

Oxidative Enolate Couplings in Complex Molecule Synthesis

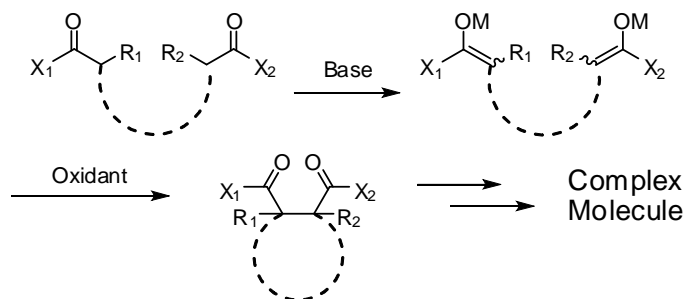
Connor L. Martin

Department of Chemistry, 1102 Natural Sciences II, University of California,
Irvine, California 92697-2025

clmartin@uci.edu

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



Oxidative enolate couplings are powerful yet underutilized carbon–carbon bond-forming reactions. Several complex molecule syntheses that have utilized this transformation are described. These syntheses demonstrate how strategic application of the oxidative enolate coupling can simplify complex molecule construction.

The oxidative coupling of carbonyl enolates^{1,2,3} has proven to be a valuable tool for the synthesis of 2,3-disubstituted-1,4-dicarbonyls, which are common fragments in natural products⁴ and medicinal compounds.⁵ This transformation results in the formation of a bond between sp^3 -hybridized carbons and requires no prefunctionalization of the coupling partners. Few methods are available to construct 2,3-disubstituted-1,4-

dicarbonyls in such a direct manner.⁶ Several elegant syntheses have utilized this reaction and demonstrated its power to simplify complex molecule construction.

Three general mechanisms for the oxidative coupling of enolates have been proposed. A mechanism that involves coupling of α -carbonyl radicals is shown below (Scheme 1, eq 1). In this generic iodine-promoted coupling, enolate **1** undergoes oxidation with iodine by a single electron transfer (SET) process to form α -iodocarbonyl **3**.⁷ This α -iodocarbonyl undergoes another SET process with enolate **1** to generate a pair of radicals coordinated to a metal cation **4**. These radicals combine to give the 1,4-dicarbonyl product **2**.⁸ A mechanism involving coupling of metal-bridged radicals has been proposed for $TiCl_4$ -promoted couplings, as well.⁹

¹ For the first report, see: Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76–78.

² For early development of this reaction, see: (a) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605–4606. (b) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912–2914. (c) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487–1493. (d) Frazier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408–5411.

³ For a review of stereoselective oxidative enolate couplings, see: Csáký, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313–320.

⁴ Use of modern search engines reveals that over 1000 known natural products possess a 2,3-disubstituted-1,4-dicarbonyl fragment.

⁵ (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735–2776. (b) Fujisawa, T.; Igeta, K.; Otake, S.; Morita, Y.; Yasuda, J.; Morikawa, T. *Bioorg. Med. Chem.* **2002**, *10*, 2569–2581.

⁶ The Stetter reaction is another direct but complementary method.

⁷ Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745–3752.

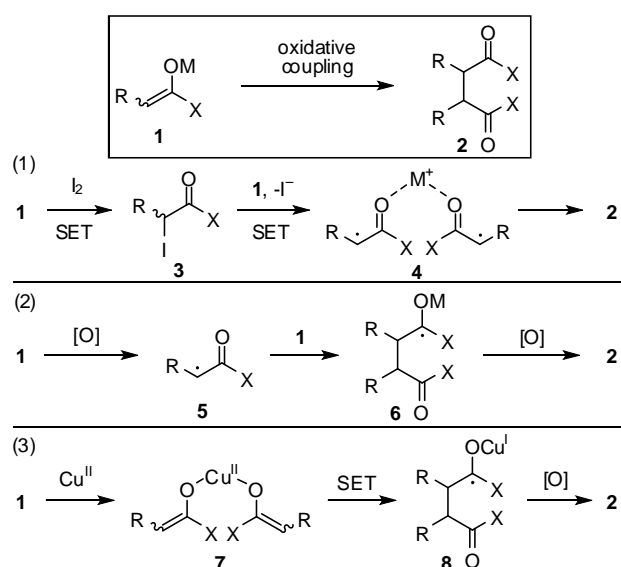
⁸ (a) Langer, T.; Illich, M.; Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409–4412. (b) Langer, T.; Illich, M.; Helmchen, G. *Synlett* **1996**, 1137–1139.

⁹ Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697–2708.

A mechanism of oxidative enolate couplings that involves addition of an α -carbonyl radical to an enolate has also been proposed (Scheme 1, eq 2). In this mechanism, enolate **1** undergoes single electron oxidation to give α -carbonyl radical **5**. This electrophilic radical reacts with enolate **1** to give ketyl radical **6**. Ketyl radical **6** is oxidized further to give **2**. This mechanism appears to be general for Fe(III)-promoted couplings¹⁰ and operates in iodine-mediated couplings of enolates derived from glycine ester derivatives.¹¹

Another distinct mechanism operates in Cu(II)-promoted enolate couplings (Scheme 1, eq 3). In this mechanism, two enolates undergo transmetalation with a single Cu(II) ion to form Cu(II)-enolate complex **7**. A C–C bond-forming SET process then occurs to generate ketyl radical **8**. This ketyl radical is oxidized further to give **2**.¹⁰

Scheme 1. Mechanisms of Oxidative Enolate Couplings



The intermolecular oxidative enolate coupling has proven to be a valuable tool for the construction of dibenzylbutyrolactone lignans **9** (Scheme 2). This large class of bioactive natural products contains both symmetrically ($R_1 = R_2$) and unsymmetrically ($R_1 \neq R_2$) substituted members.¹² Retrosynthetic analysis of **9** reveals that lactone ring opening and simple oxidation state adjustment unveils 2,3-dibenzyl succinate **10**, which could arise from the oxidative coupling of enolates **11a** and **11b**. Hence, oxidative enolate coupling would provide a convergent and expedient route to these lignans.

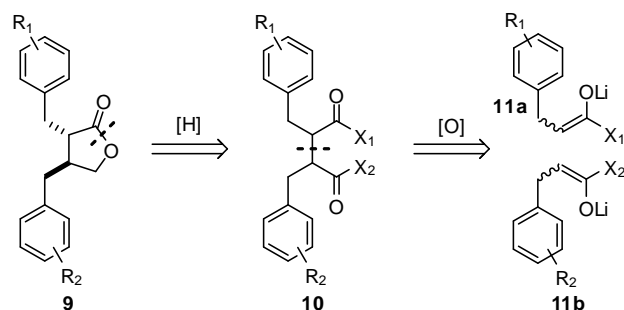
¹⁰ DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.

¹¹ Alvarez-Ibarra, C.; Csáky, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478–2482.

¹² Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75–96, and references therein.

The first oxidative enolate coupling-based approach to a dibenzylbutyrolactone lignan was reported in 1986 by Belletire (Scheme 3, eq 1).¹³ Generation of the lithium dianion of dihydrocinnamic acid **12** and treatment with iodine delivered dimer **13** as a mixture of stereoisomers in 85% yield. Dimer **13** was elaborated to (\pm)-enterolactone (**14**) in three additional steps. This approach has been applied to the synthesis of several racemic, symmetrically substituted dibenzylbutyrolactone lignans.¹⁴

Scheme 2. Dibenzylbutyrolactone Lignan Retrosynthetic Analysis



Prior to the mid 1990s, the strategy delineated above was limited in its application to the synthesis of racemates. However, in 1993 Porter reported the synthesis of enantioenriched succinamides by oxidative dimerization of enolates derived from chiral, enantioenriched *N*-acyl oxazolidines.¹⁵ Kise reported the first asymmetric synthesis of a dibenzylbutyrolactone lignan that utilized this methodology (Scheme 3, eq 2).¹⁶ A TiCl_4 -promoted dimerization of enolates derived from chiral *N*-acyl oxazolidinone **15** gave 2,3-disubstituted succinamide **16** with good simple diastereoselectivity ($R,R:R,S = 85:15$) and excellent induced diastereoselectivity (no *S,S* isomer was detected). In three additional steps, (–)-hinokinin (**17**) was prepared. Several symmetrically substituted dibenzylbutyrolactone and dibenzylbutanediol lignans have been synthesized enantioselectively in this way.^{8b,17}

Until recently, the scope of intermolecular oxidative enolate couplings had been primarily limited to dimerizations.¹⁸ Thus, unsymmetrically substituted dibenzylbutyrolactone lignans could not be synthesized using an oxidative enolate coupling-based strategy. In 2006, Baran showed that coupling of enolates derived from different functional groups was possible. Ketone or

¹³ Belletire, J. L.; Fremont, S. L. *Tetrahedron Lett.* **1986**, *27*, 127–130.

¹⁴ (a) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549–2555.

(b) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1988**, *53*, 4724–4729.

¹⁵ Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457–4460.

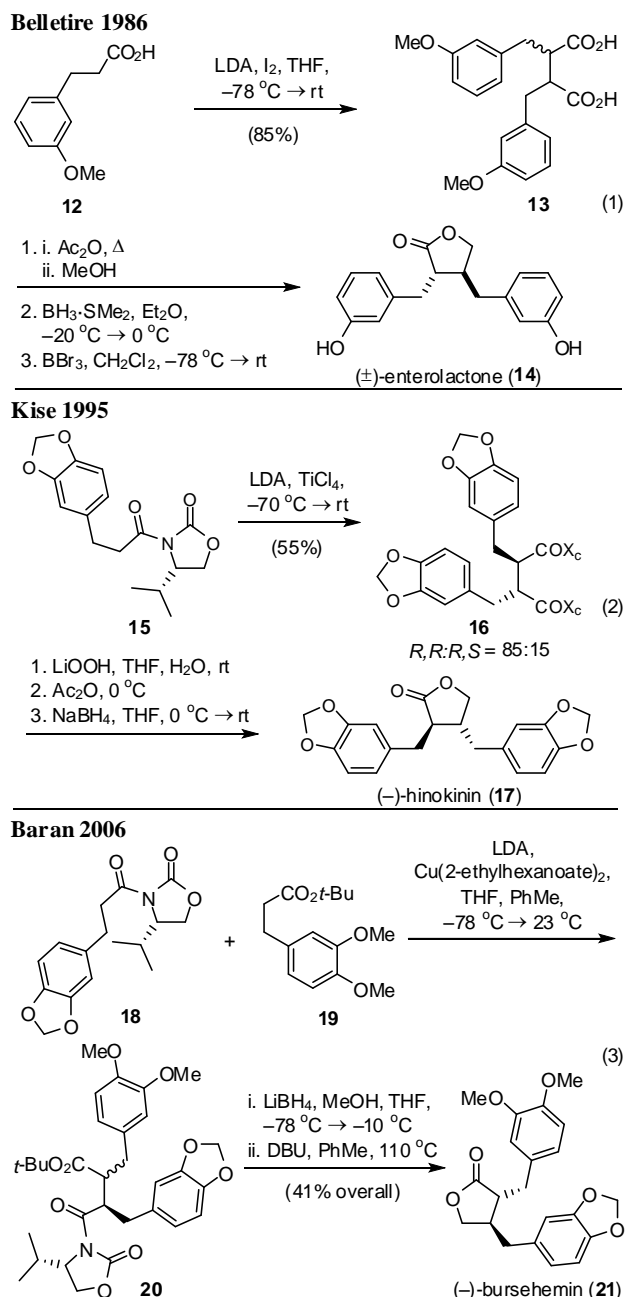
¹⁶ Kise, N.; Tokioka, K.; Aoyama, Y. *J. Org. Chem.* **1995**, *60*, 1100–1101.

¹⁷ Kise, N.; Ueda, T.; Kumada, K.; Terao, Y.; Ueda, N. *J. Org. Chem.* **2000**, *65*, 464–468.

¹⁸ For some exceptions, see reference 2b.

ester enolates could be coupled to *N*-acyl oxazolidinone enolates with the use of Fe(III) or Cu(II) oxidants to provide heterocoupled products in 51–73% yield.¹⁹ This method was applied to the synthesis of (–)-bursehemin (**21**), a dibenzylbutyrolactone bearing two different benzyl substituents (Scheme 3, eq 3). The enolates derived from *N*-acyl oxazolidinone **18** and dihydrocinnamic ester **19** were coupled with the use of Cu(II) ethylhexanoate to give 2,3-disubstituted succinic acid derivative **20** as a 1.6:1 mixture of diastereomers. The crude product mixture was submitted to chemoselective reduction with LiBH₄ followed by lactone formation and epimerization

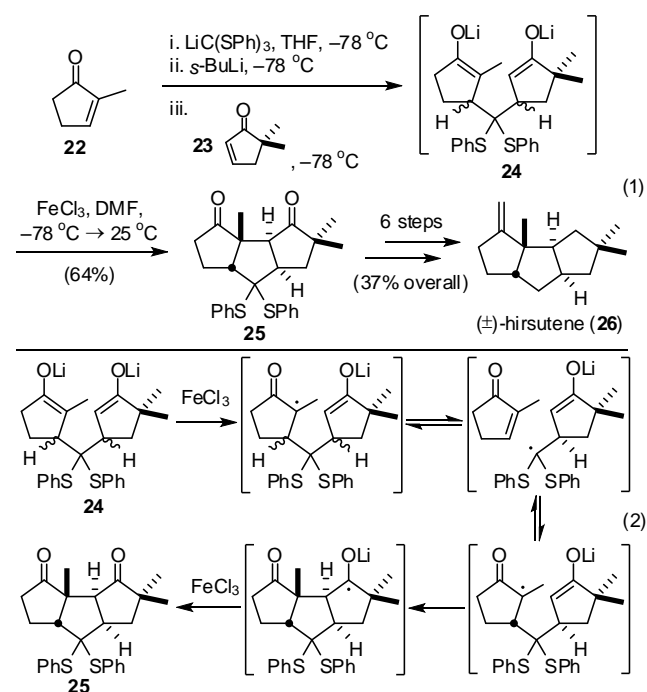
Scheme 3. Incremental Advances in Lignan Syntheses



of the *cis* diastereomer with DBU to deliver **21** in 41% overall yield.¹⁹ Whereas many other general approaches to enantioenriched dibenzylbutyrolactone lignans have been reported,²⁰ Baran's oxidative enolate coupling approach represents the most concise entry to these natural products.

Examples of intramolecular oxidative enolate couplings used to form three-, four-, five- and six-membered rings were reported throughout the late 1970s and 1980s.²¹ However, the first example of this type of coupling's use in a natural product total synthesis was not reported until 1992 when Cohen disclosed the total synthesis of (±)-hirsutene (**26**) (Scheme 4, eq 1).²² In this synthesis, an

Scheme 4. Cohen's Hirsutene Synthesis



¹⁹ Baran, P. S.; Demartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086.

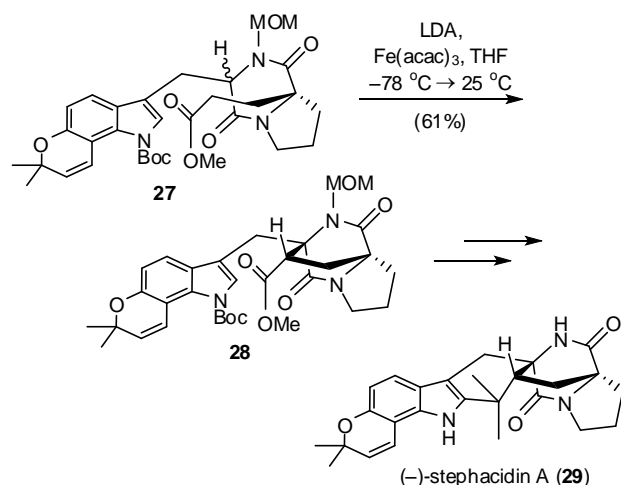
²⁰ (a) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *43*, 4340–4349. (b) Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N.; Hosoya, K. *Tetrahedron Lett.* **1990**, *31*, 7623–7626. (c) Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717–5723. (d) Honda, T.; Kimura, N.; Sato, S.; Kato, D.; Tominga, H. *J. Chem. Soc., Perkin Trans I* **1994**, 1043–1046. (e) Bode, J. W.; Doyle, M. P.; Prottopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146–9155. (f) Enders, D.; Lausberg, V.; Signore, G. D.; Berner, O. M. *Synthesis* **2002**, 515–522. (g) Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmiza, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 6922–6930. (h) Bennett, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun.* **2004**, 1392–1393.

²¹ (a) Kobayashi, Y.; Taguchi, T.; Morikawa, T. *Tetrahedron Lett.* **1978**, *19*, 3555–3556. (b) Chung, S. K.; Dunn, L. B., Jr. *J. Org. Chem.* **1983**, *48*, 1125–1127. (c) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462–3464. (d) Kawabata, T.; Sumi, K.; Hiyama, T. *J. Am. Chem. Soc.* **1989**, *111*, 6843–6845.

²² (a) Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1968–1969. (b) Cohen, T.; McNamara, K.; Kuzemko, M. A.; Ramig, K.; Landi, J. J., Jr.; Dong, Y. *Tetrahedron* **1993**, *49*, 7931–7942.

intramolecular coupling of ketone enolates was incorporated into a tandem process, which rapidly built the triquinane core of the natural product. Tris(triphenylthio)methyl lithium was added to enone **22**, followed by sequential sulfur-lithium exchange and addition of the resulting bis(diphenylthio)alkyllithium fragment to enone **23** to generate dienolate **24**. Oxidative coupling of the tethered ketone enolates was promoted by an Fe(III) oxidant to deliver tricyclic diketone **25**, which possesses an all-carbon quaternary stereocenter, as a single diastereomer in 64% yield. The stereochemical outcome of the reaction can be rationalized by considering radical isomerization pathways of the type shown in Scheme 4 (eq 2). The synthesis was completed in six additional steps. Cohen's hirsutene synthesis ranks among the most efficient reported. This fact is remarkable when one considers that over 50 reports describing the synthesis of hirsutene have been published.

Scheme 5. Baran's Stephacidin Synthesis



In all of the examples described above, early-stage oxidative enolate couplings have been incorporated into syntheses. These examples might suggest a limitation of this reaction in complex molecule synthesis. However, in 2005 Baran reported the enantioselective total synthesis of (-)-stephacidin A (**29**), which utilized a late-stage intramolecular oxidative coupling (Scheme 5).²³ Treatment of the ester and amide enolates derived from diketopiperazine **27** with an Fe(III) oxidant gave ester **28** as a single diastereomer in 61% yield.²⁴ This impressive transformation set two of the three stereocenters of **29** in the process of forging the bicyclo[2.2.2]diazaoctane core

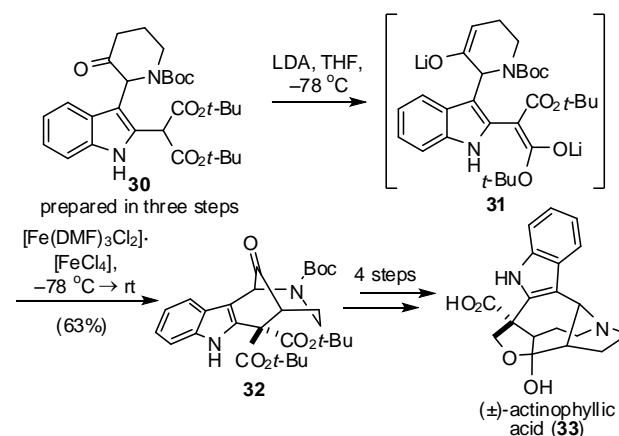
²³ (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609. (b) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

²⁴ It is proposed that the high level of diastereoselectivity is due to coordination of the carbonyl of an α -radical intermediate to the metal ion of its enolate coupling partner.

of the natural product and eventually provided access to stephacidin B and avrainvillamide.²⁵

The utility of oxidative enolate couplings in natural product synthesis was demonstrated again in 2008 when Overman reported the first total synthesis of (\pm)-actinophyllic acid (**33**) (Scheme 6).²⁶ Ketone and malonic ester enolates were generated regioselectively from indole **30** to give dienolate **31**, which was treated with an Fe(III) oxidant to deliver tetracyclic ketone **32** in 63% yield. It is noteworthy that this oxidation proceeded in the presence of an unprotected indole fragment and that this transformation was the first example of oxidative heterocoupling of ketone and malonic ester enolates. From a strategic standpoint, this oxidative coupling was highly simplifying, as it provided access to **32** from a simple starting material. In four additional steps, **32** was elaborated to actinophyllic acid (**33**).

Scheme 6. Overman's Actinophyllic Acid Synthesis



This short review is nearly comprehensive in its coverage of oxidative enolate coupling reactions used in complex molecule syntheses. Though they are few, syntheses that have incorporated this transformation span several natural product classes including lignans, terpenes and indole alkaloids. In the context of lignan natural products, an oxidative enolate coupling-based strategy proved to be convergent, efficient and, eventually, general. The oxidative enolate couplings used in the (\pm)-hirsutene (**26**), (-)-stephacidin A (**29**) and (\pm)-actinophyllic acid (**33**) syntheses were highly simplifying and led to remarkably concise syntheses. It is anticipated that this powerful transformation will undergo further development and find wider application in complex molecule synthesis.

²⁵ Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892–3895.

²⁶ Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569.