr	89/11	91
10	**w**	(4-CF_3)C_6H_4	Ph	86/14	88
11	**x**	*o*-tol	Ph	70/30	42
12	**y**	Ph	CCPh	88/12	67

[a] Combined yield of *E*/*Z* isomers. [b] Determined by column chromatography separation. [c] Reaction time is 5 h.

on the basis of the chemical shift values of vinyl protons in the ^{1}H NMR and NOE NMR spectral analyses. The NOE of (*E*)-β-amino esters revealed strong correlations between the allylic protons and the phenyl protons. Otherwise, (*Z*)-β-amino esters exhibited strong correlations between the vinylic protons and allylic protons (Figure 1).

These results could be explained by a pseudopericyclic transition state, as illustrated in Figure 2.[10] Because a serious steric interaction between R^1 and ethyl ester is obvious in

Table 3. Clean Transfer of Chirality of Enantioenriched (*R*)-(*Z*)-β-Branched MBH Esters

entry		R^1	R^2	**7** ee %	**8** ee %
1	**a**	Ph	Me	89	89
2	**c**	(4-CN)C_6H_4	Me	80	79
3	**o**	(4-F)C_6H_4	*n*-C_5H_{13}	97	97
4	**s**	(4-F)C_6H_4	Et	95	96

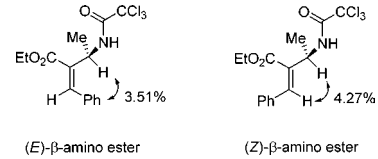

Figure 1. NOE correlation of α-alkylidene-β-amino esters.

transition state **B**, transition state **A** is favored, thereby producing mainly the (*E*)-isomer.[11]

To highlight its chemical utility, we applied this novel synthetic method to the construction of optically active β-lactams. Besides their significance as bioactive agents, the importance of β-lactams as chiral building blocks has been widely recognized in the field of organic synthesis.[12] For the synthesis of optically active β-lactams, we utilized α-alkylidene-β-amino esters, which were envisioned as suitable precursors for the preparation of various enantiomerically enriched α-alkylidene-β-lactams.

Trichloroacetamide **8a** underwent basic hydrolysis under H_2O/EtOH reflux to produce the unnatural β-amino acid **9a**. The resulting β-amino acid was treated with 2,2′-dipyridyldisulfide/PPh_3[13] to give α-alkylidene-β-lactam **10a** in two steps, with a 85% yield. Similarly, **8u** was converted to the corresponding β-lactam in good yield (Scheme 3).

As illustrated in Scheme 3, selective deprotection of the trichloroacetamide of α-alkylidene-β-amino ester **8a** with Cs_2CO_3 in DMSO delivered the corresponding free β-amino ester **11a**. This free amine can then be converted to other useful functionalized amine groups. As an example, tosylation under standard reaction conditions furnished **12a** in two steps, with a 72% yield.

The stereochemistries of the α-alkylidene-β-amino esters were determined by preparing authentic samples via nonequivalent routes (Scheme 4). Synthesis of β-lactam **13a** can be accomplished from (*S*)-(−)-1-phenylethylamine in three steps,[14] showing a rotation at the Na line of −35.5. On the other hand, α-alkylidene-β-lactam **10a** was subjected to

(10) (a) Birney, D. M.; Xu, X.; Ham, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 189. (b) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 557. (c) Çelebi-Ölçüm, N.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 6944.

(11) The Overman rearrangement of (*E*)-stereoisomer of **7a** provided **8a** in lower *E*/*Z*-ratio (~2.5/1) and 73% yield.

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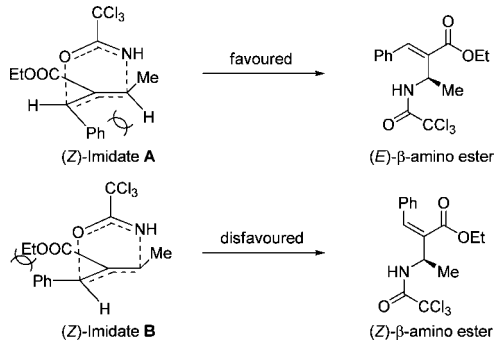
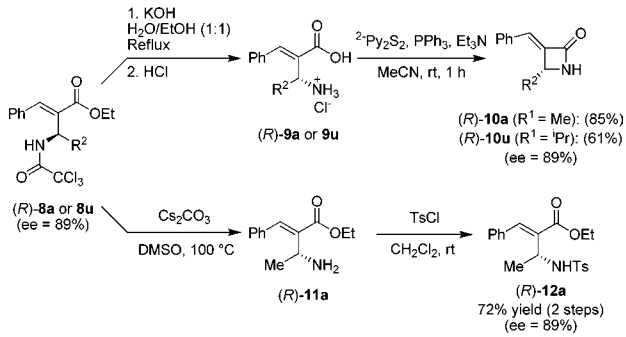


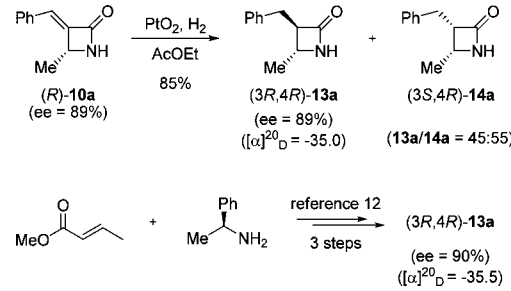
Figure 2. Proposed transition state for thermal [3,3]-sigmatropic rearrangement of β-branched MBH ester.

Scheme 3. Application of α-Alkylidene-β-amino Esters to Synthesis of Optically Active β-Lactams



catalytic heterogeneous hydrogenation[15] to form the 1:1 mixture of *cis*- and *trans*- isomers. The *trans* **13a**, which exhibited a rotation at the Na line of −35.0, established the (*R*)-absolute stereocenter for the major enantiomer of **8a** produced in the thermal rearrangement.

Scheme 4. Determination of Absolute Configuration of α-Alkylidene-β-amino Esters



In conclusion, we have developed a convenient synthetic method for the production of (*E*)-α-alkylidene-β-amino esters through thermal Overman rearrangement. We demonstrated that optically active (*Z*)-β-branched MBH esters can serve as chiral precursors to produce the corresponding rearranged products without loss of optical purity. Moreover, various α-alkylidene-β-lactam derivatives were successfully prepared using hydrolysis−intramolecular cyclization. Thus, the method described in this paper is valuable to the field of synthetic organic chemistry.

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Supporting Information Available: Experimental details and chracterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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