Organic LETTERS

Letter

pubs.acs.org/OrgLett

TMSCN/DBU-Mediated Facile Redox Transformation of α,β-Unsaturated Aldehydes to Carboxylic Acid Derivatives

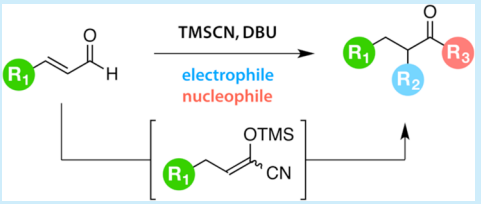
Hiromi Kaise,[†] Jun Shimokawa,[‡] and Tohru Fukuyama*[,‡]

[†]Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa, Nagoya, Aichi 464-8601, Japan

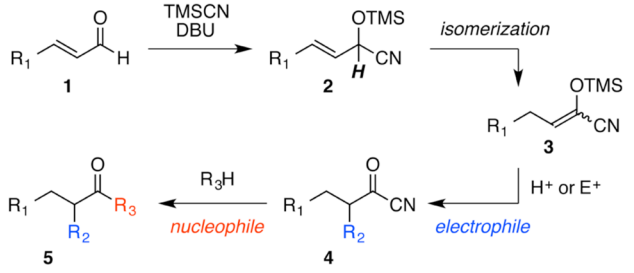
Supporting Information

ABSTRACT: Redox transformation of an α,β-unsaturated aldehyde to a carboxylic acid derivative by means of a combination of TMSCN and DBU was investigated. In addition to the wide use of the carboxylic acid derivatives provided by this reaction, temperature-dependent control of the kinetic or thermodynamic protonation pattern was found to selectively switch the stereochemistry of the acyl group in the product.



Minimization of the number of oxidation and reduction steps has recently been coveted especially from the viewpoint of the redox economy of organic synthesis.[1] One of the transformations that could benefit from reducing the number of redox steps is the conversion of an unsaturated aldehyde to a saturated carboxylic acid derivative. These transformations have often been performed by means of the umpolung chemistry of *N*-heterocyclic carbene (NHC) catalysts that has attracted growing interest over the past two decades.[2] We have been interested in a specific type of this transformation in which a homoenolate equivalent plays an important role.[3] We initiated our studies to address the synthetic difficulties associated with this type of transformation during the course of the total synthesis of gelsemoxonine.[4] We employed Hayashi's conditions that take advantage of the combination of trimethylsilyl cyanide (TMSCN) and DBU for its ability to transform an α,β-unsaturated aldehyde to a saturated ester with concomitant control of the newly generated stereochemistry.[5] Such stereoselectivity would not be successfully achieved without this specific method. The proposed mechanism of this intriguing reaction is shown in Scheme 1. The cyanohydrin TMS ether **2**, generated from the α,β-unsaturated aldehyde **1** by treatment with TMSCN and DBU,[6] underwent deprotonation by DBU to form the thermodynamically more stable α,β-unsaturated nitrile **3**. This is followed by protonation or a reaction with other electrophiles to afford the acyl cyanide intermediate **4**,[7] leading to the formation of carboxylic acid derivatives **5** by treatment with nucleophiles.

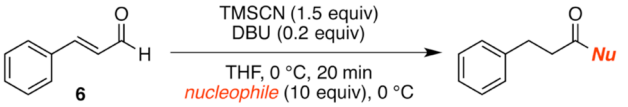
Scheme 1. Proposed Reaction Mechanism of the Redox Isomerization Reaction Mediated by TMSCN and DBU



While the NHC-catalyzed redox transformations are known to yield the intermediates corresponding to **3** or **4** that could be transformed further to more complex molecules, the specific reactivity of NHCs limits the scope of the electrophiles, nucleophiles, and their possible combination. Hence, we investigated the scope and limitations of the transformations by the use of the intermediates **3** and **4**.

We first examined the scope of the nucleophiles that are capable of protonating the intermediate **3** that is generated from **6** (Scheme 2). As reported previously, alcohols reacted smoothly to give the corresponding esters in good yield (entries 1, 2). Thioester could be formed when treated with EtSH

Scheme 2. Scope of the Protonating Nucleophiles



6

entry	nucleophile	yield (%)
1	MeOH	86
2	BnOH	95
3	EtSH	94
4	NH_4OAc	82
5	NH_3 (gas)	92
6	pyrrolidine	94
7	$N_2H_4{\cdot}H_2O$	69
8[a]	MeONHMe·HCl	60

[a]The reaction was performed in the presence of Et_3N (10 equiv).

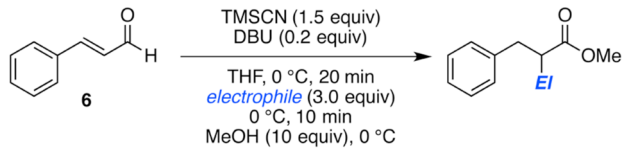
Received: November 25, 2013

 © XXXX American Chemical Society dx.doi.org/10.1021/ol403415z | *Org. Lett.* XXXX, XXX, XXX–XXX

(entry 3). Primary amides may be synthesized through the reaction of acyl cyanide with ammonium chloride, as reported previously.[8] Treatment with ammonium acetate or gaseous ammonia gave the same result (entries 4, 5). The reaction also proceeded very cleanly with pyrrolidine to give the corresponding tertiary amide (entry 6). The use of hydrazine or *N*,*O*-dimethyl hydroxylamine for the synthesis of hydrazide or Weinreb's amide are the first examples of this class of redox transformation (entries 7, 8).

Next, the reactivity of electrophiles with the intermediate **3** was examined in an effort to introduce functionalities at the α-position of the carboxylic acid unit (Scheme 3). Both α-iodo

Scheme 3. Reaction with Electrophiles To Introduce an α-Functionality

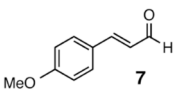
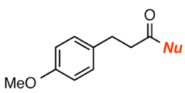
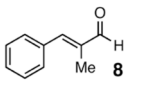
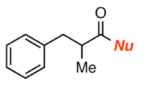
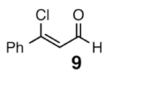
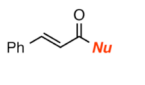


entry	electrophile	yield (%)
1	I_2	77
2	Br_2	92

and α-bromo esters could be obtained by treatment with iodine and bromine, respectively (entries 1, 2). These results supported the formation of the intermediate **3** during the transformation.

Several aldehydes were examined for the transformation to methyl ester or pyrrolidine amide (Table 1). 4-Methoxy-

Table 1. Substrate Scope for the Redox Transformation

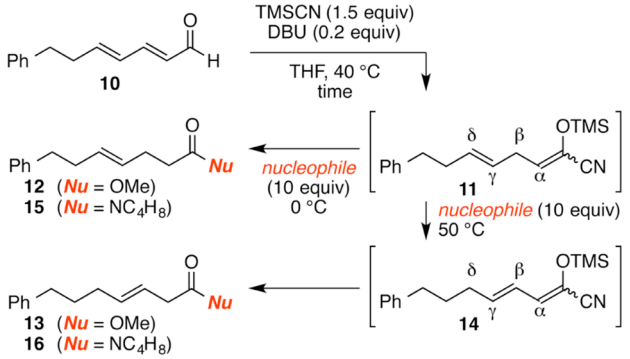
entry	aldehyde	nucleophile	product	yield (%)
1[a]		MeOH		91
2[a]		pyrrolidine		96
3[a]		MeOH		92
4[a]		pyrrolidine		99
5[b]		MeOH		59
6[b]		pyrrolidine		59

[a]Reagents and conditions: TMSCN (1.5 equiv), DBU (0.2 equiv), THF, 0 °C; nucleophile (10 equiv), 0 °C. [b]Reagents and conditions: TMSCN (1.5 equiv), DBU (0.2 equiv), THF, 0 °C; nucleophile (10 equiv), DBU (1.0 equiv), 0 °C.

cinnamaldehyde (**7**) was converted to the corresponding ester or amide in good yield (entries 1, 2). The transformation proceeded smoothly with a substrate carrying an α-methyl group (entries 3, 4). β-Chloro unsaturated aldehyde **9**, synthesized in two steps from acetophenone, gave the unsaturated carboxylic acid derivative with a concomitant elimination of the chloride ion (entries 5, 6).

We next examined the potential utility of $\alpha,\beta-\gamma,\delta$-unsaturated aldehyde **10** as a substrate (Scheme 4). Here, very interesting results were obtained from the potential intermediate **11** that would be generated by protonation at the β-position after the isomerization reaction at 40 °C. The temperature of the methanol treatment step changed the course

Scheme 4. Transformation of the $\alpha,\beta-\gamma,\delta$-Unsaturated Aldehyde

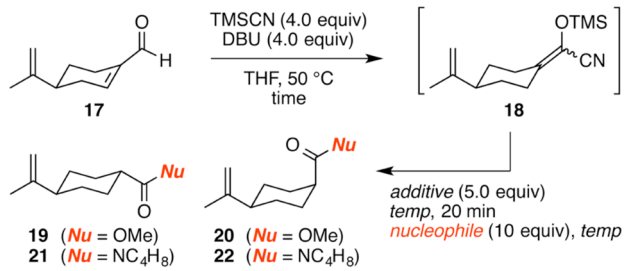


entry	time	nucleophile	temp	yield (%)
1	1 h	MeOH	0 °C	83 (**12**)
2	1 h	MeOH	50 °C	50 (**13**)
3	3 h	pyrrolidine	0 °C	93 (**14**)
4	3 h	pyrrolidine	50 °C	74 (**15**)

of the subsequent reaction. While the reaction at 0 °C gave only the γ,δ-unsaturated ester **12** (entry 1), the same reaction at 50 °C gave the β,γ-unsaturated ester **13** via the intermediacy of conjugated isomer **14** followed by protonation at the α-position (entry 2). This temperature-dependent reaction was also observed when pyrrolidine was used as the nucleophile to give **15** and **16** (entries 3, 4).

Intrigued by the stereoselective protonation that helped establish the important stereochemistry in our gelsemoxonine synthesis,[4] we attempted a diastereoselective transformation of (−)-perillaldehyde (**17**) as shown in Scheme 5. Two

Scheme 5. Redox Transformation of (−)-Perillaldehyde



entry	time	additive	nucleophile	temp	yield (%) 19	20	21	22
1	20 h	2-nitrophenol	MeOH	70 °C	80 (7.0 : 1)[a]	–	–	
2	9 h		MeOH	0 °C	56 (1 : 2.1)[a]	–	–	
3	11 h	2-nitrophenol	pyrrolidine	70 °C	–	–	67	13
4	11 h		pyrrolidine	–20 °C	–	–	16	47

[a]An inseparable mixture of **19** and **20** was obtained.

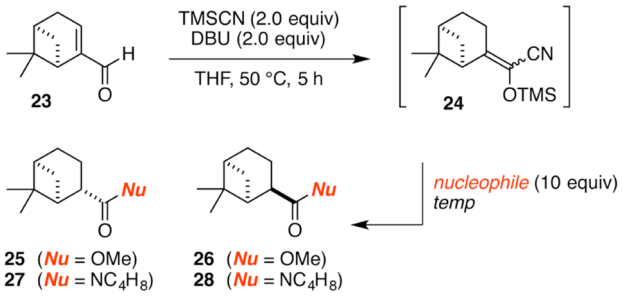
diastereomers derived from protonation of the intermediate **18** were observed. The diastereomeric ratio of the products was dependent upon the presence of the additive and the temperature at which **18** was protonated. An initial attempt without additives gave an unsatisfactory selectivity of **19** and **20**. To our delight, the thermodynamically more stable *trans* acyl cyanide intermediate was formed in the presence of the poorly nucleophilic protonating agent, 2-nitrophenol. This isomerization process of acyl cyanide was followed by the reaction with methanol to afford **19**, albeit in a moderate ratio.

dx.doi.org/10.1021/ol403415z | *Org. Lett.* XXXX, XXX, XXX−XXX

This result displays a difference to the protonation reaction that proceeded in the absence of an additive at lower temperatures to give rather the kinetic adduct **20**. Similar results were observed with pyrrolidine as the nucleophile to afford **21** and **22** as a thermodynamic and a kinetic product, respectively (entries 3, 4).

The diastereoselective transformation of (−)-myrtenal (**23**) was next examined (Scheme 6). Heating at 70 °C yielded

Scheme 6. Redox Transformation of (−)-Myrtenal



entry	nucleophile	temp	yield (%) 25	26	27	28
1	MeOH	70 °C	81 (4.2 : 1)[a]	–	–	
2	MeOH	0 °C	76 (1 : 4.2)[a]	–	–	
3	pyrrolidine	70 °C	–	–	44	54
4	pyrrolidine	–20 °C	–	–	3	83

[a]An inseparable mixture of **25** and **26** was obtained.

primarily the thermodynamically more stable *trans* product **25** (entry 1). This preference was reversed to give **26** when the reaction was performed at 0 °C (entry 2). The use of pyrrolidine as a nucleophile resulted in the protonation of **24** on both sides to give a diastereomeric mixture of **27** and **28** at 70 °C (entry 3). This result most likely stemmed from the fact that the kinetic intermediate, the *cis* acyl cyanide, did not fully isomerize prior to the formation of amide. On the other hand, the kinetic product **28** was obtained at −20 °C with very high selectivity and in very good yield (entry 4). This result underscores the potential utility of the present method for constructing complicated cyclic molecular structures.

In conclusion, we have established a useful method for the redox transformation of an α,β-unsaturated aldehyde to a carboxylic acid derivative using a combination of TMSCN and DBU. A variety of carboxylic acid derivatives could be synthesized from α,β-unsaturated aldehydes. Application of the present method to the total synthesis of complex molecules is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fukuyama@ps.nagoya-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Prof. Masahiko Hayashi (Kobe Univ.) for helpful discussions. Financial support for this research was provided by Grants-in-Aid (23590003 and 20002004) and Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

■ REFERENCES

(1) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(2) For a review, see: (a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (d) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (e) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (f) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2011**, *51*, 314. (g) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295. (h) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (i) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906.

(3) (a) Franzen, V.; Fikentscher, L. *Liebigs Ann.* **1959**, *623*, 68. (b) Nowak, R. M. *J. Org. Chem.* **1963**, *28*, 1182. (c) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (d) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (e) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (f) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (g) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (h) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (i) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (j) Zeitler, K. *Org. Lett.* **2006**, *8*, 637. (k) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (l) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (m) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098. (n) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (o) Phillips, E. M.; Wadamoto, M.; Chan, A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3107. (p) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418. (q) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416. (r) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (s) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (t) Maki, B. E.; Chan, A.; Scheidt, K. *Synthesis* **2008**, *2008*, 1306. (u) Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2009**, *11*, 677. (v) Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507. (w) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570. (x) Zeitler, K.; Rose, C. A. *J. Org. Chem.* **2009**, *74*, 1759. (y) Phillips, E. M.; Wadamoto, M.; Scheidt, K. A. *Synthesis* **2009**, *2009*, 687. (z) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345. (aa) Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810. (ab) Nair, V.; Vellalath, S.; Babu, B. P.; Varghese, V.; Paul, R. R.; Suresh, E. *Org. Biomol. Chem.* **2010**, *8*, 4861. (ac) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (ad) Choi, H. H.; Son, Y. H.; Jung, M. S.; Kang, E. J. *Tetrahedron Lett.* **2011**, *52*, 2312. (ae) Singh, S.; Yadav, L. D. S. *Org. Biomol. Chem.* **2012**, *10*, 3932. (af) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963.

(4) (a) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634. (b) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *Pure Appl. Chem.* **2012**, *84*, 1643.

(5) (a) Kawabata, H.; Hayashi, M. *Tetrahedron Lett.* **2002**, *43*, 5645. (b) Hayashi, M.; Kawabata, H.; Yoshimoto, K.; Tanaka, T. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 433.

(6) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537.

(7) Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 36.

(8) Hünig, S.; Reichelt, H. *Chem. Ber.* **1986**, *119*, 1772.