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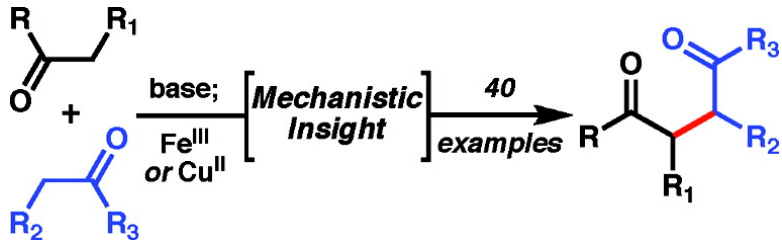

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Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application

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Abstract: This full account presents the background on, discovery of, and extensive insight that has been gained into the oxidative intermolecular coupling of two different carbonyl species. Optimization of this process has culminated in reliable and scalable protocols for the union of amides, imides, ketones, and oxindoles using soluble copper(II) or iron(III) salts as oxidants. Extensive mechanistic studies point to a metal-chelated single-electron-transfer process in the case of copper(II), while iron(III)-based couplings appear to proceed through a non-templated heterodimerization. This work presents the most in-depth findings on the mechanism of oxidative enolate coupling to date. The scope of oxidative enolate heterocoupling is extensive (40 examples) and has been shown to be efficient even on a large scale (gram-scale or greater). Finally, the method has been applied to the total synthesis of the unsymmetrical lignan lactone (−)-bursehernin and a medicinally important 2,3-disubstituted succinate derivative.

Introduction

Organic chemists' longstanding endeavor to achieve target-oriented syntheses as concisely and efficiently as possible has seen incredible progress over the course of the past decade. During this time, the development of succinct methods for the *direct* functionalization of molecules has begun to dominate the field.[1] While there generally exist a myriad of means, either direct or indirect, of accessing a particular organic moiety, the efficiency with which methods can provide a target must continually be called into question in order to continue to advance the field. For example, the 2,3-disubstituted-1,4-dicarbonyl moiety is ubiquitous within organic molecules. Figure 1 provides examples of seemingly unrelated complex natural products[2−7] and medicinal compounds.[8,9] While exhibiting great chemical diversity, they are linked through this common structural element that is found in these and countless other natural and medicinal agents. Generally, this motif is readily apparent, but it can also be masked in the form of carbon atoms at lower (or higher) oxidation states, as seen in taiwankadsurin B.[6,10] Scrutiny of the structures presented in Figure 1 reveals just how valuable a method could be in the construction of such complex molecular architectures.

The direct, convergent synthesis of unsymmetrical 2,3-disubstituted-1,4-dicarbonyl compounds from two carbonyl subunits has proven extremely difficult; several methods for the synthesis of hypothetical succinate **1** are depicted in Figure 2.[9,11] Efficient, enantioselective syntheses of such entities have escaped synthetic grasp, in spite of their presence in countless natural products and innumerable medicinal remedies. All of the methods depicted suffer from one or more of the following limitations: multistep sequences, installation of requisite disposable functionality on one or both of the monomers, and stereoselectivity problems with prefunctionalization methods and/or during the union of the two monomers. No stereoselectivity was observed or necessary for the most efficient of these methods, the Stetter reaction, as the product was subjected to a pyrrole synthesis. This report is a full account of a research program initiated originally to eliminate the first two of these issues and having since evolved to address the third. By taking advantage of an underutilized and underappreciated reactivity of carbonyl enolates, the oxidative heterocoupling of two enolates joins two different sp^3-hybridized carbon centers in a single step without requiring prefunctionalization of the corresponding monomers. In an effort to foster a more complete understanding and showcase the broadened utility of this

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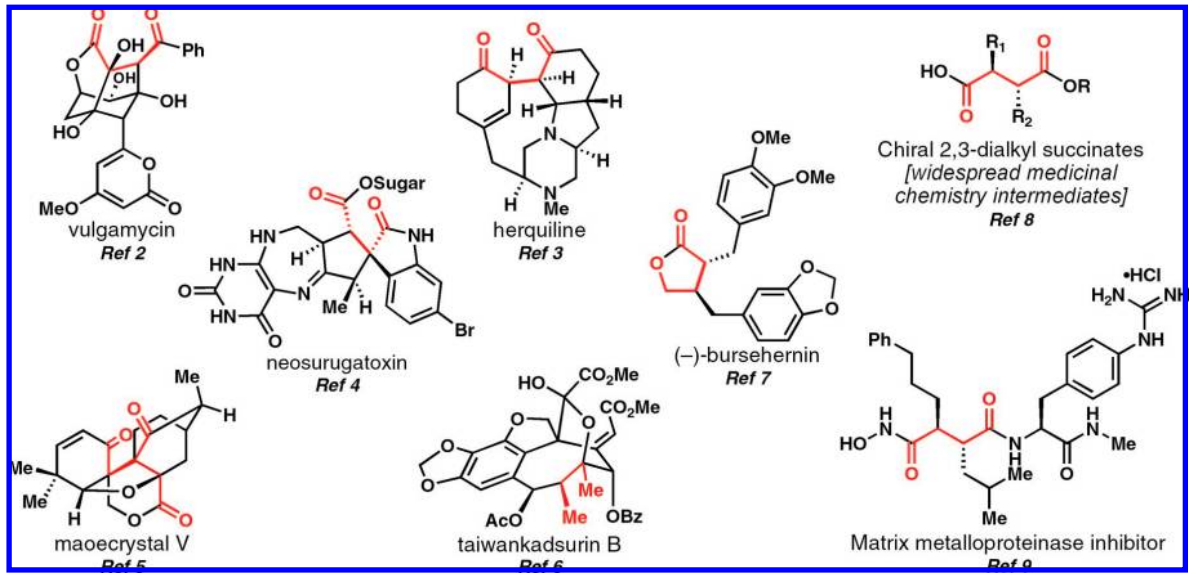

Figure 1. Selected natural products containing 1,4-dicarbonyl moieties.

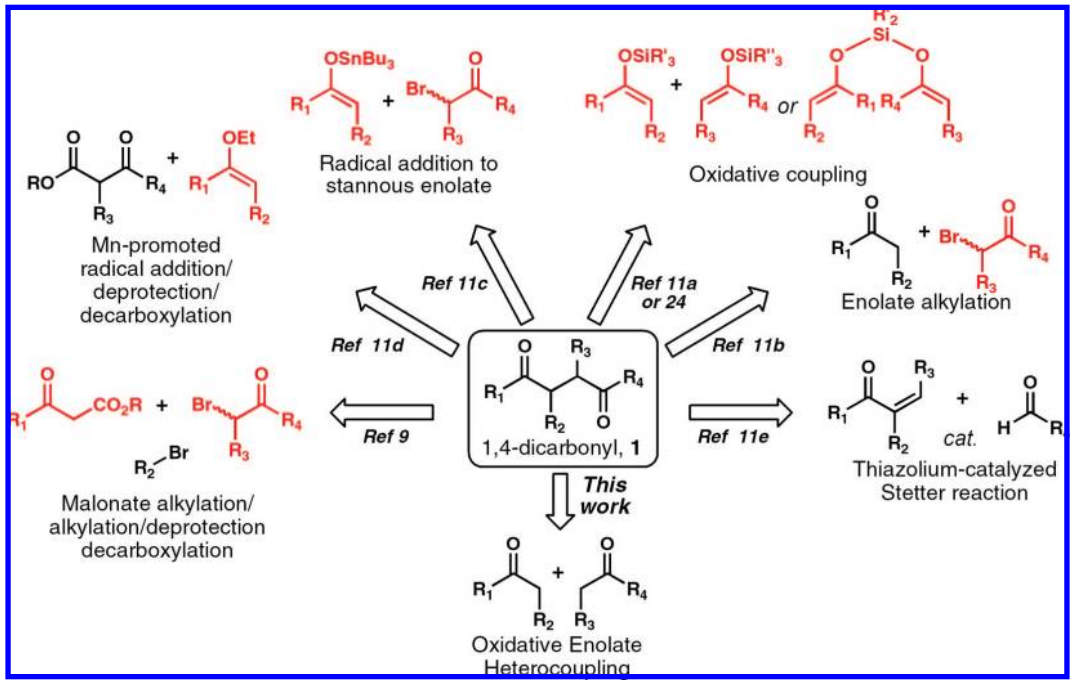

Figure 2. Prefunctionalization requirements (red = necessary prefunctionalization).

method, a detailed mechanistic study, expansion of scope, and application in target-oriented synthesis will be discussed.

Background

The seminal report of a carbonyl enolate dimerization was disclosed in 1935 by Ivanoff and Spassoff (Figure 3).[12] In this disclosure, they treated the sodium salt of a carboxylic acid with a Grignard reagent, and the carboxylate dianion was generated. Following treatment with diatomic bromine, the two carboxylate enolates were fused together at their α-carbons in a net two-electron oxidation, thus providing the corresponding symmetrical succinic acid. Although this reaction could simply proceed through a one-pot α-halogenation and subsequent S_N2 displacement, further mechanistic studies on molecular halogen-based oxidative enolate homocoupling culminated in proof that this process actually proceeds through a single-electron-transfer (SET) process.[13] Although not fully appreciated until many years later, Ivanoff and Spassoff's discovery laid the foundation for what would become a fertile area of research beginning in the late 1960s[14] and continuing to the present. The developments during this period have been recently summarized,[15] and as such, only highlights pertinent to the current studies will be mentioned herein. In 1971, Rathke and Lindert reported the use of $CuBr_2$

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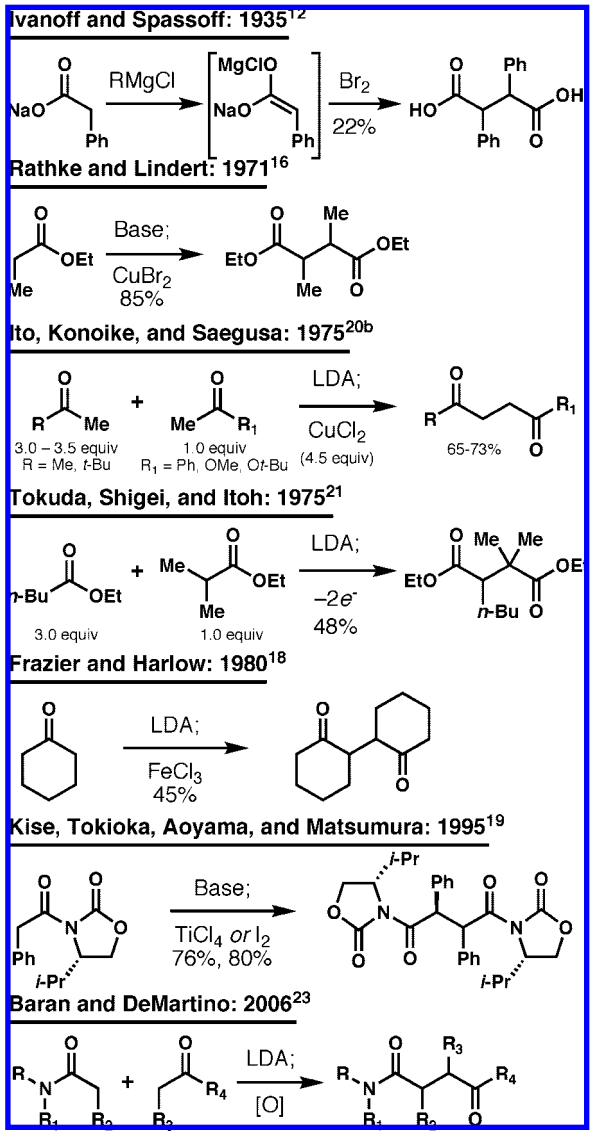

Figure 3. Pertinent intermolecular oxidative enolate coupling timeline.

and Cu(valerate)$_2$ as suitable oxidants for the homocoupling of enolates.[16] This significant study demonstrated two important and related advances: soluble metals (in contrast to the electrodes used in electrolysis[17]) were viable reagents for the coupling process, and copper(II) salts were competent oxidants for this transformation. In a related study in 1980, Frazier and Harlow illustrated that iron salts in the 3+ oxidation state were also quite competent for enolate couplings,[18] although the scope and specificity of these two metals has remained unclear. The scope of enolates used in oxidative couplings was investigated and expanded over the next 15 years, and in 1995, Kise and co-workers reported the first example of an oxazolidinone participating in an oxidative enolate homocoupling.[19]

The comprehensive list of intermolecular oxidative *hetero*-couplings of unfunctionalized carbonyl enolates is actually quite brief. Saegusa and co-workers were the first to demonstrate that this process was possible in the mid-1970s (Figure 3).[20] By using at least a 3-fold excess of one of the monomers, the union of ketones and esters was achieved through the action of $CuCl_2$, affording unsymmetrical succinate derivatives in synthetically useful yields. At the same time, Itoh and co-workers demonstrated that the oxidative union of two different esters was possible by electrolytic means, again using a stoichiometric advantage (3-fold excess) in order to selectively acquire the heterodimer.[21] These reports and their accompanying synthetic potential remained dormant for over three decades while the field was dominated by extensive studies dedicated to the parent reaction: oxidative enolate homocoupling.[22] Selective heterocouplings received no further attention until the initial communication of the current method in 2006.[23] In this full account, the discovery, optimization, mechanistic exploration, and application to medicinal and natural product chemistry are discussed for intermolecular enolate heterocoupling.

Discovery and Optimization

At the outset of this research program, one of the key challenges that needed to be addressed in oxidative heterocoupling was chemoselectivity. Indeed, enolate *homodimerization* reactions had already been demonstrated as superb standalone methods for symmetrical succinate synthesis. As previously discussed, Saegusa and Itoh circumvented this problem through the use of superstoichiometric quantities of one of the coupling partners. While this tactic certainly seems sufficient for the generation of relatively simple systems, its implementation would be greatly hindered in complex molecule synthesis. Several solutions to the problem of homo/heterodimer selectivity have been developed in recent years,[15,24] but each of these methods requires the alteration of carbonyl reactivity through a variety of different prefunctionalization strategies, rather than utilization of the innate reactivity of the free carbonyls.

Given this precedent, the prospect of selective heterodimer formation seemed daunting. Darkening the outlook even further, homodimerization, while the most troublesome byproduct, is certainly not the only side reaction that could take place in attempting this transformation (see Figure 4). Depending on the types of carbonyls employed, homo- and cross-condensation products may be envisioned as arising from Claisen or aldol reactions. This type of reactivity could even potentially dominate the product distribution if the pK_a's of the two monomers, and therefore rates of enolization, were vastly dissimilar. Products resulting from oxidation in an undesired fashion could also be problematic. For example, carbonyl α-hydroxylation[25] and dehydrogenation[26,27] are both possible under the oxidative conditions of the reaction. Moreover, the homodimers, condensation products, and even the desired heterocoupled product could be susceptible to overoxidation, thereby greatly suppressing conversion and productive reactivity. It should be noted that any bimolecular reaction of one carbonyl with another molecule

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(17) Weinberg, N. L.; Weinberg, H. R. *Chem. Rev.* **1968**, *68*, 449–523.
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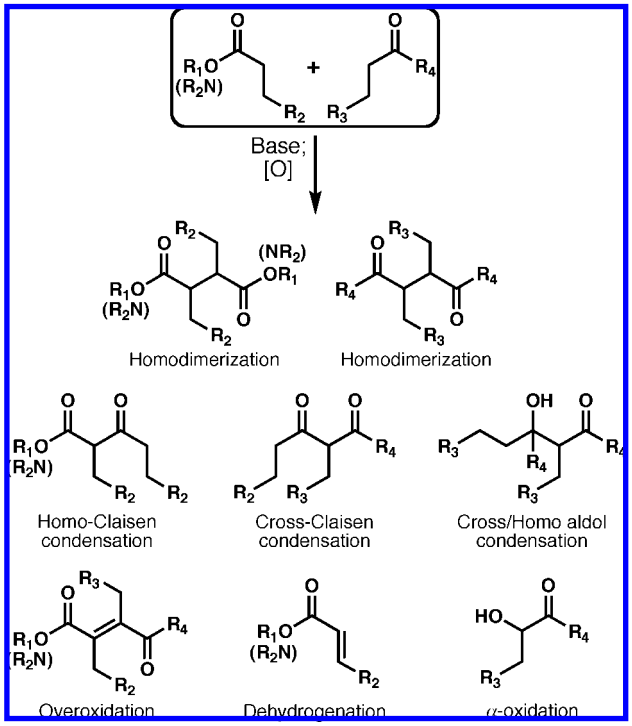
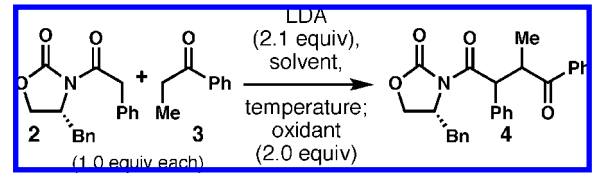


Figure 4. Possible reactions to compete with heterocoupling.

of itself would be particularly detrimental to the yield of the desired heterodimerization; for every *one* occurrence of these transformations, *two* molecules of the limiting reagent would be consumed in a nonproductive pathway. In spite of the pitfalls that were sure to be encountered, the potential power of oxidative enolate heterocoupling gave cause to pursue its development.

N-Acyloxazolidinones were chosen as one of the coupling partners for initial exploration of the oxidative heterocoupling reaction for two reasons. First, an initial long-term goal of this project was to be able to control the stereochemical course of the reaction, the prospect of which would be more realistic if the chemistry were developed around appropriate substrates. Imides of this type have proven competent substrates for oxidative coupling, as they have been employed repeatedly in the complementary homodimerization process.[19,28,29] Furthermore, simple ketones proved satisfactory for analogous couplings with indoles[15,30,31] and pyrroles,[15,32] and so propiophenone **3** was chosen to complement *N*-acyloxazolidinone **2**. The choice of oxidant, iron(III) acetylacetonate [Fe(III)], was made as a result of the recent successful *intra*molecular coupling of a tertiary amide (potentially similar to an oxazolidinone) and an ester in the context of total synthesis.[25,33] Fe(III) is also inexpensive, commercially available or easily prepared if necessary, and highly soluble in tetrahydrofuran (THF). In the

Table 1. Oxazolidinone−Propiophenone Coupling Optimization[a]



entry	condition	yield (%)
	Oxidant = Fe(acac)$_3$ = Fe(III)	
	Solvent	
1	THF	57
2	Et_2O	5
3	DME	16
4	CPME	0
5	PhMe	51
	Temperature	
6	−78 °C	0
7	−78 to 25 °C	21
8	−40 °C	0
9	−40 to 25 °C	18
10	0 °C	16
11	0 to 25 °C	24
12	25 °C	57
	Concentration	
13	0.05 M	31
14	0.10 M	31
15	0.30 M	57
16	0.50 M	39
17	1.00 M	40
	Oxidant = Cu(2-ethylhexanoate)$_2$ = Cu(II)	
	Solvent	
18	THF	55
19	Et_2O	0
20	DME	51
21	CPME	19
22	PhMe	9
	Temperature	
23	−78 °C	16
24	−78 to 25 °C	42
25	−40 °C	16
26	−40 to 25 °C	50
27	0 °C	39
28	0 to 25 °C	55
29	25 °C	26
	Concentration	
30	0.05 M	39
31	0.10 M	37
32	0.30 M	55
33	0.50 M	50
34	1.00 M	50

[a] Diastereomeric ratios determined by ^{1}H NMR integration. Diastereomeric ratios (for the methyl-bearing carbon) did not change with altered reaction conditions: Fe(III) entries, 1.8:1.0; Cu(II) entries, 1.0:1.6.

inaugural experiment, an equal stoichiometry of **2** and **3** in the same reaction vessel was treated with lithium diisopropylamide (LDA) at −78 °C. Fe(acac)$_3$ was added at this temperature, and the reaction was then placed in a room-temperature (25 °C) water bath. The result was 21% yield of the coupled product **4** (entry 7, Table 1), but more importantly, the reaction mixture consisted of only product, starting materials, and the homodimer of **3**. This was very encouraging, given the initial trepidation involving potential side reactions (*vide supra*), and provided a baseline on which to improve. A screen of common solvents indicated that THF, as expected, was indeed the optimal choice,

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(29) (a) Kim, J. W.; Lee, J.-J.; Lee, S.-H.; Ahn, K.-H. *Synth. Commun.* **1998**, *28*, 1287–1292. (b) Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697–2708. (c) Nguyen, P. Q.; Schafer, H. J. *Org. Lett.* **2001**, *3*, 2993–2995. (d) Kise, N.; Fujimoto, A.; Ueda, N. *Tetrahedron: Asymmetry* **2002**, *13*, 1845–1847.
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(32) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609–612.
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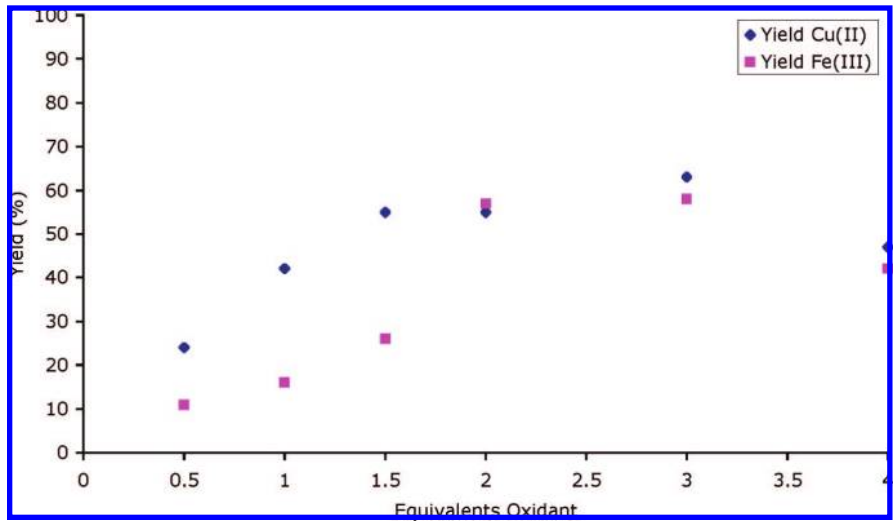
Chart 1. Heterocoupling Yield of **2** and **3** as a Function of Oxidant Stoichiometry



although toluene performed admirably as well. Several modes of oxidant addition were analyzed, including addition as a solid as well as in solution at different rates, and it was determined that fast addition of a concentrated solution (0.5 M, limit of solubility) led to the most reproducible results and highest yields. An interesting temperature effect was also realized. Oxidant addition at low temperature, followed by 30 min of stirring at that temperature before quenching (entries 6 and 8, Table 1), offered no conversion whatsoever. If, instead, the oxidant-containing cold reaction vessels were immediately placed into a room-temperature water bath, minor amounts of coupled product **4** were noted. As the reaction mixtures are homogeneous even at low temperatures, oxidant solubility is not the problem; instead, it seems that higher temperatures are necessary for the oxidative coupling to occur. This trend continued at moderate temperature (entries 10 and 11), but the best yields were observed when the oxidant addition was performed with the reaction stirring at room temperature (entry 12). A screen of initial concentrations of the coupling partners demonstrated that low concentrations suppressed the reaction (entries 13 and 14), while higher concentrations also lowered yields, but to a lesser extent. It appeared that 0.3 M (entry 15) was the ideal concentration for the Fe(III)-based cross-couplings.

Since the initial disclosure of this method,[23] it was discovered that Cu(II) 2-ethylhexanoate [Cu(II)] is also proficient in affecting the cross-coupling of oxazolidinones and ketones. This was a particularly intriguing finding, as this oxidant is also quite inexpensive and highly soluble in THF. More importantly, mechanistic investigations of a single transformation using two different metal oxidants were made feasible, the subtle distinctions of which were not appreciated until this study (*vide infra*). As such, it was prudent to systematically optimize the reaction conditions for Cu(II) as well.

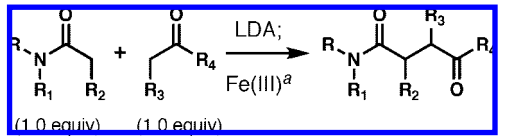
Very few changes from the method already developed for Fe(III) were actually necessary. Once again, THF (entry 18) proved the superior solvent, although dimethoxyethane (DME) also led to a high yield (entry 20), and parallel concentration effects (entries 30−34) were noted, with 0.3 M being optimal. The dependence on temperature was again the most intriguing of these optimization studies. Similar to the observation with Fe(III), a rapid increase to room temperature seemed favorable (entries 24, 26, and 28), though Cu(II) proved modestly capable of coupling the two monomers even when the reaction was carried out at low temperature (entries 23 and 25). Interestingly, when the optimized conditions for Fe(III) were executed using Cu(II) (entry 29), the homo-Claisen condensation reaction of **2** became competitive, although it is unclear why the addition of a solution of Cu(II) would promote this reactivity. Ultimately, it was found that Cu(II) addition at 0 °C, followed by immersion of the reaction vessel in a room-temperature water bath, provided optimal results.

The final reaction parameter studied was the effect of increasing or decreasing the amount of oxidant relative to a stoichiometric quantity (two equivalents of metal total, one per reacting enolate). Similar trends were observed for both metals: diminished yields at lower stoichiometry, slightly increased yields at superstoichiometric quantities, and eventual decrease in yield as a large excess of oxidant is added. The optimized condition chosen was two equivalents, as the yield improvement using three equivalents was not significant enough to justify using an extra equivalent of the oxidant in the generalized method. Two interesting observations can be gleaned from Chart 1. First, a substoichiometric amount of Cu(II) (1.5 equiv) provided an identical yield as compared to using the full stoichiometric amount.[34] Second, it is clear that Cu(II) was much more efficient than Fe(III) when substoichiometric quantities of oxidant were used. The mechanistic implications of these findings will be discussed below.

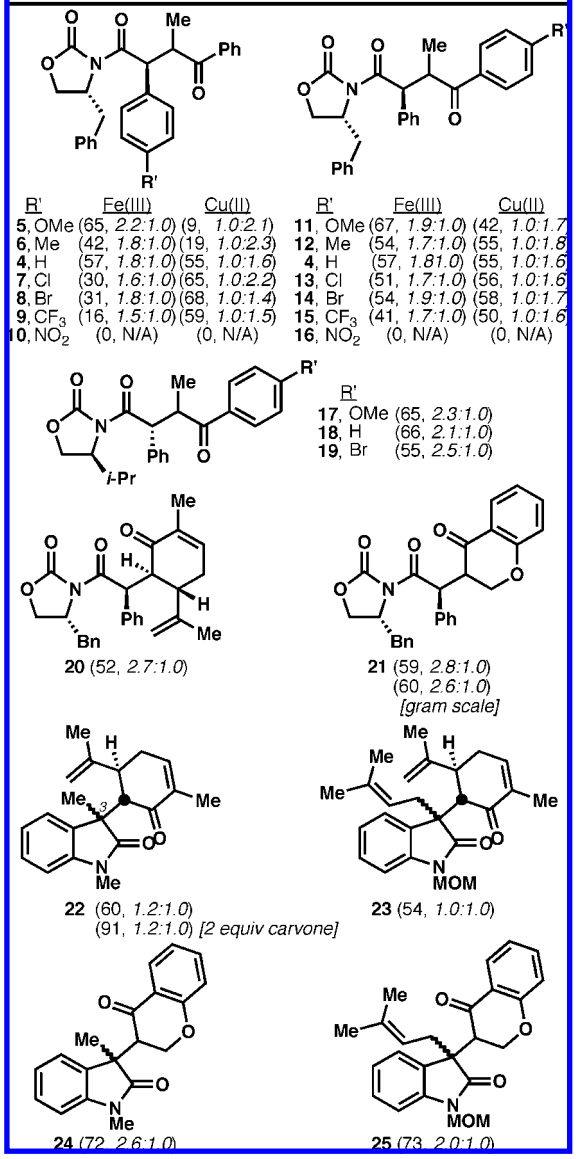
The studies performed on the oxidative coupling of oxazolidinone **2** and ketone **3** culminated in the following generalized procedure that is efficient, reliable, scalable, and operationally simple: oxazolidinone (1.0 equiv) and carbonyl compound (1.0 equiv) were dissolved in THF (0.3 M), and the solution was cooled to −78 °C. LDA (2.1 equiv) was added dropwise by syringe over 30 s, and the reaction was allowed to stir for 30 min at −78 °C. For Fe(III), the reaction was removed from the cold bath and allowed to warmed to ambient temperature (5 min), at which time a 0.5 M solution of $Fe(acac)_3$ (2.0 equiv) was added in one portion. For Cu(II), the reaction was placed in a 0 °C bath and stirred for 5 min, at which time a 0.5 M solution of Cu(2-ethylhexanoate)$_2$ (2.0 equiv) was added in one portion, followed by immediate placement of the reaction vessel

(34) Two equivalents of oxidant were still chosen for the optimized procedure, as this proved more reproducible while expanding substrate scope.

Table 2. Substrate Scope for Oxazolidinone/Oxindole−Ketone Couplings



Cross-coupled products (yield %,[b] *d.r.*[c])



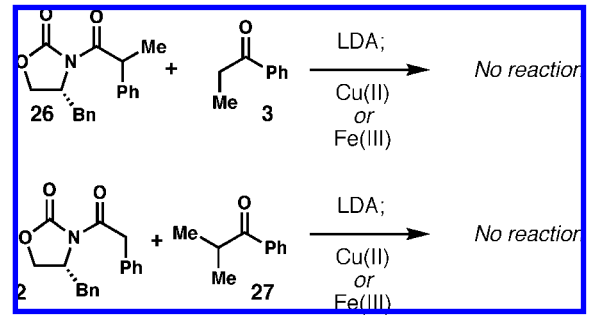
[a] $Fe(acac)_3$ used as oxidant unless otherwise stated. [b] Isolated yield. [c] Diastereomeric ratios determined by ^1H NMR integration.

in a room-temperature bath. For both metals, the reaction was stirred at ambient temperature for 30 min and then quenched.

Scope

As shown in Table 2, changes in the electronic nature of the aromatic rings of both the oxazolidinones and propiophenones greatly affected the efficiency of the reaction, the mechanistic implications of which will be discussed below. Generalizing these effects suggests that electron-neutral and electron-rich aromatic rings on both the oxazolidinone (**5**, **6**, **4**) and propiophenone (**11**, **12**, **4**) coupling partners lead to much more efficient Fe(III)-based couplings. Electron deficiency is much better tolerated on the propiophenones (**13**−**15**) than the oxazolidinone (**7**−**9**), where electron-withdrawing groups suppress coupling. Interestingly, the Cu(II)-based couplings showed the opposite trends; coupling of 4′-methoxypropiophenone (**11**) proceeded only modestly, whereas the reactions of the counterpart 4′-methoxy- and 4′-methyloxazolidinones (**5**, **6**) were stifled. Withdrawing electron density seemed to aid the reaction for both coupling partners (**7**−**9**, **13**, **14**), with the exception of 4′-trifluoromethylpropiopheneone (**15**), which was only slightly inferior to the parent ketone (**4**), and the 4′-nitro coupling partners (**10**, **16**). The nitro group is apparently incompatible with this chemistry, regardless of which metal is used. Isopropyl oxazolidinones (**17**−**19**) were also attempted in the Fe(III)-based couplings; these proved to be quite proficient, operating under the same electronic trend as before, and with the bulkier auxiliary modestly improving the diastereoselectivity. The oxazolidinones were also cross-coupled with simple enones such as carvone (**20**) as well as cyclic aryl ketones such as 4-chromanone (**21**) in good yield. The synthesis of **21** was selected to demonstrate that the reaction can be performed on gram scale with no diminution in yield.

Scheme 1. Attempted Quaternary Carbon Formation

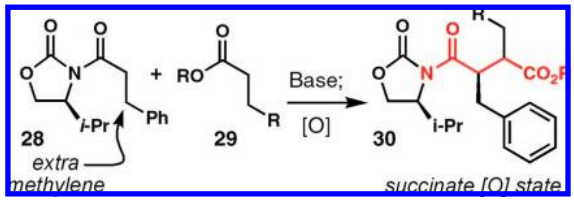


An appealing extension of this chemistry would be the construction of quaternary carbon centers by employing either one or two α-methines instead of α-methylenes on the coupling partners. This advance, however, has eluded discovery to this point. Appending a small steric entity such as a methyl group on either of the coupling partners **26** or **27** (Scheme 1) was found to completely stifle reactivity and led to no reaction with either oxidant. The formation of quaternary centers in this context remains a limitation of this chemistry.

Oxindoles are found at the nucleus of countless natural and medicinal agents,[35] and as such, their couplings would be a useful extension of this chemistry. As seen in Table 2, 1,3-dimethyloxindole smoothly adheres to carvone (**22**) in high yield, as does 1-methoxymethyl-3-prenyloxindole (**23**); these are particularly noteworthy, as the product of this transformation bears a newly formed quaternary carbon center at the C-3 position of the oxindole. If a 2-fold excess of carvone is used in this transformation, the yield of **22** can be bolstered to 91%. This result corroborates the early work of Saegusa and Itoh, showing that a stoichiometric excess of one of the coupling partners can be used to augment yields in the case of commodity chemicals. 4-Chromanone was also coupled with 1,3-dimethyloxindole (**24**) and 1-methoxymethyl-3-prenyloxindole (**25**) in very good yields.

(35) A SciFinder Scholar search of the oxindole substructure with biological activity returns over 2200 unique patent references.

Scheme 2. Extension to 2,3-Dialkylsuccinates



Unsymmetrical 2,3-dialkylsuccinic acid derivatives are useful compounds within medicinal chemistry,[8] and the rapid and efficient synthesis of these molecules has traditionally been a significant chemical challenge. While many of the solutions devised have been elegant from a synthetic standpoint,[9,36] the application of the current method to this problem could greatly streamline access to these chemical entities. As shown in Scheme 2, the heterocoupling of an oxazolidinone with an ester would allow for *direct* access to hypothetical succinyl derivative **30** in the acid/ester oxidation state. Judicious selection of coupling partners would provide a means of carbonyl differentiation to further manipulate and derivitize the molecules in subsequent synthetic operations. The presence of an additional saturated carbon atom between the carbonyl and the phenyl ring of oxazolidinone **28**, while a seemingly subtle change, caused a few unanticipated challenges, necessitating several changes to the procedure as outlined above. The first interesting observation was that Fe(III) is not capable of facilitating oxidative coupling. When Cu(II) was employed instead, the homodimerization of **28** was suddenly very competitive with the desired heterocoupling. While the addition of lithium chloride and use of toluene as a cosolvent seemed to slightly ameliorate this problem, a modest excess of the ester coupling partner (1.75 equiv) was employed in order to statistically facilitate heterodimerization. In addition, the pK_a of the α-carbon is raised substantially (likely 6−7 units[37]), thereby retarding the rate of enolization of **28**. As alluded to earlier (*vide supra*), this modification led to homo/cross-Claisen condensation products with **28** acting as the electrofuge. Enolate formation in separate reaction vessels completely resolved this setback, restoring the efficiency of the heterocoupling process.

As illustrated in Table 3, a wide range of both steric environments and functional groups are tolerated in this reaction. For example, increasing the steric demand from methyl (**31**) to isopropyl (**32**), to *tert*-butyl (**33**), or even to the bulky cyclopentyl carbocycle (**34**) had no adverse affect on the chemistry. However, when the branched substitution was shifted to the *β*-carbon of the ester, this component preferentially homodimerized, leading to substantially lower yield of heterocoupled product **40** (albeit with a bulky oxazolidinone component). Successful coupling of alkene **36** was notable, as many potential oxidative side reactions involving the α-olefin could be envisioned. The reaction also proceeded with the inclusion of ethers (**37**) or trifluoromethyl groups (**38**, **39**) in the corresponding monomers. Electron-rich (**46**−**48**), -neutral (**41**−**44**), and -deficient aromatic units (**49**, **50**) are tolerated as well, with the latter demonstrating that changing positions of the same functionality about an aromatic ring is acceptable. Methyl esters perform equally well as *tert*-butyl esters (compare **43** and **42**), but the latter were chosen for generalization so that chemical differentiation of the carbonyls in subsequent chemistry would be trouble-free. Significantly, **42** was synthesized on a gram scale, once again demonstrating the scalability of this method. Moreover, one gram of this material was donated to the Bristol-Myers Squibb Co. (BMS) for an ongoing medicinal chemistry project. In addition, succinates **39** and **40** were also provided to BMS as intermediates toward potential drug candidates in an entirely different project. The fact that three unsymmetrical succinate derivatives were useful in two *different* medicinal chemistry projects further demonstrates the utility of this method in drug discovery. Compound **45** is an interesting example in this series due to the facility of the enolate coupling, even in the presence of an indole nucleus. Indoles are extremely electron-rich heterocycles and, as such, are susceptible to a variety of oxidative reaction pathways.[38] In fact, *N*-H indoles,[15,30] the related *N*-H pyrroles, and even an *N*-alkyl pyrrole (intramolecular)[15,32] are capable of participating in oxidative couplings with enolates! The efficiency with which dihydrocoumarin **35** is formed implies that lactones are also compatible, which is not surprising since these moieties likely behave electronically similarly to their acyclic counterparts. Compounds **47** and **48** demonstrate that modifications of the aromatic core on the oxazolidinone are acceptable, as is the incorporation of an alkyl chain in lieu of the aryl nucleus (**39**−**41**). The trifluoromethyl group (**38** and **39**), indoles (**45**), biphenyls (**44**), and arylfluorides (**49** and **50**) are all extremely important pharmacaphores, again suggesting that this method will likely find use in the pharmaceutical industry.

It is important to note that the syntheses of unsymmetrical 2,3-dialkylsuccinic acid derivatives in Table 3 proceed with diastereoinduction in accord with that expected from an alkylation of the same oxazolidinones, affording a single epimer at the oxazolidinone α-carbon. Significantly, an anecdotal mention was made in the original communication of this work that the oxidative coupling reactions using oxazolidinone **2** proceed with the opposite stereoinduction at the oxazolidinone α-carbon, as would be expected (see Scheme 3). At that time, this anomaly was not understood because there was no reason to expect the bond formation to occur on the same face as the bulky steric element of the auxiliary. Clarity to this end has since been achieved. The pK_a of the *product N*-(phenylacetyl)-oxazolidinones is apparently still low enough that the products formed from the heterocoupling reactions are susceptible to a deprotonation−protonation event, resulting in net epimerization under the reaction conditions. This was confirmed when a set of the minor diastereomers from the coupling reaction (**14a**, α-phenyl as pictured) were isolated, treated with LDA, and quantitatively epimerized to the *β*-phenyl oxazolidinones **14b**, with no change in diastereomeric ratio at the methyl-bearing center (Scheme 3). With these results, it is assumed that the bond-forming process initially occurs directed away from the steric element on the oxazolidinone and is subsequently epimerized. This result also demonstrates that a single oxazolidinone enantiomer can provide controllable access to two diastereomeric sets of products.

Both of the methods outlined above proceed in relatively low diastereoselectivities at the *β*-carbon in couplings involving oxazolidinones. This problem can be circumvented when this chemistry is *strategically* implemented in a target-oriented

(36) (a) Xue, C.-B.; et al. *J. Med. Chem.* **2001**, *44*, 2636–2660. (b) Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. *J. Med. Chem.* **2002**, *45*, 2289–2293.

(37) Bordwell, F. G.; Harrelson, J. A., Jr. *Can. J. Chem.* **1990**, *68*, 1714–1718.

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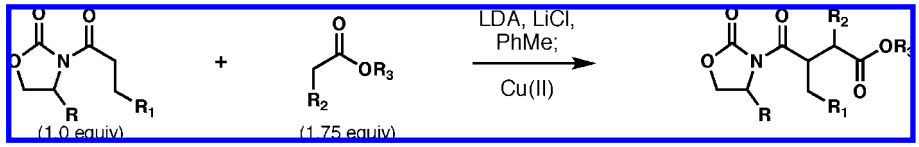
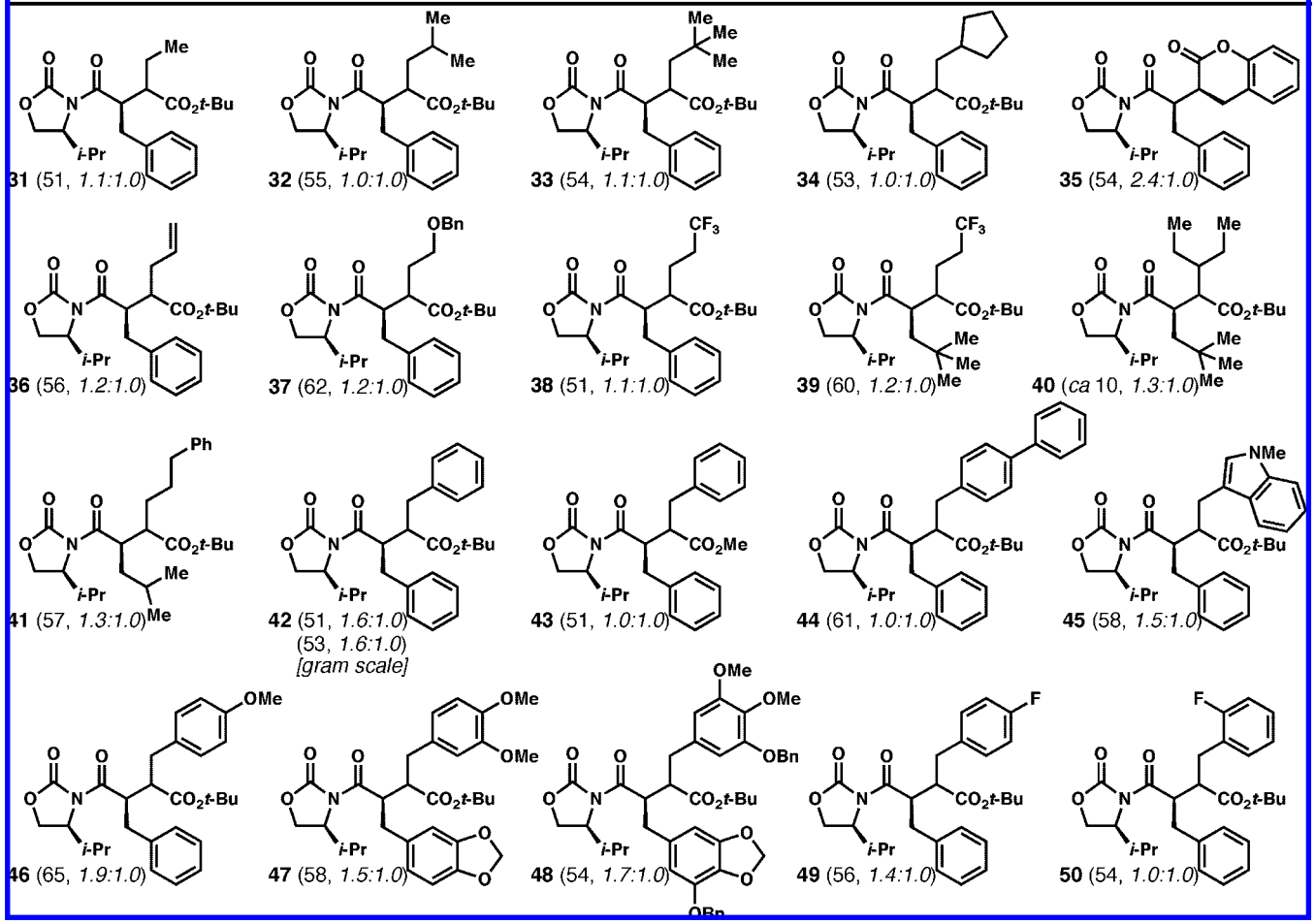
Table 3. Scope of 2,3-Dialkylsuccinate Couplings

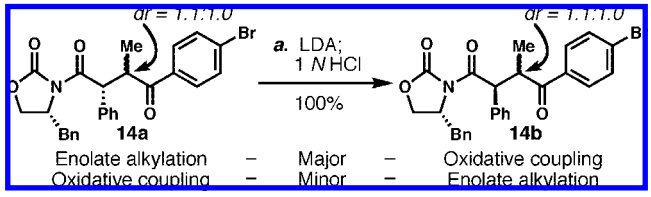


Cross-coupled products (yield %,[a] *d.r.*[b])



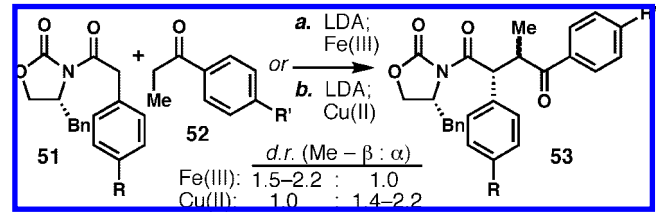
[a] Isolated yield. [b] Diastereomeric ratios determined by ^{1}H NMR integration.

Scheme 3. Diastereoselectivity Discrepancy[a]



[a] Reagents and conditions: (a) LDA (1.1 equiv), THF, −78 °C (30 min) to 25 °C (5 min); 1 N HCl, 100%.

Scheme 4. Metal-Based Change in Diastereoselectivity[a]



[a] Reagents and conditions: (a) LDA (2.1 equiv), THF, −78 °C (30 min) to 25 °C (5 min); $Fe(acac)_3$, 16−67%; (b) LDA (2.1 equiv), THF, −78 °C (30 min) to 0 °C (5 min); Cu(2-ethylhexanoate)$_2$, 25 °C, 9−68%.

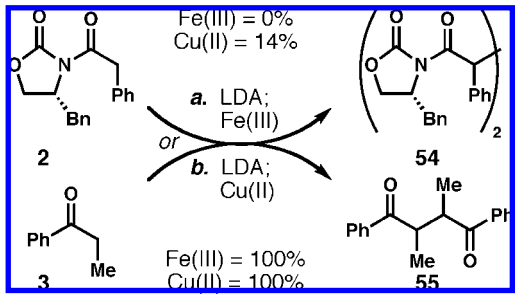
synthesis (*vide infra*, bursehernin synthesis). The use of alternate auxiliaries (sultam- or menthol-based) led to inefficient couplings (mostly homodimer of the auxiliary containing monomer) and did not ameliorate the β-selectivity. This issue remains a limitation of the enolate heterocoupling methodology.

Mechanism

With the initial investigations, optimization, and scope exploration complete, a comprehensive mechanistic understanding was sought. A series of observations have been made and experiments completed toward that end, leading to the most complete understanding of the oxidative coupling reaction to date.

As seen in Scheme 4, a subtle but significant contradiction was noted in the coupling of *N*-(phenylacetyl)oxazolidinones **51** with propiophenones **52**. The diastereomeric ratios of the methyl-bearing carbon in **53**, while low for both metals, were

Scheme 5. Homodimerization Control Experiments[a]



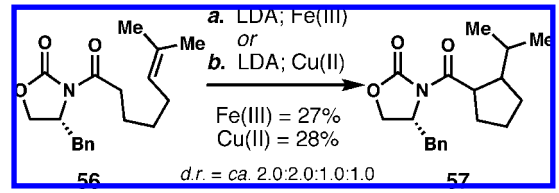
[a] Reagents and conditions: (a) LDA (1.1 equiv), THF, −78 °C (30 min) to 25 °C (5 min); $Fe(acac)_3$; (b) LDA (2.1 equiv), THF, −78 °C (30 min) to 0 °C (5 min); Cu(2-ethylhexanoate)$_2$, 25 °C.

uniformly reversed as a function of the oxidant employed. While Fe(III) afforded selectivity for β-stereochemistry, this trend was reversed when Cu(II) was used, exhibiting a preference for α-stereochemistry. These data inspired the hypothesis that the two metals were potentially operating through disparate mechanisms and guided experimentation aimed at validation of this theory.

It seemed reasonable to begin this investigation by performing control experiments to determine the fate of each carbonyl when no cross-coupling is possible (Scheme 5). When oxazolidinone **2** was treated with LDA followed by Fe(III), no homodimer **54** was formed. However, Cu(II) was capable of promoting dimerization, albeit in low yield. Interestingly, when the same experiments were performed using propiophenone **3**, both metals promoted quantitative dimerization to the 1,4-diketone **55**. This suggests that the cross-couplings employing Fe(III) occur through an initial oxidation of the ketone enolate, as oxidation of the oxazolidinone either is not possible or occurs reversibly at a rate such that none of the bimolecular process can occur. No such conclusive statement can be made for the Cu(II) mechanism, but it is certainly likely that a similar deduction is true, given the yields of the corresponding control experiments. Although strongly suggestive of initial ketone oxidation by Cu(II), this experiment does not rule out the possibility of more than one operable mechanism for this oxidant.

While an SET mechanism has been repeatedly alluded to in the literature for both iron(III)[26,27,39,40] and copper(II),[16,28,41−44] little proof has been offered to this end.[44] Radical trapping experiments involving the cyclization of the purported α-radical onto a pendant α-olefin in order to prove that I_2[13] and $TiCl_4$[45] operate through SET-based mechanisms have been unsuccessful, although no such studies have been attempted with Fe(III) or Cu(II). Discreet oxazolidinone α-radicals (formed through carbon−halogen bond homolysis) have been independently

Scheme 6. Single-Electron-Transfer-Induced Intramolecular Cyclizations[a]



[a] Reagents and conditions: (a) LDA (1.1 equiv), THF, −78 °C (10 min) to 0 °C (10 min) to −78 °C (10 min) to 25 °C (5 min); $Fe(acac)_3$, 27%; (b) LDA (2.1 equiv), THF, −78 °C (10 min) to 0 °C (10 min) to −78 °C (10 min) to 0 °C (5 min); Cu(2-ethylhexanoate)$_2$, 25 °C, 28%.

demonstrated to be sufficiently electrophilic to cyclize with tethered electron-rich olefins.[46] Therefore, the ability of Fe(III) and Cu(II) to promote such a cyclization was investigated. When the enolate of oxazolidinone **56** is treated with either Fe(III) or Cu(II), both oxidants promote cyclization to cyclopentane **57** (Scheme 6).[47] This evidence strongly suggests that both metal oxidants indeed execute enolate couplings through two single electron transfers rather than a concerted two-electron oxidation, and implies that the copper(II) and iron(III) enolates lead to electrophilic enolate carbon atoms that may be thought of as at least reasonable surrogates of carbonyl α-radicals. This result may seem in conflict with the apparent inability of Fe(III) to oxidize oxazolidinone **2**, but the oxidation potential of the corresponding enolates is likely different, given the presence of the phenyl group. Moreover, the homodimerization is a bimolecular reaction, whereas the cyclization would be unimolecular. As such, a reversible oxidation of the enolate would be more likely to result in trapping by a tethered nucleophile.

If the supposition that a SET-based mechanism is indeed operable, the venerable radical-induced cyclopropylmethyl fragmentation should relay valuable mechanistic information.[48] The pioneering studies of Newcomb have shown that radicals adjacent to the 2,2-diphenylcyclopropyl moiety fragment with picosecond kinetics, faster than the limit of diffusion, and therefore would out-compete even the fastest first-order and all second-order processes.[49] By flanking such functionality to the α-carbons of either coupling partner, fragmentation should be the dominant pathway (over any bimolecular coupling process). When cyclopropanes **58** and **60** (synthesized as shown in Scheme 7) were subjected to the cross-coupling conditions with their corresponding coupling partners **3** (Scheme 8a) and **2** (Scheme 8b), dissimilar results were once again observed for the two metals. As anticipated, no cyclopropane-containing coupled products (homo- or heterodimers) were isolated in either case. The Cu(II) oxidation of cyclopropane **58** led to appreciable quantities—20% combined yield—of a 1:1 mixture of two ring-opened products: alkene **59a** and diene **59b**. As Scheme 9 illustrates, both compounds presumably arise from a concerted SET oxidative cyclopropyl ring opening to intermediate **69**,

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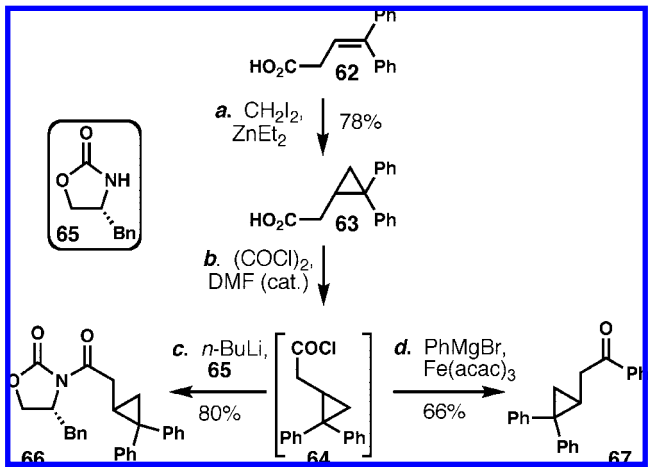
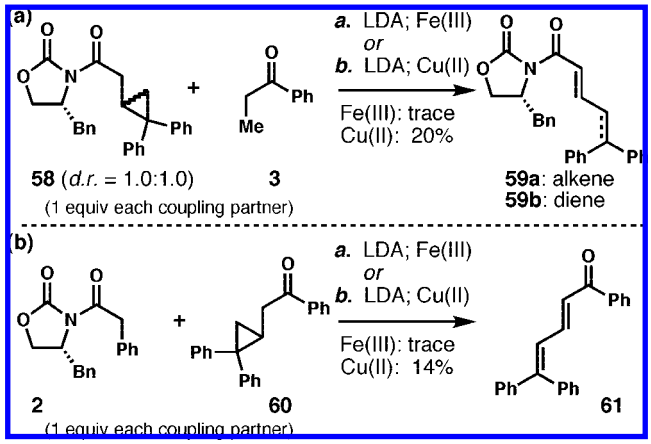
(45) Ojima, I.; Brandstadter, S. M.; Donovan, R. J. *Chem. Lett.* **1992**, 1591–1594.
(46) Yang, D.; Zheng, B.-F.; Gu, S.; Chan, P. W. H.; Zhu, N.-Y. *Tetrahedron: Asymmetry* **2003**, *14*, 2927–2937.
(47) For precedent of proton abstraction from carbon radicals, see Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692–700.
(48) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024–7026. (b) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981–7984.
(49) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10915–10921.

Scheme 7. Cyclopropane Syntheses[a]



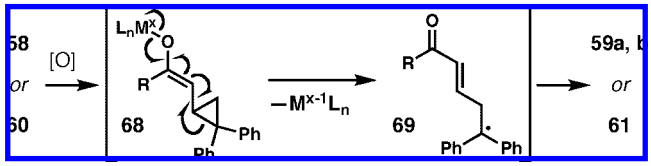
[a] Reagents and conditions: (a) Et_2Zn (5 equiv), CH_2I_2 (10 equiv), CH_2Cl_2, 0 to 25 °C, 15 h, 78%; (b) $(COCl)_2$ (2.5 equiv), DMF (2 drops), 0 to 25 °C, 2.5 h; (c) *n*-BuLi (1.01 equiv), 65 (1.0 equiv), THF; **64** (1.0 equiv), 80%; (d) $Fe(acac)_3$ (0.03 equiv), PhMgBr (1.3 equiv), −78 °C, THF, 66%. DMF = dimethylformamide.

Scheme 8. Single-Electron-Transfer-Induced 2,2-Diphenylcyclopropylmethyl Opening[a]



[a] Reagents and conditions: (a) LDA (2.1 equiv), THF, −78 °C (10 min) to 0 °C (10 min) to −78 °C (10 min) to 25 °C (5 min); $Fe(acac)_3$; (b) LDA (2.1 equiv), THF, −78 °C (10 min) to 0 °C (10 min) to −78 °C (10 min) to 0 °C (5 min); Cu(2-ethylhexanoate)$_2$, 25 °C.

Scheme 9. Cyclopropane Fragmentation



followed by either proton abstraction (**59a**)[50] or the removal of a second electron (**59b**). Cyclopropane **60** was similarly opened and oxidized with Cu(II), affording diene **61** in 14% yield (only trace amounts of the corresponding proton extraction product, not pictured, were observed in this case). Interestingly, when the same experiments were performed with Fe(III) as the oxidant, only trace quantities (<5%) of ring-opened products were detected, in spite of the known propensity of iron(III) salts to be single-electron oxidants.[40,51] This suggests that, while both metal enolates are electrophilic at the α-carbon, the reactivity of copper(II) enolates more closely resembles that of discreet carbonyl α-radicals than that of iron(III) enolates. That being said, these data, in combination with the intramolecular cyclization results discussed above, suggest that both of these metals lead to enolates electrophilic at the α-carbon atom and, more importantly, operate through SET-type mechanisms.

Having sufficiently demonstrated that an SET-based mechanism is likely operable, a clearer picture of the bond-forming process was desired. As discussed earlier, the oxidant-induced change in diastereoselectivity in the coupling of oxazolidinones **51** and propiophenones **52** is strongly suggestive of disparate mechanisms (Scheme 4). Two distinct mechanistic possibilities include biradical (or non-lithium enolate) coupling and a metal-chelated mechanism. Enolate homodimerizations using iron(III)[39] and copper(II)[16,28,42] have both been explained by the former, while the latter has been cursorily mentioned for Cu(II)[43,52] and was also found to be operable for indole−enolate couplings.[15] When the yields for the couplings between oxazolidinone **2** and propiophenone **3** (as oxidant stoichiometry is altered) are adjusted to reflect oxidant efficiency (based on an SET mechanism)[53] and the data are again plotted as a function of oxidant stoichiometry, another distinction between the two oxidants is unearthed (Chart 2): Cu(II) is an exceedingly efficient oxidant for this reaction at low oxidant stoichiometry, but this effectiveness decreases linearly as the Cu(II) stiochiometry is increased. This trend is consistent with a metal-templating effect in the bond formation. At low oxidant concentration, there is a much higher probability that the two enolate coupling partners would adhere to the *same* copper atom. At higher oxidant concentration, there is increased likelihood of non-productive Cu(II)−enolate interactions. There is no such trend for the Fe(III)-based couplings: the oxidant efficiency is essentially consistent through changes in oxidant stoichiometry, suggesting that the bond-forming process is not aided by a metal chelate.

The experiments detailed above were designed in order to gain insight into the mechanisms of Fe(III)- and Cu(II)-promoted oxidative heterocouplings, and the evidence accrued suggests that the metals are operating by different mechanisms. In the case of Fe(III), the following mechanism is proposed (Scheme 10). The ketone lithium enolate **71** is transmetalated to the iron(III) enolate **74**, an entity that can be thought of as an oxidized enolate, where the unpaired electron is delocalized over the four-atom system, as in **73**. Once this transmetalation occurs, the electronics of the enolate are altered such that the α-carbon is now electrophilic and therefore susceptible to attack by the lithium enolate of the oxazolidinone in the presumed bimolecular rate-determining step. The consequence of this polarity reversal is explained in Scheme 11. The approach of the coupling partners can be depicted in a Newman projection in which there are six possible staggered projections that can be drawn (two diastereotopic sets of three). The two that likely dominate the reaction would align the lithium enolate dipole and the umpolung ferric enolate dipole in the same direction while positioning

(50) For precedent of proton abstraction from carbon radicals, see: Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692–700.

(51) Lide, D. R.; Frederikse, H. P. R. *CRC Handbook of Chemistry and Physics: A Ready-Reference Book of Chemical and Physical Data*; CRC: Boca Raton, FL, 1995.

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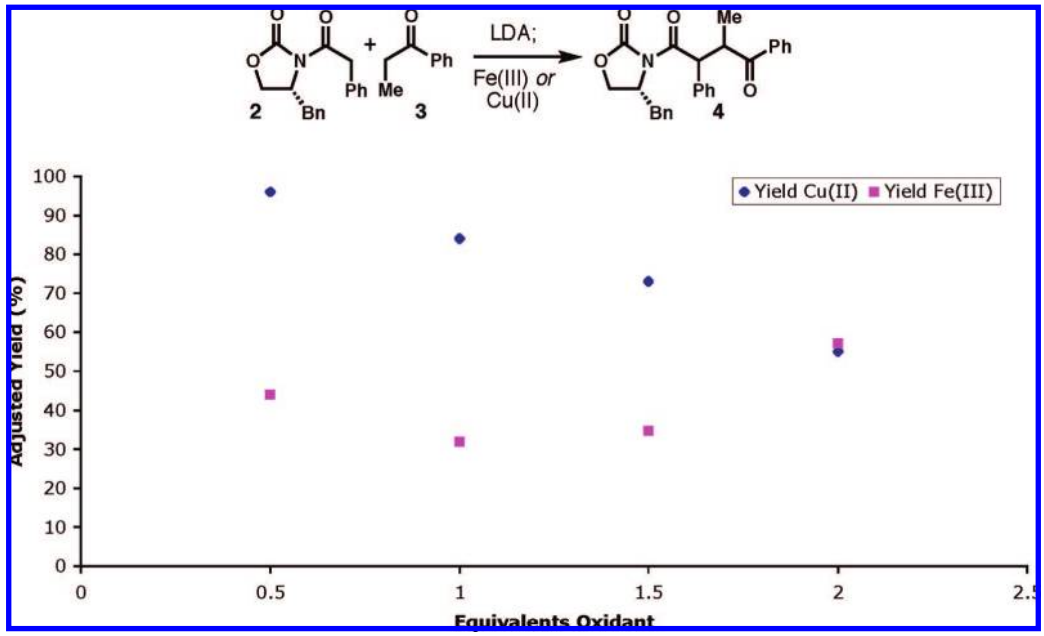
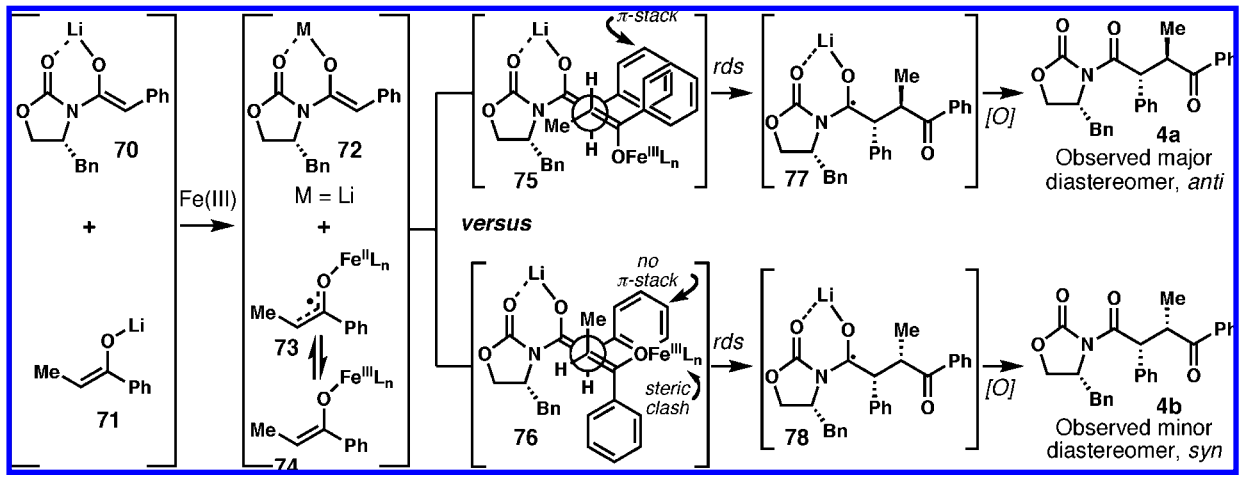
(53) Oxidant efficiency, or adjusted yield, is defined as the yield of oxidative coupling divided by the maximum theoretical yield based on an SET mechanism (one electron transferred per molecule of metal).

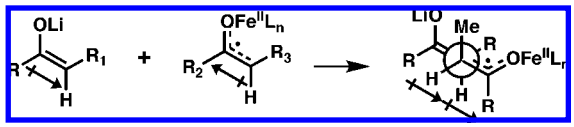
Chart 2. Adjusted Coupling Yield (**2** and **3**) as a Function of Oxidant Stoichiometry



Scheme 10. Proposed $Fe(acac)_3$ Mechanism



Scheme 11. Newman Projection Alignment

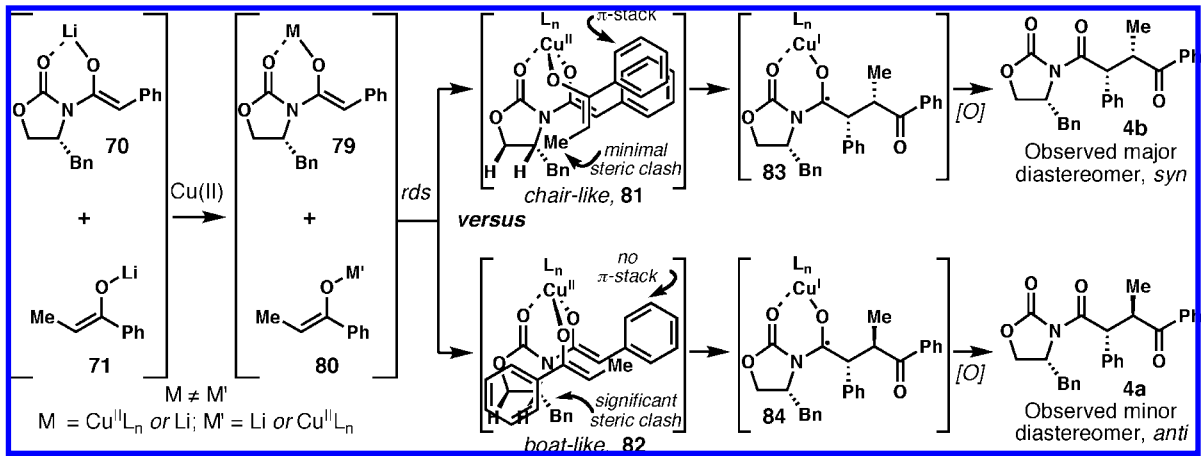


the opposite charge-bearing carbons in close, bond-forming proximity.[54] This rationale narrows the possible Newman projections to **75** and **76**.[55] The low diastereoselectivities obtained at the methyl-bearing carbon are indicative of the admittedly subtle effects differentiating the two modes of approach. In the favored transition state **75**, the presumably bulky iron ligand sphere is as far from any other steric element as possible, and a potentially beneficial π-stacking interaction between the two aromatic rings is geometrically feasible (depending on the electronics of the aryl rings). This type of approach would favor formation of the *anti*-diastereomer **4a**, as observed, and is consistent with the stereochemical result of the analogous homodimerization of two "discreet radicals".[55] Conversely, a potential steric clash between the iron ligand sphere and the proximal phenyl ring would likely raise the relative energy of **76** and lead to the observed minor *syn*-diastereomer **4b**. The electrophilic ferric enolates are then attacked by the lithium oxazolidinone enolates to afford radical anions **77** and **78**, from which one additional electron is removed by another molecule of Fe(III) to provide **4a** and **4b**.

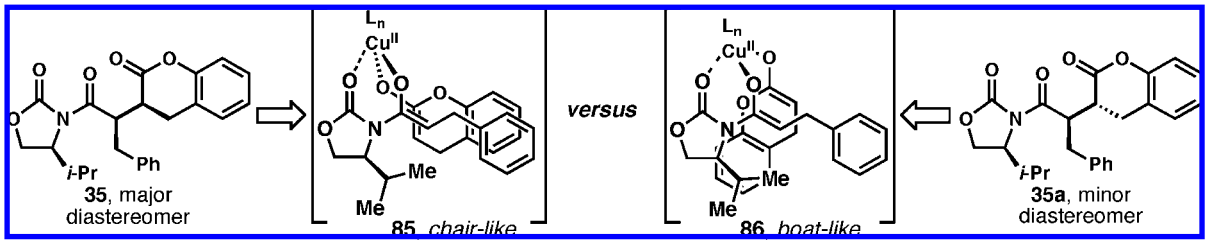
The proposed mechanistic picture changes significantly when Cu(II) is instead employed as the oxidant. In this case, although it is not clear which enolate is transmetalated (as Cu(II) promotes the homodimerization of both monomers, see Scheme 12), it seems more likely that the ketone enolate is exchanged, based on the corresponding efficiencies of the control experiments. This turns out to be inconsequential, as both enolates are appended to a single copper atom in the presumed rate-limiting step: the second-order complexation of the copper enolate with the remaining lithium enolate to yield diastereotopic transition

(54) For a discussion on intermolecular dipole interactions, see: Atkins, P. W. *Physical Chemistry*; Oxford University Press: Oxford, UK, 1995.
(55) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809–2812.

Scheme 12. Proposed Cu(2-ethylhexanoate)$_2$ Mechanism



Scheme 13. Cu(II)-Chelated Transition States Leading to **35** and **35a**



structures **81** and **82**. Once again, subtle steric and electronic effects can be invoked to explain the observed diastereoselection. Complex **81** shows that the new carbon−carbon bond would be formed through an energetically favorable chair-like transition state, affording the observed major *syn*-diastereomer **4b**, minimizing the steric clash between the methyl group and the top face of the oxazolidinone ring and potentially benefiting from a favorable π-stacking interaction between the two aryl rings. In contrast, complex **82** proceeds through a higher energy boat-like transition state with considerable steric clash between the aryl ring and the hydrogen atoms atop the auxiliary, leading to the observed minor *anti*-diastereomer **4a**. The exact nature of the second oxidation is still unclear, with a minimum of three possibilities. Radical anions **83** and **84** could be oxidized by the pendant copper(I) species, expelling copper(0). This seems an unlikely prospect, as no deposition of metallic copper(0) is observed from the reaction mixture. In addition, while copper(I) has been employed in carbanion and enolate homodimerization, it is exercised in conjunction with a cooxidant such as O_2[56] or I_2[57] and has been shown to be incapable of acting as the lone oxidant.[52] These examples imply that copper in its 2+ oxidation state is indeed the active oxidant and has thus been most commonly utilized for enolate couplings. Alternatively, the copper(I) radical anions could transmetalate to another molecule of Cu(II), followed by the second SET process. This also seems doubtful, as the relative kinetics for the mechanism of the second-order transmetalation would be too slow to satisfy the presumably high-energy radical anions. Lastly, and most compelling, a second molecule of copper(II) could reoxidize the pendant copper(I), which would then complete the net two-electron oxidation. This process seems, *a priori*, bimolecular as well, and therefore kinetically too slow for the removal of the second electron. However, X-ray analysis of copper(II) hexanoate, assumed to be structurally related, reveals a dimeric paddlewheel structure in the crystalline state, with the four hexanoate ligands bridging the two *bonded* copper atoms.[58] Moreover, the dimeric structure persists in a solution of acetonitrile.[59] With the presence of the copper−copper bond, copper(II) oxidation of the copper(I) radical anions **83** and **84** seems to be the most likely conclusion of the mechanism.

If the copper-chelated mechanism is correct, then it should be able to explain the diastereoselectivity observed in the syntheses of unsymmetrical succinates (Table 3). Although the reaction proceeded with minimal selectivity for linear esters, the diastereomeric ratio was elevated (albeit still modest) for lactone **35**, at 2.4:1. Examining the potential transition states reveals that analogous chair- and boat-like transition states (**85** and **86**, respectively) effectively predict the stereochemical outcome of the reaction (Scheme 13). Once again, chair-like transition state **85**, while inherently lower in energy, also poses no steric clash with the underside of the chiral auxiliary and could potentially benefit from a favorable π-stacking interaction, leading to the observed major diastereomer. The higher energy boat-like transition state **86** includes an adverse steric relationship with the dihydrocoumarin and bottom face of the oxazolidinone, thus leading to the observed minor diastereomer, **35a**.

Hammett analysis has historically been one of the most valuable tools aiding mechanistic elucidation, often providing clarity with regard to the rate-determining step and transition-

(56) (a) Kauffmann, T.; Beissner, G.; Berg, H.; Koeppelmann, E.; Legler, J.; Schoenfelder, M. *Angew. Chem., Int. Ed.* **1968**, *7*, 540–541. (b) Kauffmann, T.; Beissner, G.; Koeppelmann, E.; Kuhlmann, D.; Schott, A.; Schrecken, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 131–132.
(57) Hampton, K. G.; Christie, J. J. *J. Org. Chem.* **1975**, *40*, 3887–3889.
(58) (a) Doyle, A.; Felcman, J.; Gambardella, M. T. d. P.; Verani, C. N.; Tristao, M. L. B. *Polyhedron* **2000**, *19*, 2621–2627. (b) Mishra, S.; Daniele, S.; Hubert-Pfalzgraf, L. G. *Chem. Soc. Rev.* **2007**, *36*, 1770–1787.
(59) Lah, N.; Giester, G.; Lah, J.; Segedin, P.; Leban, I. *New J. Chem.* **2001**, *25*, 753–759.

Chart 3

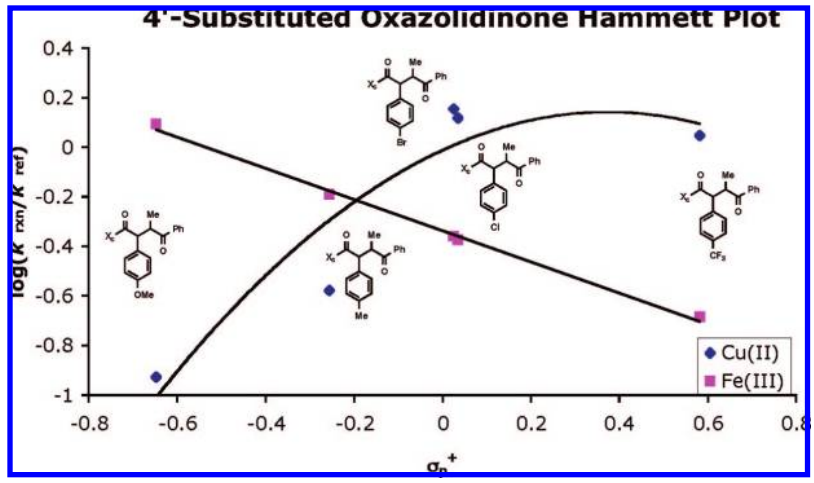
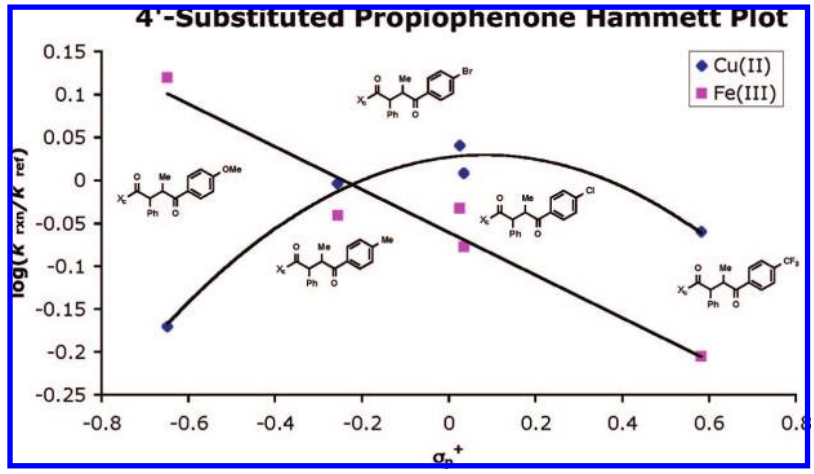


Chart 4



state structure.[60] These linear free energy relationships between rate constant (k_{rxn}/k_{ref}) and substituent parameter (σ_p^+)[61] allow analysis of the change in charge distribution as the reaction proceeds from the ground state to the transition state. Hammett plots were constructed using the data collected in Table 2 for the cross-couplings of 4′-substituted *N*-(phenylacetyl)oxazolidinones with propiophenone **3** (Chart 3) and *N*-(phenylacetyl)-oxazolidinone **2** with 4′-substituted propiophenones (Chart 4) for both oxidants. In the case of Fe(III), linear relationships were observed when varying substitution on either partner. Altering the substitution on the oxazolidinone partner revealed a linear correlation with a ρ-value (ρ_{ox}) equal to -0.63 ($R^2 = 0.996$).[62] A similarly linear correlation was observed upon varying the substitution on the propiophenone coupling partner, providing a ρ-value (ρ_{prop}) equal to -0.25 ($R^2 = 0.934$).[63] These negative reaction constants are indicative of a net loss of charge on the enolate carbon on going from the ground state to the transition state, as explained by the conversion of the full anion enolates to the corresponding *formal* radicals. The small magnitudes are indicative of one-electron chemistry; a considerably larger absolute value would be expected if the rate-determining step proceeds through a two-electron mechanism.[60] This reaction constant is consistent with the proposed mechanism, wherein the rate-determining step is the bond-forming process between the metal enolate **73** and oxazolidinone lithium enolate **72**, yielding radical anions **77** and **78**. The relative magnitudes of the ρ-values ($\rho_{ox} \approx 2.6\rho_{prop}$) reveal deeper insight into the nature of the transition-state structure. These reaction constants suggest a late transition state wherein the oxazolidinone enolate **72** has lost more electron density through nucleophilic attack on the electrophilic ferric enolate **74** than has the ferric enolate through Fe^{III}-to-Fe^{II} oxidation. This could suggest that the ground-state iron enolate is "partially oxidized" in a fast equilibrium between

(60) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: Sausalito, CA, 2006.
(61) Swain, C. G.; Lupton, E. C., Jr *J. Am. Chem. Soc.* **1968**, *90*, 4328–4337.

(62) k_{ref} is the rate constant for coupling of oxazolidinone **2** and propiophenone **3**; k_{rxn} is the rate constant for coupling of substituted oxazolidinones **51** with propiophenone **3**. For the determination of ρ_{ox}, the following expression was used: $k_{rxn}/k_{ref} = \log[1 - x_p/x_r]/\log[1 - y_p/y_r]$, where ρ_{ox} is the reaction constant, x_p is the millimoles of coupled product formed from substituted oxazolidinone, x_r is the initial millilmoles of propiophenone, y_p is the millimoles of product formed from unsubstituted oxazolidinone, and y_r is the initial millimoles of propiophenone.
(63) k_{ref} is the rate constant for coupling of oxazolidinone **2** and propiophenone **3**; k_{rxn} is the rate constant for coupling of oxazolidinone **2** with substituted propiophenones **52**. For the determination of ρ_{prop}, the following expression was used: $k_{rxn}/k_{ref} = \log[1 - x_p/x_r]/\log[1 - y_p/y_r]$, where ρ_{prop} is the reaction constant, x_p is the millimoles of coupled product formed from substituted propiophenone, x_r is the initial millimoles of oxazolidinone, y_p is the millimoles of product formed from unsubstituted propiophenone, and y_r is the initial millimoles of oxazolidinone.

73 and **74** (Scheme 10) and can most accurately be described as residing within the continuum between the full anion ferric and formal α-radical ferrous enolates.

Interestingly, no such linear correlations were observed for the corresponding experiments using Cu(II) as the oxidant (Charts 3 and 4). Given the suggested mechanism (Scheme 12), such proportionality would not be expected. The proposed rate-determining step is the complexation of a lithium enolate and a copper enolate, the end result of which, complexes **81** and **82**, are isoelectronic with the ground-state reacting partners at the carbon atom of the corresponding enolates. Instead, non-linear plots were observed in both cases, which is generally indicative of a change in mechanism or rate-determining step as the substituents are altered.[64] As discussed earlier, the control experiments (Scheme 5) show that Cu(II) is clearly capable of binding to and oxidizing both partners. As such, one might anticipate two complementary transmetalation/chelation sequences involving **79** and **80** (thus a change in mechanism and rate-determining step), the diversion of which might be governed by differing electronics of the corresponding lithium enolates.

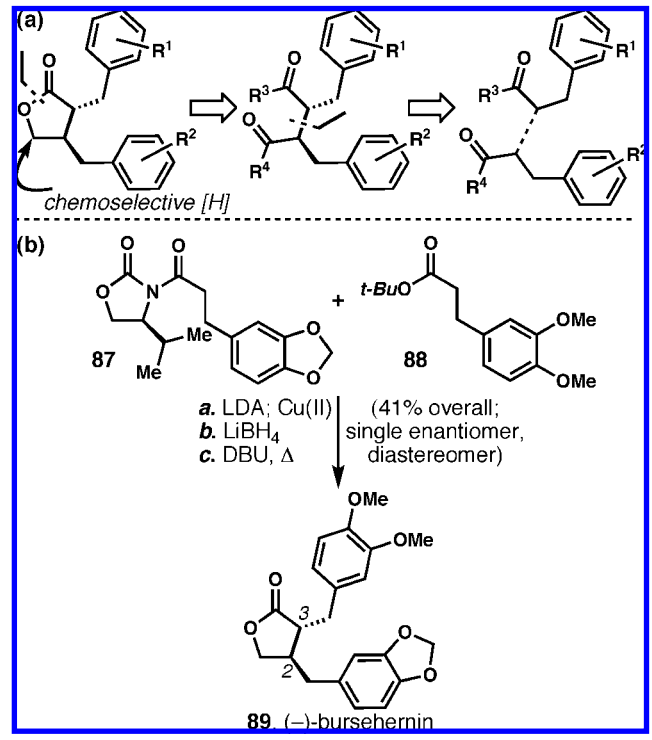
Application

The ultimate validation for the development of any new method is its application to relevant target-oriented synthesis. Oxidative coupling of two different types of enolates has been sparingly employed in complex natural product synthesis,[23,25,65] likely as a consequence of the absence of an intermolecular heterocoupling method. By way of demonstration, two simple case studies were chosen in order to highlight the utility of the oxidative heterocoupling of enolates.

Bursehernin (**89**, Scheme 14b) is a lignan lactone isolated by McDoniel and Cole in 1972.[7] **89** was isolated from the organic extracts of *Bursera schlechtendalii*, a Mexican plant, and was found to exhibit antitumor activity against the cancer test system, 9KB (adenocarcinoma of nasal pharynx). This lactone is a member of an extremely large class of natural products known as lignans. Lignans are biosynthetically derived from the oxidative dimerization of cinnamic alcohols through single-electron oxidation of phenols.[10] Much more complex lignans are derived from these simple dimers through a vast array of oxidative transformations, including selective differential oxidation of the two aromatic rings. From this biosynthetic pathway arises symmetric and unsymmetric dibenzyl lignan lactones, the latter being the category to which bursehernin belongs. Retrosynthetically, it seemed that an intuitive method for constructing any lignan lactone would be through the oxidative coupling of enolates (Scheme 14a). Many groups have reported the synthesis of symmetric dibenzyl lactones through use of oxidative enolate homocoupling.[27,66] However, enolate heterocoupling provided an avenue to access unsymmetric dibenzyl lactones by this retrosynthetic strategy for the first time.

As shown in Scheme 14b, the oxidative union of oxazolidinone **87** and *tert*-butyl ester **88** proceeded smoothly, furnishing **47** in 58% yield, as an inconsequential (*vide infra*) 1.6:1 mixture of diastereomers (see Table 3). Chemoselective reductive

Scheme 14. (a) Lignan Lactone Retrosynthesis and (b) Total Synthesis of (−)-Bursehernin[a]



[a] Reagents and conditions: (a) **87** (1.0 equiv), LDA (1.15 equiv), LiCl (5.0 equiv), PhMe, −78 °C (10 min) to 0 °C (10 min) to −78 °C (10 min), **88** (1.75 equiv), PhMe, LDA (1.85 equiv), −78 °C, 30 min, then Cu(2-ethylhexanoate)$_2$, −78 to 25 °C, 20 min; (b) $LiBH_4$ (10 equiv), MeOH (5.0 equiv), THF, −78 to −10 °C, 1.5 h; (c) DBU (10 equiv), PhMe, 110 °C, 24 h, 41% overall.

removal of the chiral auxiliary with lithium borohydride afforded a primary alcohol (not pictured), which was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene to cyclize to the lactone. The basic conditions of this final step also served to epimerize the α-carbon (C-3), efficiently funneling to a single diastereomer favoring the α,*β-trans*-dialkyl lactone. The result of this sequence was a three-step, enantio- and diastereoselective total synthesis of (−)-bursehernin proceeding in 41% overall yield. It also marked a significant advance in the synthetic efficiency (both yield and number of steps) of unsymmetric dibenzyl lignan lactones,[67a,b] adding to Sibi's elegant approach to lignans, with which these lactones might also be rapidly accessed.[67c] It is noteworthy that lignan lactones have been synthetically elaborated to many lignan subclasses,[10] and thus, this advance represents a general entry into this family of natural products.

Matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes known to aid the degradation and reconstruction of connective tissue.[8] As such, MMPs have been active targets of pharmaceutical research toward the cures for oncological, cardiovascular, and inflammatory diseases. Discovered 22 years ago, 2,3-dialkylsuccinylhydroxamic acid derivatives **91** (Scheme 15a) have proven one of the most broadly potent class of MMP inhibitors and have dominated the therapeutic strategies ever since.[8] Succinic half-esters/amides **90** are

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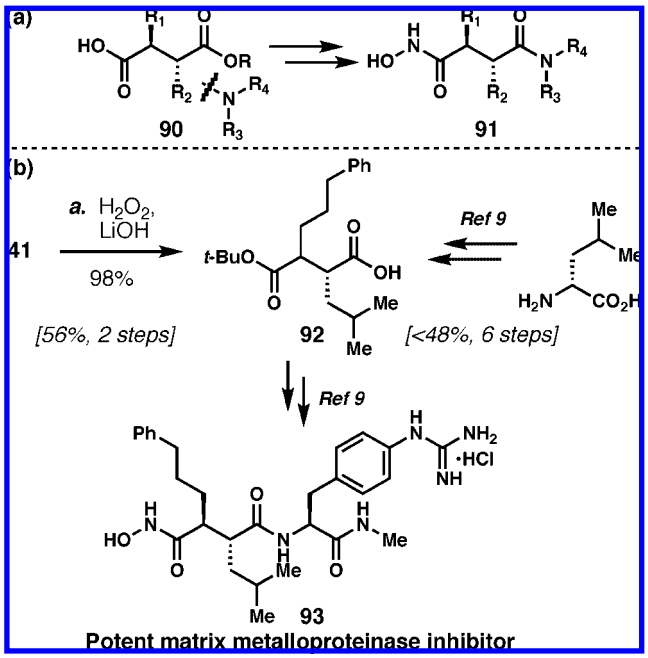
(65) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569.
(66) (a) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549–2555. (b) Kise, N.; Ueda, T.; Kumada, K.; Terao, Y.; Ueda, N. *J. Org. Chem.* **2000**, *65*, 464–468.
(67) (a) Honda, T.; Kimura, N.; Sato, S.; Kato, D.; Tominaga, H. *J. Chem. Soc., Perkin Trans.* **1994**, *1*, 1043–1046. (b) Enders, D.; Lausberg, V.; Del Signore, G.; Berner, O. M. *Synthesis* **2002**, 515–522. (c) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-X. *J. Org. Chem.* **2002**, *67*, 1738–1745.

Scheme 15. (a) Hydroxamic Acid Synthesis and (b) Synthesis of MMP Inhibitor Intermediate[a]



[a] Reagents and conditions: (a) H_2O_2 (10 equiv), LiOH (5 equiv), THF/H_2O (3:1), 0 to 25 °C, 36 h.

regularly employed as intermediates in the syntheses of these drug candidates, but the enantioselective routes to such compounds generally suffer from lengthy sequences and low overall yields.[9,36] This is a particularly debilitating problem in a discovery setting, where an innumerable quantity of structurally diverse analogues must be generated in order to appropriately probe the structure−activity relationships between the inhibitors and enzymes. For example, guanadinium hydroxamate **93** was recently found to be a potent dual inhibitor of MMPs and tumor necrosis factor α, converting enzymes with high water solubility (Scheme 15b);[9] the synthesis of this inhibitor is reported in 12 steps and 7.6% overall yield. Part of the inefficiency of this sequence can be attributed to the synthesis of succinic half-ester **92**, a key common intermediate for the generation of all of the reported analogues, which required six steps to procure in less than 48% yield (yields for two steps not reported). Oxidative enolate heterocoupling provides an alternate route to **92**: coupling of the appropriate oxazolidinone and *tert*-butyl ester (not pictured) provides oxazolidinone **41** (see Table 3), the hydrolysis of which (under non-epimerizing conditions) proceeded smoothly, thus intercepting the published synthesis. This two-step sequence, proceeding in 56% overall yield, is a highly efficient approach to the core of this inhibitor and further demonstrates the power and utility of oxidative intermolecular heterocoupling of enolates.

Conclusions

The power and potential utility of oxidative enolate coupling was unveiled upon its initial discovery in 1935. This admittedly non-intuitive chemistry provides a one-step means of forging a carbon−carbon bond *directly*, with no need for superfluous prefunctionalization of the monomeric starting materials. The reaction was limited to homodimerization for 38 years, when the only two studies involving the analogous cross-coupling were reported. Surprisingly, these accounts were not expanded upon until this research program was initiated in 2006, geared at broadening the utility of the chemistry through an intimate understanding of the reaction. Carefully designed exploratory investigations have illuminated the strengths and limitations of this method and have led to the most complete mechanistic understanding of this type of chemistry to date. Exploiting the innate oxidation state of the monomeric carbonyl species allows for highly convergent access to complex molecules that would be difficult to procure by other chemical methods. This convergency has been demonstrated through streamlined access to lignan natural products and medicinally relevant compounds. While oxidative enolate heterocoupling is a field still in its infancy, it has been demonstrated to greatly simplify complex synthetic problems.[25,31,33,65,68] It is anticipated that this area of research will continue to be fruitful and will find wide application in the synthetic community.

Acknowledgment. We thank Drs. D. H. Huang and L. Pasternack for NMR spectroscopic assistance, Dr. G. Siuzdak for mass spectrometric assistance, and Drs. A. Rhinegold and R. Chadha for X-ray crystallographic assistance. Financial support for this work was provided by The Scripps Research Institute, Amgen, AstraZeneca, the Beckman Foundation, Bristol-Myers Squibb, DuPont, Eli Lilly, GlaxoSmithKline, Pfizer, Roche, the Searle Scholarship Fund, the Sloan Foundation, and the NIH (NIGMS).

Supporting Information Available: Full characterization, including ^1H and ^{13}C NMR spectra, and experimental procedures for selected compounds; complete refs 11e and 36a; X-ray crystallographic data, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA804159Y

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