Oxidative C–C Coupling

DOI: 10.1002/anie.200603024

Intermolecular Oxidative Enolate Heterocoupling**

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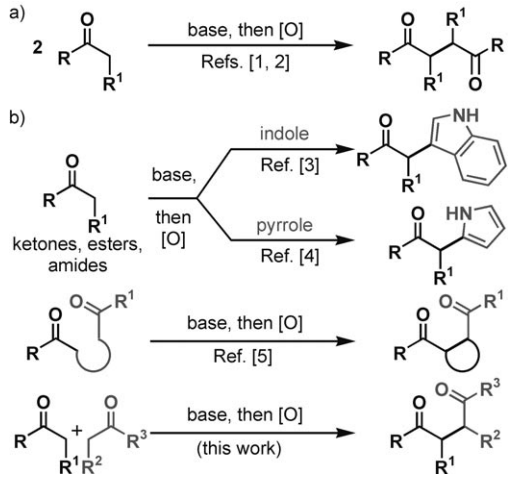
Oxidative dimerization of enolates has been known since 1935[1] and was studied further by Saegusa, Mislow, and others in the 1970s (Scheme 1 a).[2] Formally, this transformation



Scheme 1. Oxidative C–C bond formation via enolates.

accomplishes the direct union of two identical sp^3-hybridized carbon atoms with no substrate prefunctionalization by exploiting their innate oxidation state. The analogous process using two different types of coupling partners has remained unexplored.[2d,e] In 2004, we presented a method for the direct coupling of NH-containing heterocycles to various carbonyl compounds through enolate heterocoupling (Scheme 1 b).[3,4] It was later shown that two *different* types of carbonyl species can be coupled in an intramolecular sense (ester-amide).[5]

Herein, this approach is explored in an intermolecular setting with application to the enantioselective synthesis of medicinally relevant compounds[6] and the anticancer natural product (−)-bursehernin (**1**).

The intermolecular heterocoupling of two enolates is a particularly challenging chemical transformation given the potential background reactions that can occur. These include, but are not limited to, α-hydroxylation of each monomer, dehydrogenation of either the monomers or the newly forged C–C bond, intermolecular cross- and homo-Dieckmann/aldol condensations, and oxidative homodimerization of either coupling partner. In fact, if the intermolecular cross- and homocoupling processes alone were governed by only statistics, the heterocoupling of an equimolar mixture of two enolate species would take place with a maximum of 50 % conversion. Cross-coupling of two different ketones has been reported, but required a large excess of one partner (3–3.5 equiv, along with additional base and oxidant).[2d,e] In principle, intermolecular heterocoupling of enolates could be synthetically pragmatic if sufficient differences existed in their respective oxidation potentials and/or relative rates of homodimerization, such that equimolar ratios of the starting materials can be used. As depicted in Table 1, the cross-couplings of imides with ketones (entries 1–8), esters (entries 9–11), and lactones (entry 12) are now possible. Lactams such as oxindoles were also found to be amenable to cross-coupling (entries 13–17). In nearly all cases, equimolar ratios of the carbonyl species are employed and synthetically useful yields (greater than the 50 % statistical limit) were obtained, even when performed on a gram scale (entries 3 and 11, Table 1). In all cases, the remaining material was largely recovered monomer, although minor amounts of imide/oxindole homodimer were produced in entries 9–17. Notably, in entries 9–12 (Table 1), products with stereochemistry analogous to those of Evans' model for the diastereoselective alkylation of *N*-acyl oxazolidinones were produced,[7] whereas in entries 1–8, the adducts obtained were epimeric at this carbon center. This empirical observation is not fully understood at this time, and the mechanistic basis for this finding is under investigation. Although the diastereoselectivity is modest in most cases, this method offers a clear strategic benefit when forging such C–C bonds and thus provides molecules that would be difficult to access directly through use of current methods. Moreover, products may be amenable to thermodynamic equilibration, as in the following application to natural product synthesis.

(−)-Bursehernin (**1**) is a member of a large class of naturally occurring bioactive γ-butyrolactone lignans.[8] Inspection of **1** reveals that oxidative coupling of two dihydrocinnamic acid derivatives would be an intuitive and expedient route to construct these lignan lactones (Scheme 2 a). Indeed, symmetric dibenzyl lignan lactones ($R^1 = R^2$) have been synthesized in this manner.[9] Prior to this work, however, methodology necessary to accomplish intermolecular heterocoupling for the synthesis of unsymmetrical dibenzyl lignans was unavailable. Using the simple method described above, the oxidative union of oxazolidinone **2** and dihydrocinnamic ester **3** was accomplished (d.r. = 1.6:1). The crude mixture was submitted directly to chemoselective

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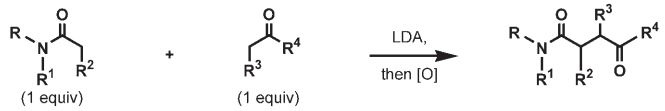
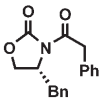
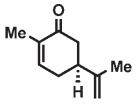
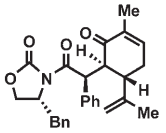
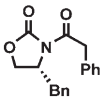
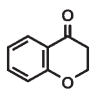
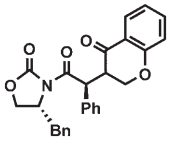
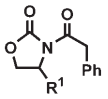
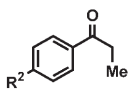
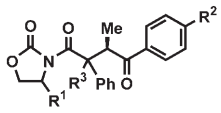
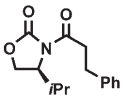
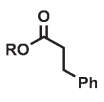
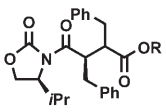
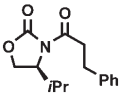
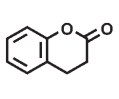
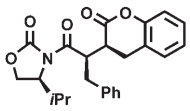
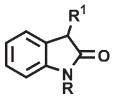
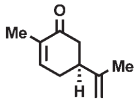
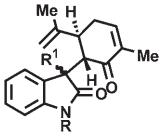
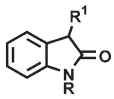
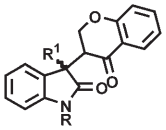
[**] We thank Dr. D. H. Huang and Dr. L. Pasternak for NMR spectroscopic assistance, and Dr. G. Suizdak and Dr. R. Chadha for mass spectrometric and X-ray crystallographic assistance, respectively. We are grateful to Professor M. G. Finn for the use of his cyclic voltammetry apparatus and Tomás Llamas for early contributions to the project. Financial support for this work was provided by The Scripps Research Institute, Amgen, Bristol-Myers Squibb, DuPont, Eli Lilly, GlaxoSmithKline, Roche, the Searle Scholarship Fund, and the NIH/NIGMS (GM071498).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Intermolecular oxidative enolate couplings.[a]

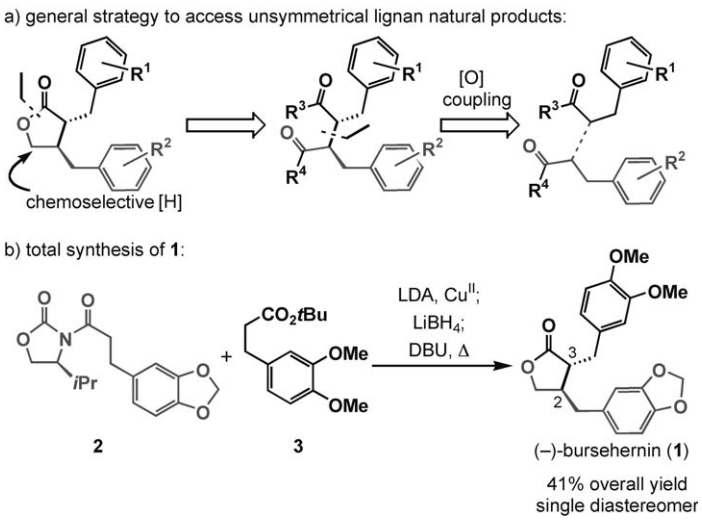


Entry	Carbonyl compound 1	Carbonyl compound 2	Oxidant	Product	Yield [%][b] (d.r.)[c]
1			Fe^{III}		52 (2.7:1) (X-ray)
2			Fe^{III}		59 (2.8:1)
3					60 (2.6:1)[d]
			Fe^{III}		
4	R^1 = α-Bn	R^2 = H		R^3 = α-H	57 (2.8:1)
5	R^1 = α-Bn	R^2 = OMe		R^3 = α-H	67 (2.5:1)
6	R^1 = β-*i*Pr	R^2 = Br		R^3 = β-H (X-ray)	55 (2.5:1)
7	R^1 = β-*i*Pr	R^2 = H		R^3 = β-H	66 (2.1:1)
8	R^1 = β-*i*Pr	R^2 = OMe		R^3 = β-H	65 (2.3:1)
			Cu^{II}		
9[e]		R = Me			51 (1.0:1)
10[e]		R = *t*Bu			51 (1.6:1)
11[e]		R = *t*Bu			53 (1.6:1)[f]
12[e]			Cu^{II}		54 (2.4:1) (X-ray)
			Fe^{III}		
13[g]	R = R^1 = Me				91 (1.2:1)
14	R = R^1 = Me				60 (1.2:1)
15	R = MOM, R^1 = prenyl				54 (1.0:1)
			Fe^{III}		
16	R = R^1 = Me				72 (2.6:1)
17	R = MOM, R^1 = prenyl				73 (2.0:1)

[a] Stereochemistry of α-carbon (oxazolidinone) for entries 2–3 and 5–11 for the major diastereomers has been assigned by analogy to those confirmed by X-ray crystallographic analysis (entries 1, 6, and 12). [b] Isolated yields after chromatography. [c] Diastereomeric ratios refer to carbon β-carbon (oxazolidinone) for entries 1–12. [d] Gram scale (3.7 mmol). [e] 1.75 equiv ester/lactone used. [f] Gram scale (4.3 mmol). [g] 2 equiv ketone used. Fe^{III} = [Fe(acac)$_3$] (acac = acetylacetonate), Cu^{II} = copper(II) 2-ethylhexanoate, LDA = lithium diisopropylamide, Bn = benzyl, MOM = methoxymethyl.

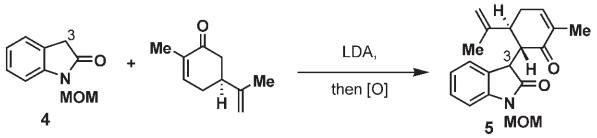
reduction of the oxazolidinone using lithium borohydride, followed by treatment with DBU to furnish (−)-bursehernin (Scheme 2b). The NMR spectral data of synthetic **1** was identical to that reported for the natural substance.[10] Notably, the low diastereoselectivity (at C3) observed in the coupling step was inconsequential as this center was easily epimerized and driven to the *trans*-configured product. Strategic use of oxidative coupling facilitated the first, concise (three sequential synthetic operations with one purification), and enantioselective synthesis of **1**, accomplished in 41% overall isolated yield. By comparison, previous unsymmetrical lignan syntheses required a minimum of six steps proceeding overall in much lower yields.[11]

While α-aryl imides, oxindoles, and diketopiperizines[5] couple most effectively using Fe^{III}-based oxidants, simple imides, indoles,[3a] and pyrroles[4] require Cu^{II}-based oxidants. The precise role of the oxidants in enolate coupling has not been clearly determined and it was assumed[2] that they function as simple electron acceptors (possibly through an outer-sphere electron-transfer process).[12] To determine if the oxidative heterocoupling of enolates is amenable to reagent control, the coupling of oxindole **4** and carvone was studied (Table 2). In this case, homodimerization of the components is preferred over the desired heterocoupling using the standard copper- and iron-based oxidants, resulting in diminished yields. The absence of 3-substitution on oxindole coupling partner **4** is the apparent cause, as a steric bias disfavoring homodimerization is not present (compare with entry 15, Table 1). Notably, Fe(*t*BuCOCHCOCF$_3$)$_3$[10] furnished the heterocoupled product **5** in 83% isolated yield (entry 5, Table 2). In control reactions using either **4** or carvone alone, this oxidant was still competent in promoting homodimerization. Cyclic voltammetry revealed a unique oxidation potential for each oxi-



Scheme 2. Short, enantioselective synthesis of (−)-bursehernin (**1**). Reagents and conditions: **2**, LDA (THF, 1.15 equiv), LiCl (5.0 equiv), PhMe, −78→0→−78 °C (10 min each), **3** (1.75 equiv), PhMe, LDA (THF, 1.85 equiv), −78 °C, 30 min, then Cu^{II}, −78→23 °C, 20 min; $LiBH_4$ (10 equiv), MeOH (5.0 equiv), THF, −78→−10 °C, 1.5 h; DBU (10 equiv), PhMe, 110 °C, 24 h, 41% overall. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2: Oxidative coupling is amenable to reagent control.[a]



Entry	Oxidant	E_{ox} [eV][b]	Yield [%][c]
1	Cu(2-ethylhexanoate)$_2$	−1.65	15
2	PhI(OAc)$_2$	−1.53	≈10
3	[Fe(acac)$_3$]	−1.14	45
4	Fe(PhCOCHCOMe)$_3$	−1.07	30
5	**Fe(*t*BuCOCHCOCF$_3$)$_3$**	**−0.60**	**83**
6	Fe(MeCOCHCOCF$_3$)$_3$	−0.51	40
7	Fe(C$_{10}$H$_7$COCHCOCF$_3$)$_3$	−0.46	40

[a] 2 equiv carvone used. [b] Oxidation potentials measured using cyclic voltammetry, relative to ferrocene/ferrocenium standard. [c] Isolated yields after chromatography.

dant employed, suggesting that rationally controlled hetero-coupling of enolates is possible. This trend, as well as the success of reagent-controlled coupling, underscores great mechanistic complexity and is the subject of further study.[5c]

This work has demonstrated for the first time that oxidative C–C bond formation through the intermolecular union of two different types of enolates can be accomplished by exploiting the natural electronic or steric differences in coupling partners. Furthermore, undesirable homocoupling processes can sometimes be stifled by careful reagent control. As demonstrated in the total synthesis of **1**, conservation of the oxidation state of the starting material prior to the coupling event eliminates the need for prefunctionalization of the substrate (e.g. enol-silane formation or halogenation). It is anticipated that this conceptually unique method for merging sp^3-hybridized carbon atoms will continue to find useful applications in synthesis.[13]

Experimental Section

General procedure for Fe-based couplings (see Supporting Information). Oxazolidinone or oxindole (0.10 mmol, 1.0 equiv) and carbonyl compound (0.10 mmol, 1.0 equiv) were dissolved in benzene (1.0 mL), and the solvent was removed in vacuo. This process was repeated a second time (azeotropic water removal). The starting materials were then dissolved in THF (340 μL, 0.3 M), and the solution was cooled to −78 °C. A solution of LDA (0.50 M in THF, 428 μL, 2.1 equiv) was added dropwise by syringe over 30 s. The reaction was allowed to stir for 30 min at −78 °C and then warmed to ambient temperature. After 5 min of stirring at 23 °C, a solution of [Fe(acac)$_3$] (0.50 M, 408 μL, 2.0 equiv) was added all at once (less than 1 s addition time). The reaction mixture was stirred at ambient temperature for 20 min and then quenched by the addition of 1 N HCl (1 mL). The aqueous layer was partitioned with EtOAc (2 mL), separated, and then extracted twice with EtOAc (2 mL). The organic portions were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica gel) of the crude reaction afforded pure coupled product.

General procedure for Cu-based couplings (see Supporting Information). Oxazolidinone (0.33 mmol, 1.0 equiv) and powdered lithium chloride (1.64 mmol, 5.0 equiv) were taken up in benzene (1.0 mL), and the solvent was removed in vacuo. This process was repeated a second time (azeotropic water removal). Toluene (546 μL, 0.6 M) was added to this mixture, and the resulting solution was cooled to −78 °C. A solution of LDA (0.50 M in THF, 759 μL, 1.15 equiv) was added by syringe down the sides of the reaction vessel over 10 s. After stirring at −78 °C for 10 min, the solution was warmed to 0 °C for 10 min (color change from pale to bright yellow), and then cooled to −78 °C for 5 min. In a separate reaction vessel, the carbonyl compound (0.57 mmol, 1.75 equiv) was dissolved in benzene (1.0 mL) and the solvent was then removed in vacuo. This process was repeated a second time. Toluene (546 μL, 0.6 M) was added to the carbonyl compound, and the solution was cooled to −78 °C. A solution of LDA (0.50 M in THF, 1.2 mL, 1.85 equiv) was added by syringe down the sides of the reaction vessel over 10 s, and the resulting solution was stirred at −78 °C for 25 min. At this time, the carbonyl enolate solution was transferred by canula into the oxazolidinone enolate solution. The reaction mixture was stirred at −78 °C for an additional 5 min, at which time a solution of copper(II)-2-ethylhexanoate (0.3 M in toluene, 3.0 mL, 2.75 equiv) at −78 °C was transferred into the reaction vessel by canula. Immediately following addition, the vessel was quickly removed from the −78 °C bath and placed into a room-temperature water bath, which led to a color change from light blue to brown. The reaction mixture was stirred for 20 min and subsequently quenched by the addition of 5% aqueous NH_4OH (5 mL). The aqueous layer was partitioned with EtOAc (5 mL), separated, and then extracted twice with EtOAc (2 mL). The organic portions were combined, washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica gel) of the crude reaction afforded pure coupled product.

Received: July 27, 2006
Published online: September 29, 2006

Keywords: C–C coupling · enolates · lignans · synthetic methods · total synthesis

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[13] Detailed experimental procedures, copies of spectral data, and full characterization of compounds are contained in the Supporting Information. CCDC 617245–617247 (Table 1, entries 12, 1, and 6, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

