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Construction of Successive Chiral Centers Adjacent to a Chiral Tetraalkylated Quaternary Center Using an Asymmetric Aldol Reaction

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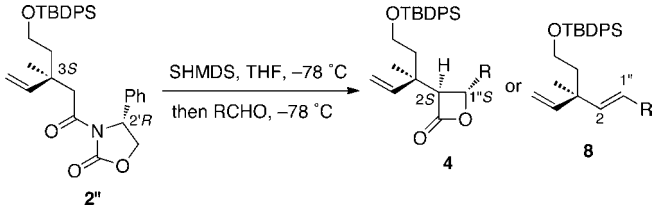
ABSTRACT



The aldol reaction of 2″ with a variety of different aldehydes gave the corresponding β-lactones 4 bearing successive asymmetric centers adjacent to a chiral tetraalkylated quaternary center or the (*E*)-alkenes 8. The use of electronically neutral or electron-deficient aldehydes led to 4 in excellent yields with high diastereoselectivities, whereas electron-rich aldehydes performed poorly and underwent decarboxylation to afford 8.

Structural units consisting of successive chiral centers adjacent to a chiral tetraalkylated (all-carbon) quaternary center (Figure 1) are frequently encountered in a variety of different natural products,[1] and a series of different methods aimed at providing access to structural units of this particular type have been developed by a number of different groups.[2]

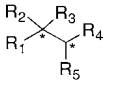


Figure 1. General structure of successive asymmetric centers adjacent to tetraalkylated quaternary center.

For example, Shibasaki[3] used an enantioselective Diels–Alder reaction catalyzed by a chiral Fe^{3+}-pybox complex to construct a series of chiral cyclohexane carboxylic acid derivative (76–87% ee), whereas Carter[4] reported the use of an enantioselective Robinson annulation reaction as

(1) Selected examples for the biologically active natural products possessing successive asymmetric centers with chiral tetraalkylated quaternary center: (a) Fukuyama, Y.; Minami, H.; Takeuchi, K.; Kodama, M.; Kawazu, K. *Tetrahedron Lett*. **1996**, *37*, 6767–6770. (b) Tang, W.; Kubo, M.; Harada, K.; Hioki, H.; Fukuyama, Y. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 882–886. (c) Nakamura, H.; Wu, H.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett*. **1984**, *25*, 2989–2992. (d) Hayashi, K.-I.; Nakanishi, Y.; Bastow, K. F.; Cragg, G.; Nozaki, H.; Lee, K.-H. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 345–348. (e) Rudi, A.; Benayahu, Y.; Kashman, Y. *Org. Lett*. **2007**, *9*, 2337–2340. (f) Sing, I. P.; Sidana, J.; Bharate, S. B.; Foley, W. *J. Nat. Pro. Rep*. **2010**, *27*, 393–416. (g) Ciochina, R.; Grossman, R. B. *Chem. Rev*. **2006**, *106*, 3963–3986. (h) Whitson, E. L.; Thomas, C. L.; Henrich, C. J.; Sayers, T. J.; MacMahon, J. B.; Mackee, T. C. *J. Nat. Prod*. **2010**, *73*, 2013–2018. (i) Guo, D.-X.; Zhu, R.-X.; Wang, X.-N.; Wang L.-N.; Wang, S.-Q.; Lin, Z.-M.; Lou, H.-X. *Org. Lett*. **2010**, *12*, 4404–4407. (j) Cantrell, C. L.; Klun, J. A.; Bryson, C. T.; Kobaisy, M.; Duke, S. O. *J. Agric. Food Chem*. **2005**, *53*, 5948–5953. (k) Song, Z.-J.; Xu, X.-M.; Deng, W.-L.; Peng, S.-L.; Ding, L.-S.; Xu, H.-H. *Org. Lett*. **2011**, *13*, 462–465. (l) Wang, J.-D.; Zhang, W.; Li, Z.-Y.; Xiang, W.-S.; Guo, Y.-W.; Krohn, K. *Phytochemistry* **2007**, *68*, 2426–2431. (m) De Rosa, S.; Cristpino, A.; De Giulio, A.; Iodice, C.; Amodeo, P.; Tancredi, T. *J. Nat. Prod*. **1999**, *62*, 1316–1318. (n) Lamshöft, M.; Schmickler, H.; Marner, F.-J. *Eur. J. Org. Chem*. **2003**, 727–733. (o) Yoo, H.-D.; Cremin, P. A.; Zeng, L.; Garo, E.; Williams, C. T.; Lee, C. M.; Goering, M. G.; O'Neil-Johnson, M.; Eldridge, G. R.; Hu, J. *J. Nat. Prod*. **2005**, *68*, 122–124. (p) Anderson, N. R.; Lorck, H. O. B.; Rasmussen, P. R. *J. Antibiot*. **1983**, *36*, 753–760. (q) Xu, J.; Harrison, L. J.; Vittal, J. J.; Xu, Y. J.; Goh, S. W. *J. Nat. Prod*. **2000**, *63*, 1062–1065. (r) Gunesekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc*. **1996**, *118*, 8759–8760.

(2) Das, J. P.; Marek, I. *Chem. Commun*. **2011**, *47*, 4593–4623.

(3) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett*. **2004**, *6*, 4387–4390.

(4) Yang, H.; Carter, R. G. *Org. Lett*. **2010**, *12*, 3108–3111.

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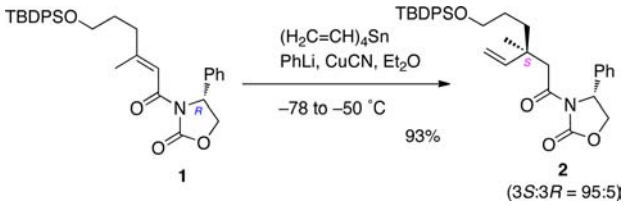
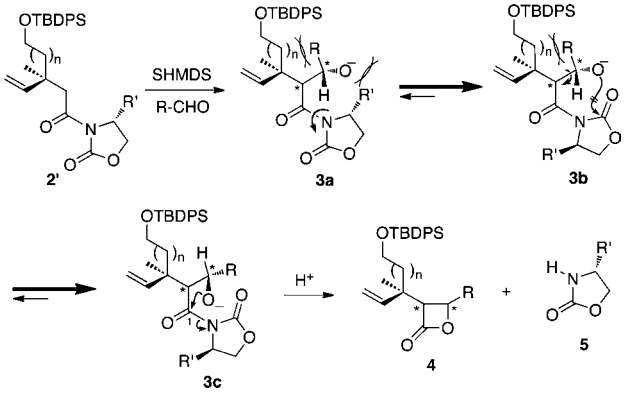
part of a multicomponent coupling reaction process in the presence of a chiral *N*-(arylsulfonyl)pyrrolidinecarboxamide catalyst to afford a series of chiral cyclohexene derivatives with acceptable enantioselectivities and high diastereoselectivities (54.6−91.8% ee, >90.4% de). Recently, Minko et al.[5] reported the successful construction of a tetraalkylated quaternary center α to a carbonyl group via the carbocupration to the triple bonds of a series of alkyne derivatives bearing a chiral oxazolidinone auxiliary, followed by oxidation and aldol reaction in one pot (45−62%, 80−88% de). We recently reported the asymmetric 1,4-addition reaction of $(H_2C{=}CH)_2Cu(CN)Li_2$ to the α,β-unsaturated carboxylic acid derivative **1** to give the corresponding 1,4-adduct **2** bearing a chiral tetraalkylated quaternary center β to the carbonyl group (Scheme 1).[6] This reaction proceeded in excellent yield (93%) with a high diastereoselectivity (90% de).

Scheme 1. Asymmetric 1,4-Addition Reaction of $(H_2C{=}CH)_2Cu(CN)Li_2$ to an α,β-Unsaturated Carboxylic Acid Derivative

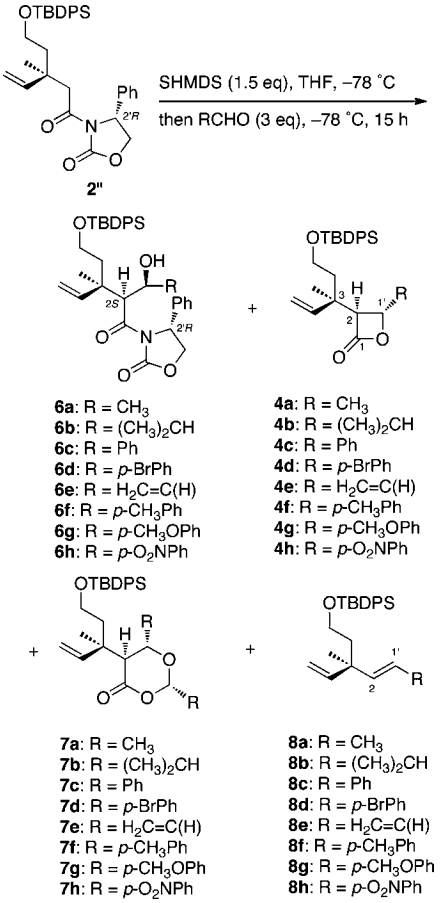


Scheme 2. Potential One-Pot Transformation of the Chiral Oxazolidinone Derivative **2′** Involving a Tetraalkylated Carbon



The retention of the chiral oxazolidinone auxiliary in the 1,4-adduct **2** provided the opportunity for further asymmetric induction at the position α to the carbonyl group, and compound **2** would therefore allow for the construction of an additional asymmetric center adjacent to the chiral tetraalkylated quaternary center. With this in mind,

Table 1. Aldol Reaction of Chiral Oxazolidinone **2″** with a Variety of Different Aldehydes



entry	RCHO	**6**:**4**:**7**:**8** (%)	**6** + **4** + **7** + **8** (%)
1	CH_3CHO	0:65:7:0	72
2	$(CH_3)_2C(H)CHO$	0:89:0:0	89
3	PhCHO	0:84:0:0	84
4	*p*-BrPhCHO	0:99:0:0	99
5	$H_2C{=}C(H)CHO$	0:86:0:0	86
6	*p*-CH_3PhCHO	0:0:0:95	95
7	*p*-CH_3OPhCHO	0:0:0:76	76
8	*p*-O_2NPhCHO	0:67:33:0	100

the decision was made to subject **2** to an asymmetric aldol reaction.[7,8] Kende[9] reported that the chiral oxazolidinone derivative of isobutyric acid was transformed to 1,3-oxazine-2,6-dione by an asymmetric aldol reaction followed by the ring-opening reaction of the oxazolidinone in one pot. The driving force for the second step in the sequence was reported to be the steric repulsion between the α,α-dimethyl and isopropyl groups of the oxazolidinone.

(5) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522–526.

(6) Esumi, T.; Shimizu, H.; Kashiyama, A.; Sasaki, C.; Toyota, M.; Fukuyama, Y. *Tetrahedron Lett.* **2008**, *49*, 6846–6849.

(7) (a) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 1−343. (b) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 1−328. (c) Aya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947.

(8) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

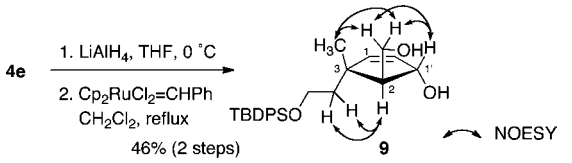
(9) Kende, A. S.; Kawamura, K.; Orwat, M. *Tetrahedron Lett.* **1989**, *30*, 5821–5824.

This implied that the oxazolidinone moiety of the aldol adduct **3a** derived from **2′** could be removed to give β-lactone **4** under basic conditions, because the α-alkoxy group of aldol adduct **3a** would repel not only the alkyl group of the oxazolidinone but also the alkyl chain bearing the tetraalkylated quaternary center. The system would therefore prefer to adopt conformation **3c** as opposed to **3b**, which would be disfavored because of steric repulsion between the α-alkoxy group and the alkyl chain. Conformation **3c** would then undergo the intramolecular nucleophilic attack of the oxyanion on the carbonyl carbon (C1), leading to β-lactone **4** and oxazolidinone **5** (Scheme 2).

On the basis of our prediction for this transformation, we examined the aldol reaction of **2″** under basic conditions. (2′*R*)-2-Phenyloxazolidinone derivative **2″** was treated with SHMDS (1.5 equiv) in THF for 30 min at −78 °C and then reacted with a variety of different aldehydes (3 equiv) for 15 h at the same temperature. The results for these reactions are shown in Table 1. The simple aldol adducts **6** were not obtained in all of the entries, whereas the β-lactones **4** were obtained as anticipated. When acetoaldehyde was used, β-lactone **4a** (R = CH_3) and dioxanone **7a** (R = CH_3) were obtained in 65 and 7% yields, respectively (Table 1, entry 1). When bulkier aldehydes such as isobutylaldehyde, benzaldehyde, and *p*-bromobenzaldehyde were used in the transformation, the reactions proceeded cleanly to afford the β-lactones **4b**–**d** (R = $(CH_3)_2CH$, Ph, and *p*-BrPh) in high yields without the formation of any of the other stereoisomers or dioxanone **7** (Table 1, entries 2–4). The formation of the β-lactone **4e** (R = $H_2C{=}CH$) occurred *via* a 1,2-addition reaction in 86% yield (Table 1, entry 5). Surprisingly, when aromatic aldehydes bearing electron-donating substituents were used in the reaction, including *p*-methyl- and *p*-methoxybenzaldehyde, the (*E*)-alkenes **8f** and **8g** were formed as the sole products (R = *p*-CH_3Ph and *p*-CH_3OPh) (Table 1, entries 6 and 7).[10] In contrast, when the reaction was conducted with aromatic aldehydes bearing electron-deficient substituents, such as *p*-nitrobenzaldehyde, the yield of the corresponding dioxanone **7h** (*p*-O_2NPh) was found to increase (Table 1, entry 7). In addition, (2′*R*)-2′-phenyloxazolidinone was recovered in quantitative yield from all of the reaction mixtures by silica gel column chromatography. It is worthy of note that all of our attempts to trap the enolate formed in situ following the 1,4-addition were unsuccessful.

The absolute configuration of **4e** was determined to be (2*S*,3*S*,1′*S*) following analysis of the nuclear Overhauser

Scheme 3. Determination of the Absolute Configuration of **4e**



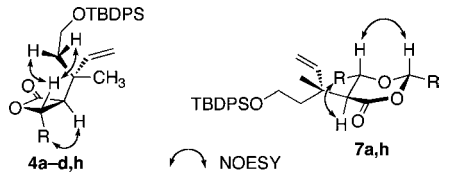
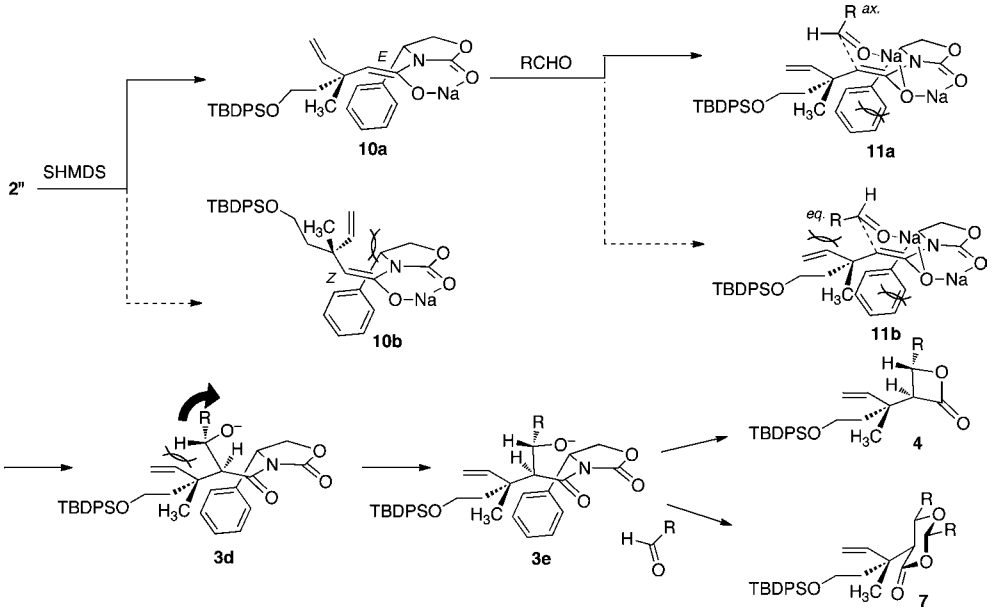


Figure 2. Assertion of absolute configuration for β-lactones **4a**–**d** and **4h** and the dioxanones **7a** and **7h**.

Scheme 4. Proposed Mechanism for the Induction of Stereochemistry for the Aldol Reaction and the Generation of **4** and (*E*)-Alkene **7**



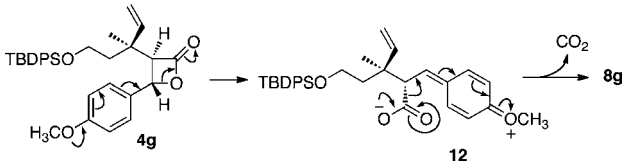
effect spectroscopy (NOESY) correlation spectrum of cyclopentene derivative **9**, which was prepared by $LiAlH_4$ reduction of **4e** followed by a ring closing metathesis reaction catalyzed by Grubbs' reagent (first generation) (Scheme 3).

The absolute configuration of the other compounds, **4a**–**d** and **4h** (R = CH_3, $(CH_3)_2CH$, Ph, *p*-BrPh, *p*-O_2NPh) and **7a** and **7h** (R = *p*-CH_3Ph, *p*-CH_3OPh), were assumed by comparison of their NMR spectra with that of **4e** and NOESY correlation experiments (Figure 2).

Based on these results, we proposed a mechanism for the induction of the stereochemistry of the aldol reaction and the generation of the dioxanone **7** and (*E*)-alkene **8** products, as shown in Schemes 4 and 5. Treatment of **2″** with SHMDS leads to the formation of a six-membered cyclic chelate with Na^+. The (*E*)-enolate **10a** would then be formed because of steric repulsion between the alkyl chain carrying the tetraalkylated quaternary center and the oxazolidinone moiety. Given that the α-face of the (*E*)-enolate **10a** would be blocked by the phenyl group of the oxazolidinone, the aldehyde would approach from the *β*-face and the aldol reaction would then proceed *via* a six-membered chair transition state. The alkyl group of aldehyde in the cyclic transition state would then be placed in a pseudoaxial orientation because of steric repulsion between the alkyl chain of the tetraalkylated quaternary center and the alkyl group of the aldehyde, and the reaction would therefore proceed *via* transition state **11a** and adopt configuration **3**. Furthermore, the bulky tetraalkylated quaternary center would force the oxyanion close to the carbonyl carbon (C1), resulting in the formation of the *β*-lactone **4**. The use of a small or electrophilic alkyl group on the aldehyde, however, such as a methyl or a *p*-nitrophenyl group, respectively, would allow the oxyanion to attack another aldehyde, leading to the formation of dioxanone. In contrast, for aromatic aldehydes bearing electron-donating substituents on their aromatic ring such as *p*-methoxyphenyl, the resulting *β*-lactone ring would be opened through the donation of electrons, resulting in the formation of quinone methylide **12**, which would be converted to arylalkene **8g** together with the elimination of CO_2, with the electron being pushed back to the electron-deficient aromatic ring.

(10) Example for CO_2-elimination from *β*-lactone by thermolysis: (a) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000–2006. (b) Mulzer, J.; Speck, T. *Tetrahedron Lett.* **1995**, *36*, 7643–7646.

Scheme 5. Proposed Mechanism for the Formation of **4g**



In conclusion, we have developed an efficient method for constructing successive chiral centers adjacent to chiral tetraalkylated quaternary centers using a sequential asymmetric 1,4-addition/aldol reaction. The aldol reaction between the 1,4-adduct **2″** and a variety of different aldehydes except for aromatic aldehydes bearing electron-donating substituents afforded the *β*-lactones **4a**–**e** and **7h** and the dioxanones **7a** and **7h** with excellent stereocontrol. To the best of our knowledge, the current work represents the first report describing the construction of successive chiral centers adjacent to a quaternary carbon in one pot. In addition, the reaction producing an aryl alkene could be used as an alternative C–C bond formation reaction. The scope and limitations of these reactions and their application to the syntheses of a variety of different natural products are currently being investigated in our laboratory.

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

The authors declare no competing financial interest.