J|A|C|S COMMUNICATIONS

Published on Web 07/24/2009

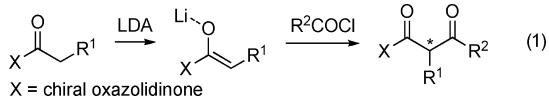
Stereoselective Synthesis of α-Alkyl-β-keto Imides via Asymmetric Redox C−C Bond Formation between α-Alkyl-α-diazocarbonyl Compounds and Aldehydes

Takuya Hashimoto, Hisashi Miyamoto, Yuki Naganawa, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

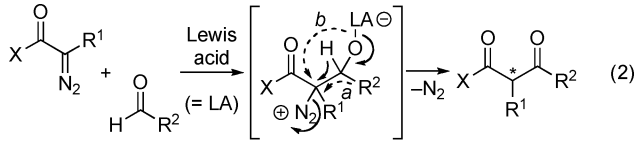
Received April 30, 2009; E-mail: maruoka@kuchem.kyoto-u.ac.jp

Asymmetric Claisen condensation of chiral imide enolates and acyl halides reported by Evans et al. in 1984 succeeded in shedding new light on the property of chiral nonracemic α-alkyl-β-keto imides, wherein condensation products could be isolated without epimerization due to the low kinetic acidity of the α-hydrogen (eq 1).[1] Although several landmark studies on its application in the preparation of complex polyol side chains underlined the synthetic value of this method,[2] the requirement of two activated reaction partners for the C−C bond formation would become a limitation in the cases where the reactions use substrates with labile functionalities.



(1)

Meanwhile, Lewis acid catalyzed reaction of alkyl diazoacetates with aldehydes, known as a Roskamp reaction, is a well established synthetic method which gives α-unsubstituted β-keto carbonyl compounds (R^1 = H, eq 2).[3] Conceptually, it is easily anticipated that its extension to the asymmetric reaction using α-alkyl-α-diazocarbonyl compounds (R^1 = alkyl) would offer an attractive alternative to the Evans's protocol. The whole process should be an asymmetric redox system, composed of the net oxidation of aldehydes, the reduction of the diazo compounds, and the transfer of the chiral information, thus successfully bypassing the use of labile higher oxidation state species, acyl halides.

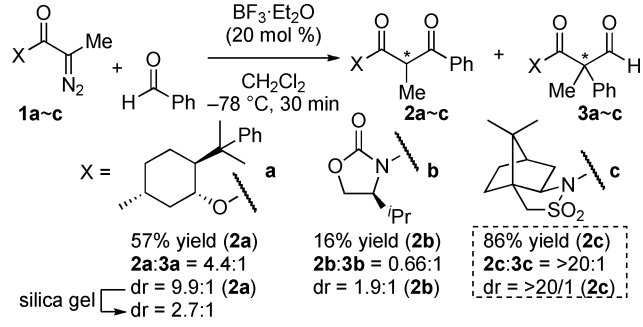


(2)

Although two decades have passed since the original report by Roskamp et al.,[3a] such a synthetic plan has not been materialized yet, even in the case of the racemic one,[4] and remained as a nontrivial task. The first issue that must be addressed is the chemoselective transfer of the hydride in preference to the R^2 group[5,7b] (eq 2, dashed arrow *a*) while suppressing the competitive epoxide formation (*b*),[3c,6] which is an intrinsic problem of the classic Roskamp reaction. Secondarily, a suitable stereocontroller is required which imparts its chiral information to the product with high efficiency. Finally, the so-generated stereogenic center must be kinetically stable enough to be isolated and utilized in further transformations without epimerization.

A clue to the solution appeared during the course of our continuous study on the synthetic use of α-substituted α-diazocarbonyl compounds in acid catalysis,[7] wherein the boron Lewis acid catalyzed reaction of (−)-phenylmenthyl α-methyl-α-diazoacetate **1a** and benzaldehyde afforded the corresponding β-keto ester **2a** with moderate chemoselectivity and promising diastereoselectivity (Scheme 1). However, the α-chiral center gradually epimerized during isolation as expected. In this context, two sets of commonly utilized chiral auxiliaries, (*S*)-4-isopropyl-2-oxazolidinone (**b**) and (−)-camphorsultam (**c**),[8,9] were then examined in the prospect of offering a high kinetic barrier against enolization, thus epimerization, of the product due to their large steric bulk.[1,10] Whereas the reaction with **1b** furnished the α-methyl-β-keto imide **2b** in disappointingly low yield and low selectivity concomitant with the formation of a considerable amount of the epoxide (not shown), use of (−)-camphorsultam-derived α-diazocarbonyl compound **1c** provided the α-methyl-β-keto imide **2c** exclusively, with remarkably high diastereoselectivity.[11,12] No erosion of the selectivity was observed during isolation.[13]

Scheme 1. Effect of Chiral Auxiliaries

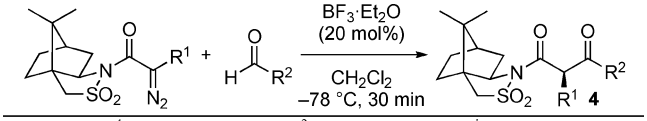


After finding an ideal solution, we commenced the detailed study of this unprecedented transformation. As for the substituent pattern of aromatic aldehydes, *o*-, *m*-, and *p*-substituents, as well as fused ring and the electron-withdrawing group, were all tolerated, providing the corresponding β-keto carbonyl compounds with uniformly high selectivity (entries 1−5). Although the use of *p*-anisaldehyde was found to be unproductive, this issue could be circumvented by introducing the acyloxy group instead of the methoxy group (entry 6). A broad range of aliphatic aldehydes could also be transformed into the desired product without difficulty (entries 7−15). Especially noteworthy is the compatibility with various functionalities such as alkenyl, β-alkoxy, and keto moieties (entries 10−13). Use of ethyl substituted diazocarbonyl compound **1d** was tolerated (entries 16−18). Following these basic studies, we moved our attention to the reaction of enantioenriched aldehydes having α-chirality as a specific task of this asymmetric redox C−C bond formation.[14] Although the use of a stoichiometric amount of Lewis acid was required, both α-alkyl and α-hydroxy aldehydes could be transformed into the expected compounds **4s** and **4t** in

10.1021/ja903500w CCC: $40.75

good yields (entries 19 and 21). Additionally, use of (+)-camphorsultam as a chiral auxiliary (**1c′**) allowed facile access to the diastereomeric products **4s′** and **4t′** (entries 20 and 22).

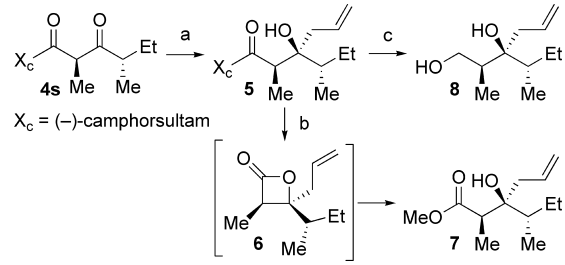
Table 1. Asymmetric Redox C−C Bond Formation[a]



entry	R^1		R^2	% yield[b]		dr[c]
1	Me	**1c**	2-tolyl	78	**4a**	>20/1
2	Me		3-tolyl	86	**4b**	>20/1
3	Me		4-tolyl	92	**4c**	>20/1
4	Me		2-Np	75	**4d**	>20/1
5	Me		4-ClC_6H_4	75	**4e**	>20/1
6[d]	Me		4-$PivOC_6H_4$	62	**4f**	>20/1
7	Me		Me	81	**4g**	>20/1
8	Me		Et	99	**4h**	>20/1
9	Me		CH_2CH_2Ph	81	**4i**	>20/1
10	Me		$CH_2CH_2CH{=}CH_2$	78	**4j**	>20/1
11	Me		$(CH_2)_4OBn$	76	**4k**	>20/1
12	Me		CH_2CH_2OTBS	81	**4l**	>20/1
13	Me		$CH_2CH_2COCH_3$	79	**4m**	>20/1
14	Me		^{i}Pr	82	**4n**	>20/1
15	Me		Cy	70	**4o**	>20/1
16	Et	**1d**	Ph	56	**4p**	>20/1
17	Et		Me	77	**4q**	>20/1
18	Et		Cy	74	**4r**	>20/1
19[d]	Me	**1c**	OHC, Et	95	**4s**	>20/1
20[d]	Me	**1c'**	Me	91	**4s'**	>20/1
21[d]	Me	**1c**	OHC, O, O	67	**4t**	>20/1
22[d]	Me	**1c'**		70	**4t'**	>20/1

[a] Reactions were performed with aldehyde (0.24 mmol) and **1** (0.20 mmol) in the presence of 20 mol % $BF_3 \cdot Et_2O$ (0.04 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Performed with 100 mol % $BF_3 \cdot Et_2O$.

Scheme 2. Diastereoselective Allylation and Nondestructive Removal of the Chiral Auxiliary[a]



[a] Conditions: (a) $TiCl_4$, $H_2C{=}CHCH_2SnBu_3$, CH_2Cl_2, −20 °C, 94%; (b) BuLi, MeOH, THF, 0 °C, 75%; (c) $LiAlH_4$, THF, 70%.

To expand the synthetic utility of this protocol, the diastereoselective functionalization of the β-carbonyl moiety of the product and nondestructive removal of the auxiliary were examined (Scheme 2). In this regard, implementation of $TiCl_4$-mediated allylation[15] of **4s** furnished the compound **5** as an essentially single isomer in 94% yield, thus offering a facile route to the enantioenriched compound with three contiguous stereocenters.[16] Whereas all of the trials to apply conventional methods using a combination of hydrogen peroxide and a base for the detachment of the auxiliary from **5** failed to afford any desired hydrolysis product,[17] use of lithium alkoxide was found to be promising.[18] Namely, treatment of **5** with lithium methoxide, generated *in situ* from methanol and butyllithium, provided the corresponding methyl ester **7** in 75% yield without epimerization. Noteworthy is the intermediacy of β-lactone **6** as confirmed by ^{1}H NMR and ESI-MS.[19] In an alternative way, reductive removal of the auxiliary of **5** by treatment with lithium aluminum hydride was also feasible, giving the diol **8** as a single stereoisomer in 70% yield.

In summary, we successfully renovated the classical Roskamp reaction to the unprecedented asymmetric redox C−C bond forming reaction. The key feature of our finding is the attachment of the camphorsultam as an auxiliary of the diazocarbonyl compounds which is critically important to not only impart its chirality but also determine the fate of the transient diazonium intermediate leading to the desired compounds chemoselectively.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from MEXT, Japan. T.H. thanks a Grant-in-Aid for Young Scientists (B). Y.N. thanks the Research Fellowships of JSPS for Young Scientists.

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

References

(1) (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.
(2) For selected examples, see: (a) Evans, D. A.; Polniaszek, R. P.; DeVries, K. M.; Guinn, D. E.; Mathre, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 7613. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (d) Evans, D. A.; Nagorny, P.; McRae, K. J.; Reynolds, D. J.; Sonntag, L.-S.; Vounatsos, F.; Xu, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 537. (e) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219. (f) Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257. (g) Lister, T.; Perkins, M. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 2560.
(3) (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. (b) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, Li. *J. Org. Chem.* **1990**, *55*, 5297. (c) López-Herrera, F. J.; Valpuesta-Fernández, M.; Garía-Claros, S. *Tetrahedron* **1990**, *46*, 7165.
(4) For very limited examples, see: (a) Jephcote, V. J.; Jowett, I. C.; John, D. I.; Edwards, P. D.; Luk, K.; Slawin, A. M.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2187. (b) Murata, H.; Ishitani, H.; Iwamoto, M. *Tetrahedron Lett.* **2008**, *49*, 4788.
(5) Use of arylaldehydes tends to give the aryl transfer products dominantly; see: (a) Mahmood, S. J.; Hossain, M. M. *J. Org. Chem.* **1998**, *63*, 3333. (b) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055.
(6) Cufini, M.; Epigano, F.; Marcotullio, M. C.; Rosati, O. *Eur. J. Org. Chem.* **2002**, 1562.
(7) (a) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434. (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *130*, 6614.
(8) Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 15016.
(9) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
(10) Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A.; Molins, E. *Tetrahedron* **1995**, *51*, 10795.
(11) Trace amounts of the epoxide and **3c** were detected by ^{1}H NMR, which could be separated by column chromatography on silica gel.
(12) For the determination of the relative configuration and the discussion on the stereochemical outcome, see Supporting Information.
(13) Treatment of **2c** with Et_3N in CH_2Cl_2 for 3 days led to the predominant formation of the opposite diastereomer (dr = 1:3).
(14) For recent examples of Roskamp reaction with α-chiral aldehydes, see: (a) Toueg, J.; Prunet, J. *Org. Lett.* **2008**, *10*, 45. (b) Schweizer, E.; Gaich, T.; Brecker, L.; Mulzer, J. *Synthesis* **2007**, 3807. (c) Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048.
(15) (a) Taniguchi, M.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 645. (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2001**, *42*, 6093.
(16) Zinc borohydride reduction and nucleophilic addition of MeMgI also proceeded with high diasteroselectivity. See Supporting Information.
(17) (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (b) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767. (c) Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 883.
(18) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(19) For the synthetic applications of β-lactones, see: Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403.

JA903500W