Directed Aldol Condensation

Susumu Saito and Hisashi Yamamoto*[a]

Abstract: The present article covers the progress in directed aldol condensation, which can be divided into three different classes. First, the mixed aldol condensation that uses general acids or bases under protic conditions. Second, stepwise enolization – aldolization sequence that utilizes various metal enolates under aprotic conditions. Third, a novel mixed aldol condensation that makes use of a bulky Lewis acid and a lithium amide under aprotic conditions. The scope and limitation of each of three aldol strategies is discussed.

Keywords: aldol reactions · C–C coupling · cross-coupling · enols

Conventional Mixed Aldol Condensation

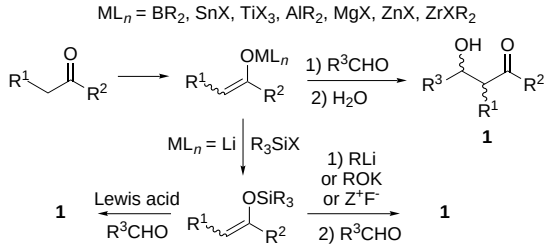
Crossed aldol condensation has traditionally been carried out by mixing two different carbonyl units under protic conditions with general acids or bases as the triggers of the reaction.[1] Development in this area has significantly expanded the scope of directed aldol condensation. Its synthetic potential has been particularly well-featured by those reactions that occurr in an intramolecular manner, such as Robinson annulation[2] and Dickemann condensation;[3] their analogous processes[4] have also been found quite attractive. Unfortunately, because of difficulties in directing the coupling intermolecularly, the conventional aldol condensatiton has serious disadvantages:

1) It gives low selectivities including stereo-, regio- and chemoselectivity involved in both enolization and aldolization processes.
2) It cannot necessarily suppress dehydration; this leads to α,β-unsaturated carbonyl compounds that can undergo further side reactions, such as Michael addition with enolates, to contaminate the reaction. This sometimes leads to further oligomerization and/or polymerization.
3) The method often suffers from proton transfer from a carbonyl compound to a reactive enolate; this results in multiple functionalization. As a consequence, a desirable cross-coupling is significantly retarded or completely suppressed.

[a] Prof. Dr. H. Yamamoto, Dr. S. Saito
Graduate School of Engineering, Nagoya University, CREST
Japan Science and Technology Cooperation (JST), Furo-cho
Chikusa, Nagoya 464-8603 (Japan)
Fax: (+81) 52-789-3222
E-Mail: j45988a@nucc.cc.nagoya-u.ac.jp

Stepwise Enolization – Aldolization Sequence

To circumvent the above limitations and to satisfy demands for control of aldol condensation, new methods with various metal enolates have been utilized for the directed aldol condensation. The general principle is represented in Scheme 1, and involves a stepwise enolization – aldolization sequence under aprotic conditions.



Scheme 1. Directed aldol condensation by a stepwise enolization – aldolization sequence.

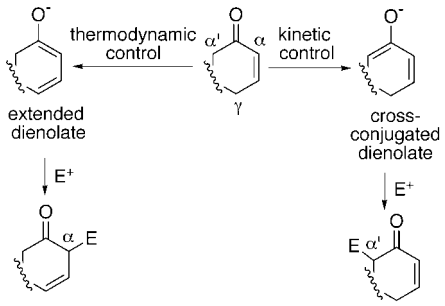
Such reactions are normally carried out by converting a carbonyl compound to serve as a nucleophile to an enolate. This nucleophile is then allowed to react with a second carbonyl compound. More details on these and closely related subjects have been discussed elsewhere.[5]

Aldol Condensation of α,β-Unsaturated Carbonyl Compounds

There has also been continuous interest on another important subject; this concerns the control of reactivity and selectivity of conjugated carbonyl compounds as precursors of enolates. Directed aldol condensation involving conjugated carbonyl compounds that offer multiple sites for enolization and subsequent alkylation (α vs. α' vs. γ) is a challenging problem yet to be solved. It is generally accepted that under kinetic

  0947-6539/99/0507-1959 $ 17.50+.50/0

control cross-conjugated dienolates are the dominant species, whereas extended dienolates are produced preferentially under thermodynamic conditions, such as when MO*t*Bu or MH (M = Na, K) is used (Scheme 2).[6] Thus, the cross-conjugated dienolates can be generated by treatment with



Scheme 2. Two possible dienolates generated from an α,β-unsaturated ketone.

strong bases such as LDA (LDA = lithium diisopropylamide) to afford predominantly α'-alkylation with a given electrophile. In contrast, the extended dienolates are invariably prone to α-functionalization.

These chemical events were attributed to the more pronounced electronic distribution at the α-carbon atom than at the γ-carbon atom;[7] the γ-aldolization hence has little precedence except in those reactions that proceed intramolecularly.[8] Despite the fact that the aldol process indicated in Scheme 1 is potentially useful, it does not offer a way around this problem. For example, although the extended dienolates with zinc[9] or copper[10] as the counter metal exhibit better γ selectivities than those with lithium, the regiochemical potential is usually disappointing. In some instances, arylsulfonyl,[11] enamino,[12] or alkoxy[13] directing groups have been incorporated into a conjugated carbonyl substrate to achieve anomalous γ functionalization (Figure 1).

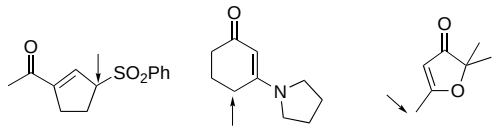
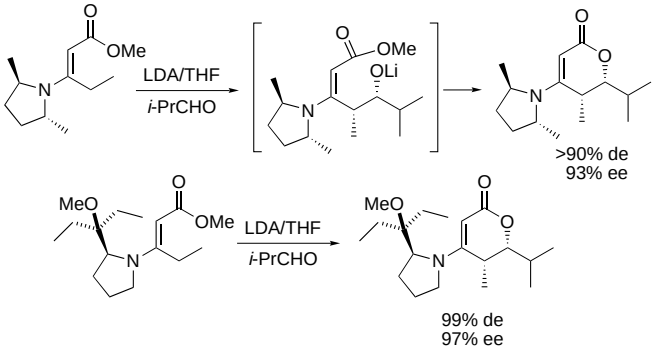


Figure 1. Specific substrates for directed γ alkylation (→=alkylation site).

Abstract in Japanese:

本概説は、立体、位置、官能基選択性を指向した、２種の異なるカルボニル化合物間の交差アルドール反応（Directed Aldol Reaction＝選択性指向型アルドール反応）を３種類の合成戦略に分類して記述する。古くは、２種のカルボニル化合物の混合系に、一般酸・塩基を作用させてアルドール反応を行っていた。この手法は分子内アルドール反応には有効だが、分子間反応では適用できるカルボニル基質が限定される。そこで、非プロトン性条件下でメタルエノラートを発生させた後、第２のカルボニル化合物を反応させる手法がその後一般的に用いられ、最近特に、不斉アルドール反応の開発に大きく貢献している。しかしこの手法も、α,β－不飽和カルボニル化合物のγ－選択的アルドール反応には無力である。この問題に対して最近、アルミニウム　トリス(2,6－ジフェルフェノキシド)(ATPH)とリチウムアミドを用いる手法が開発された。このアルドール法は、カルボニル化合物の代わりに、嵩高いルイス酸－カルボニル複合体を用いることにより、広い基質一般性とγ－選択性を示す。

More recently, asymmetric γ aldolization of an α,β-unsaturated ester bound with a chiral pyrrolidine auxiliary at the β-carbon atom was reported.[14] *Syn* lactones were formed with high diastereo- and enantiomeric excess (*de*% and *ee*%, respectively) on reaction with *i*PrCHO (Scheme 3).



Scheme 3. γ Aldolization with vinylogous urethane.

Presumably all of these ingenious methodologies basically utilized the hypothesis that product stability will be more significant if a late transition state can be involved under conditions in which the degree of dienolate stabilization is increased.[11] However, a lack of substrate generality in the conventional γ functionalizations has left much to be desired.

Directed Mixed Aldol Condensation between Two Different Carbonyl Compounds.

Other efforts have been focused on a conceptually new, directed mixed aldol condensation, which was recently developed by our group.[15] Since the electronic and thermodynamic factors are principally examined in the conventional mixed aldol condensation, the incorporation of steric factors into the reaction becomes of fundamental importance. One alternative is to form complexes of two different carbonyl compounds with a bulky Lewis acid (Figure 2). Lewis acids

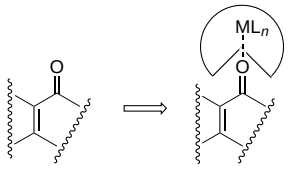


Figure 2. The use of the bulky Lewis acid/carbonyl complex in place of a carbonyl compound itself.

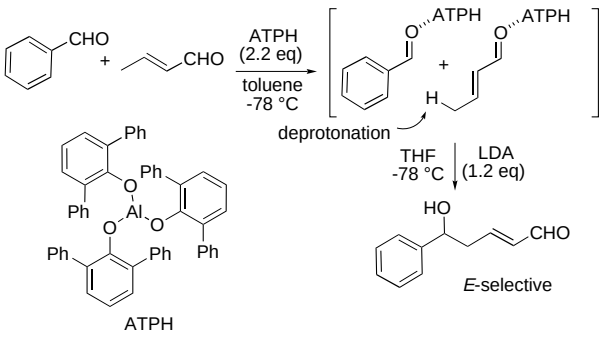
generally form a relatively stable 1:1 complexes with various carbonyl compounds under aprotic conditions with similar effectiveness.[16] We first hypothesized that a steric environment applied in the Lewis acid–base complexation would:

1) Kinetically adjust site-selective deprotonation with a strong base in a system in which two different carbonyl compounds, which offer multiple sites for enolization, coexist.

0947-6539/99/0507-1960 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7

2) Kinetically stabilize the resulting bulky enolates by retarding the rate of proton transfer or other undesirable side reactions.

A second carbonyl compound that serves as an electrophile can be activated electronically (but sterically deactivated) by complexation with a bulky Lewis acid. This activation would allow rapid in situ capture of an enolate intermediate generated on deprotonation. Aluminum tris(2,6-diphenylphenoxide) [ATPH][17] was the reagent of choice, since it could effectively encapsulate a number of α,β-unsaturated carbonyl compounds.[18] Our initial effort concerned a basic system that has a single site for deprotonation: the reaction between crotonaldehyde and benzaldehyde, both of which were precomplexed with ATPH. With LDA as a deprotonating agent, both deprotonation and subsequent aldolization proceeded exclusively at the γ-carbon of crotonaldehyde (Scheme 4).



Scheme 4. Mixed aldol condensation between crotonaldehyde and benzaldehyde with ATPH and LDA.

Fortunately, such a solution proved quite general and contributed to resolving the basic dilemma of unfavorable electron distributions in extended dienolates. For example, crossed reactions between aldehyde and conjugated aldehyde,[15] conjugated ketone,[15] and conjugated ester,[19] and conjugated ketone and conjugated ester proved successful under similar reaction conditions affording γ aldolization (Figure 3). The characteristics of this transformation warrant explanation:

1) Neither the α-carbon atom of aromatic ketones nor the α'-carbon atom of α,β-unsaturated ketones was the directed site for deprotonation (control of the deprotonation site).
2) Thus, deprotonation and the ensuing alkylation were quite regioselective at a benzylic or allylic terminus (control of the alkylation site). Of particular note is the regioselective aldolization of highly conjugated esters that have several possible sites for functionalization.
3) High E selectivity with respect to the γ aldolization (contol of the stereoselectivity).

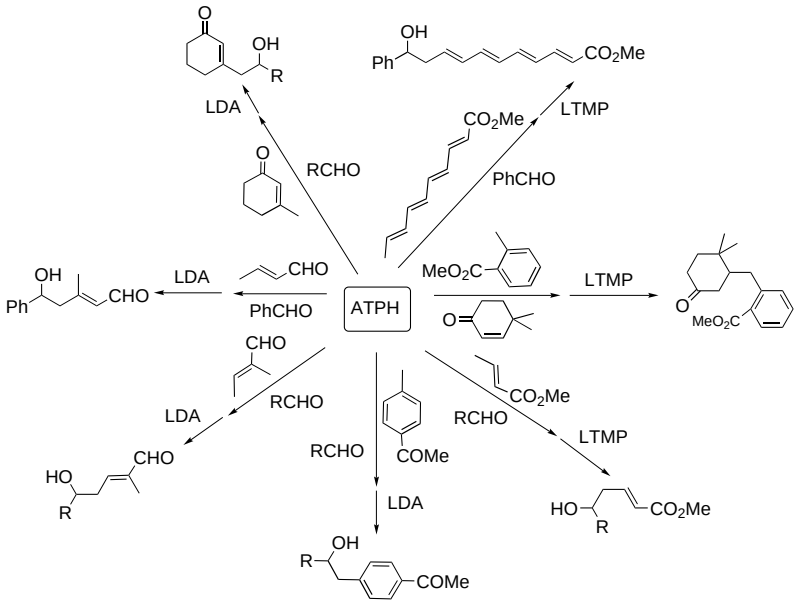


Figure 3. Directed aldol condensation with ATPH.

The important prospects of the stereoselectivity of the reaction at an allylic terminus that comprises methylene or methine is now under scrutiny.

Closing Remarks

A starting point of the search for directed aldol condensation was based on two different carbonyl compounds being mixed together prior to treatment with a deprotonating agent under protic conditions. Owing to substantial drawbacks encountered in this process, a sequential enolization–aldolization strategy was established under aprotic conditions to determine synthetic versatility in controlling crossed aldolization. Since this second approach proved unsuccessful for directing the γ aldolization of α,β-unsaturated carbonyl compounds, a novel variant for directed, mixed crossed aldol condensation was explored with great success by the use of a combination of ATPH and a strong base of LDA or LTMP (LTMP = lithium 2,2,6,6-tetramethylpiperidide). The directed aldol condensation described here is one of the possibilities available. Hence, the search for a new and practical directed aldol condensation remains a challenge in selective organic synthesis.

[1] a) A. T. Nielsen, in *Organic Reactions* (Eds.: A. C. Cope, R. Adams, A. H. Blatt, V. Boekelheide, T. I. Cairns, D. J. Cram, H. O. House), Wiley, New York, **1968**, pp. 1; b) O. H. House, in *Modern Synthetic Reactions* (Ed.: R. Breslow), W. A. Benjamin, Menlo Park, **1972**, chapter 10, pp. 629; c) C. H. Heathcock, in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 133.
[2] E. C. du Feu, F. J. McQuilline, R. Robinson, *J. Chem. Soc.* **1937**, 53.

[3] W. Dieckmann, *Ber.* **1894**, *27*, 102.
[4] a) G. I. Fujimoto, *J. Am. Chem. Soc.* **1951**, *73*, 1856; b) B. Belleau, *J. Am. Chem. Soc.* **1951**, *73*, 5441; c) M. E. Jung, *Tetrahedron* **1976**, *32*, 3; d) R. E. Gawley, *Synthesis* **1976**, 777.
[5] a) T. Mukaiyama, in *Organic Reaction, Vol. 28* (Eds.: G. A. Boswell, Jr., R. F. Hirshmann, S. Danishefsky, A. S. Kende, H. W. Gschwend, L. A. Paquette, R. F. Heck, G. H. Posner, B. M. Trost, B. Weinstein), Wiley, New York, **1982**, pp. 203; b) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, 9, 357; c) H. Gröger, E. M. Vogel, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137.
[6] D. Caine, in *Comprehensive Organic Synthesis, Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 21.
[7] R. Gompper, H-U. Wagner, *Angew. Chem.* **1976**, *88*, 389; *Angew. Chem. Int. Ed. Engl*. **1976**, *15*, 321.
[8] D. Caine, in *Carbon–Carbon Bond Formation*, (Ed.: R. L. Augustine), Dekker, New York, **1979**, pp. 85.
[9] a) I. Fleming, J. Goldhill, I. Paterson, *Tetrahedron Lett*. **1979**, 3209; b) I. Fleming, T. V. Lee, *Tetrahedron Lett*. **1981**, *22*, 705; c) T. Hudlicky, M. G. Natchus, L. D. Kwart, B. L. Colwell, *J. Org. Chem*. **1985**, *50*, 4300.
[10] a) J. A. Katzenellenbogen, A. L. Crumrine, *J. Am. Chem. Soc.* **1976**, *98*, 4925; b) E. Wenkert, T. E. Goodwin, B. C. Ranu, *J. Org. Chem*. **1977**, *42*, 2137; c) P. M. Savu, J. A. Katzenellenbogen, *J. Org. Chem*. **1981**, *46*, 239; d) M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, V. Snieckus, *J. Org. Chem*. **1981**, *46*, 2029.
[11] a) P. T. Lansbury, R. W. Erwin, D. A. Jeffrey, *J. Am. Chem. Soc*. **1980**, *102*, 1602; b) P. T. Lansbury, G. E. Bebernitz, S. C. Maynard, C. J. Spagnuolo, *Tetrahedron Lett*. **1985**, *26*, 169.
[12] a) M. Yoshimoto, N. Ishida, T. Hiraoka, *Tetrahedron Lett*. **1973**, 39; b) T. A. Bryson, R. B. Gammill, *Tetrahedron Lett*. **1974**, 3963.
[13] a) A. B. Smith, III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough, Jr., P. M. Wovkulich, *J. Am.Chem. Soc*. **1981**, *103*, 1501; b) M. Koreeda, Y. P. Liang Chen, *Tetrahedron Lett*. **1981**, *22*, 15; c) M. Koreeda, S. G. Mislankar, *J. Am. Chem. Soc*. **1983**, *105*, 7203.
[14] a) R. H. Schlessinger, E. J. Iwanowicz, J. P. Springer, *J. Org. Chem*. **1986**, *51*, 3070; b) R. H. Schlessinger, T.-J. Li, D. J. Von Langen, *J. Org. Chem*. **1996**, *61*, 3226.
[15] S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.
[16] a) S. L. Schreiber, in *Comprehensive Organic Synthesis*, *Vol. l* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 283; b) S. Shambayati, W. E. Crowe, S. L. Schreiber, *Angew. Chem.* **1990**, *102*, 273; *Angew. Chem. Int. Ed. Engl*. **1990**, *29*, 256.
[17] S. Saito, H. Yamamoto, *Chem. Commun*. **1997**, 1585
[18] K. Maruoka, H. Imoto, S. Saito, H. Yamamoto, *J. Am. Chem. Soc*. **1994**, *116*, 4131.
[19] S. Saito, M. Shiozawa, H. Yamamoto, *Angew. Chem.*, in press.

Received: December 28, 1998 [C1514]

0947-6539/99/0507-1962 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 7