

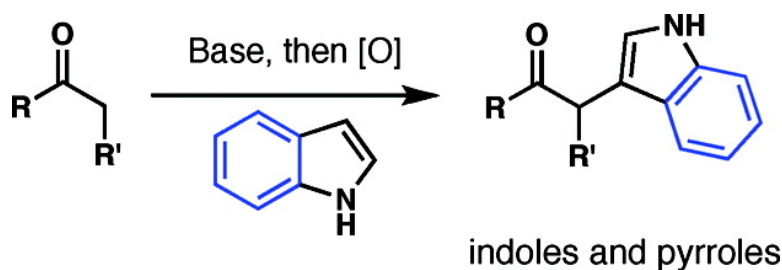
Article

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J. Am. Chem. Soc., **2007**, 129 (42), 12857-12869 • DOI: 10.1021/ja074392m • Publication Date (Web): 27 September 2007

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Scope and Mechanism of Direct Indole and Pyrrole Couplings Adjacent to Carbonyl Compounds: Total Synthesis of Acremoauxin A and Oxazinin 3

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Abstract: Full details are provided for a recently invented method to couple indoles and pyrroles to carbonyl compounds. The reaction is ideally suited for structurally complex substrates and exhibits high levels of chemoselectivity (functional group tolerability), regioselectivity (coupling occurs exclusively at C-3 of indole or C-2 of pyrrole), stereoselectivity (substrate control), and practicality (amenable to scaleup). In addition, quaternary stereocenters are easily and predictably generated. The reaction has been applied to a number of synthetic problems including total syntheses of members of the hapalindole family of natural products, ketorolac, acremoauxin A, and oxazinin 3. Mechanistically, this coupling protocol appears to operate by a single electron-transfer process requiring generation of an electron-deficient radical adjacent to a carbonyl which is then intercepted by an indole or pyrrole anion.

Introduction

Chemoselectivity stands as one of the greatest challenges to overcome in the invention of useful synthetic methodologies for carbon-carbon bond formation between two different organic entities (cross-coupling). Figure 1 depicts such a cross-coupling scenario using indole as an example. Of these five different paradigms, the union of heteroaryl boronic acids with halogenated sp^2 and sp^3 hybridized carbon atoms (Suzuki coupling, e.g., 1) is the most widely employed.¹ Indeed, strategic substrate prefunctionalization has historically served as the most reliable means by which to direct such couplings. In the second type of coupling, a functionalized, protected indole is merged with an unfunctionalized substrate. A Heck reaction is an example of this transformation.² The third type of coupling is another version of the Heck reaction, involving the union of an unfunctionalized, N-protected indole with a suitably functionalized substrate.³ The fourth tactic involves merging unfunctionalized N-protected indole with an unfunctionalized substrate.⁴ This method has been successfully demonstrated numerous times in both inter- and intramolecular contexts based on the ability of electron-rich aromatics to undergo electrophilic palladation.

The fifth and final coupling paradigm requires no prefunctionalization or protection and relies solely on the innate reactivity of the indole and substrate. A regioselective Friedel-Crafts alkylation⁵ would fit into this or the previous category. Several of the coupling strategies shown in Figure 1 might be aptly marketed under the banner of "C-H functionalization".⁶ In this full account, the scope, mechanism, and application of a new reaction fitting into the fifth category will be discussed. This reaction accomplishes the coupling of unfunctionalized indoles⁷ and pyrroles⁸ with various carbonyl compounds such as esters, imides, lactones, lactams, ketones, and amides. The reaction exhibits high levels of chemoselectivity (functional group tolerability), regioselectivity (coupling occurs exclusively at C-3 of indole or C-2 of pyrrole), stereoselectivity (substrate control), and practicality (amenable to scaleup). As a meaningful demonstration of its utility, the method has been applied effectively to a number of problems in total synthesis, including several members of the hapalindole family,^{7,9} ketorolac,⁸ acremoauxin A, and oxazinin 3.

Background and Historical Context

This research program initiated in 2003 when the hapalindole family of natural products was targeted for synthesis (see Chart

- (1) Suzuki, A.; Brown, H. C. *Organic Syntheses Via Boranes*, Vol. 3, *Suzuki Coupling*; Aldrich Chemical Company, Inc.: Milwaukee, WI, 2003.
- (2) For example, see: (a) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *49*, 2657–2662. (b) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338.
- (3) For example, see: (a) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317–3320. (b) Kozikowski, A. P.; Ma, D.; Brewer, J.; Sun, S.; Costa, E.; Romeo, E.; Guidotti, A. *J. Med. Chem.* **1993**, *36*, 2908–2920.
- (4) (a) This reaction has extensive precedent, see: Itahara, T. *J. Chem. Soc., Chem. Commun.* **1981**, 254–255. (b) For additional examples, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, 2nd ed.; Elsevier: San Diego, CA, 2007. (c) For a microwave-mediated variant, see: Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175.

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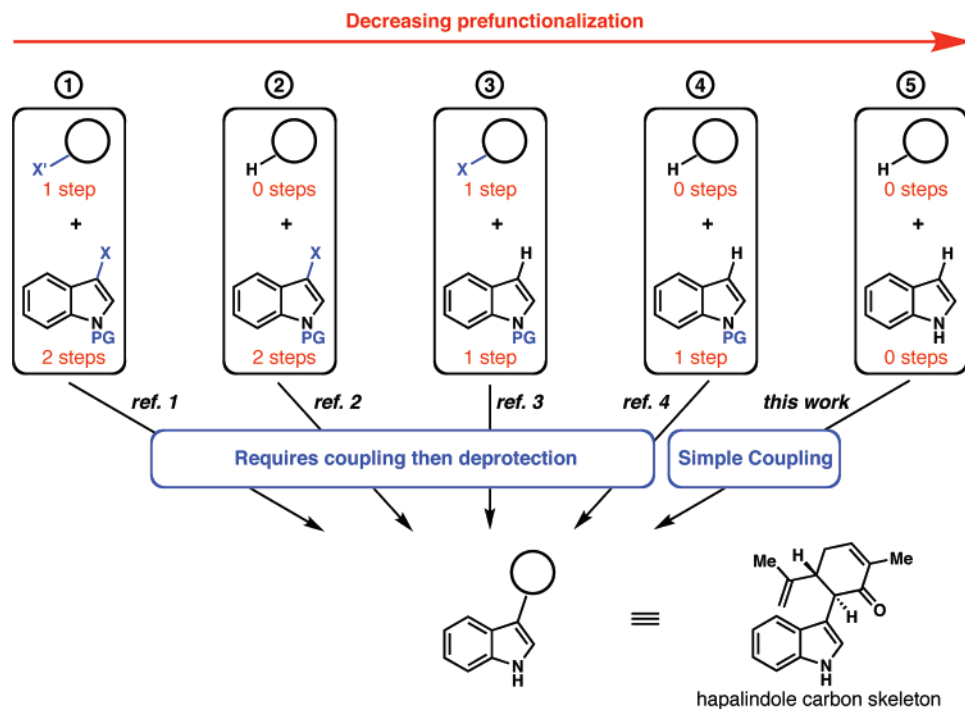
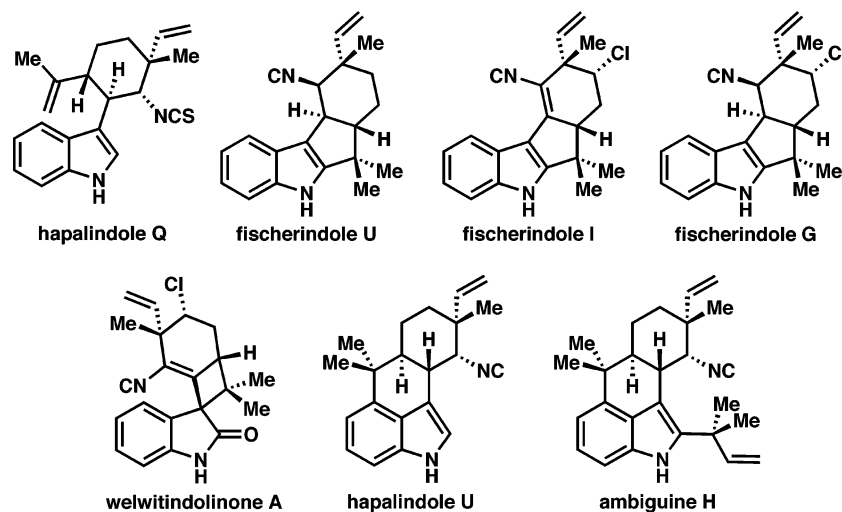


Figure 1. Cross-coupling paradigms.

Chart 1. Representative Members of the Hapalindole Family of Natural Products



1).¹⁰ In principle, the most efficient means to secure the core of these molecules would be *via* the direct attachment of indole to a terpene such as carvone.¹¹ The literature revealed only one method that directly attaches two such compounds in the desired manner,¹² ironically also reported in the context of an elegant total synthesis of hapalindole Q. As delineated in Scheme 1, this coupling falls into the first category (see Figure 1) and as such required prefunctionalization of both substrates in order to achieve the desired reactivity. Although this is a clever solution to the problem, a different approach was sought that

could avoid any “preprogramming” of the substrates. In addition, potential regioselectivity issues could arise as a consequence of using the enol-acetate derived from carvone as a coupling partner in the Albizati approach (i.e., the coupling could occur on any one of the three olefins present).¹³

Barton’s classic synthesis¹⁴ and structural reassignment¹⁵ of usnic acid (**11**) provided invaluable inspiration for the development of an alternative route to the desired indole–carvone adduct (Figure 1). In Barton’s synthesis, treatment of phenol **6** with potassium ferricyanide oxidized it to the delocalized phenoxy radical, initiating a cascade reaction. Two of the resonance contributors, **7** and **8**, selectively heterodimerized to

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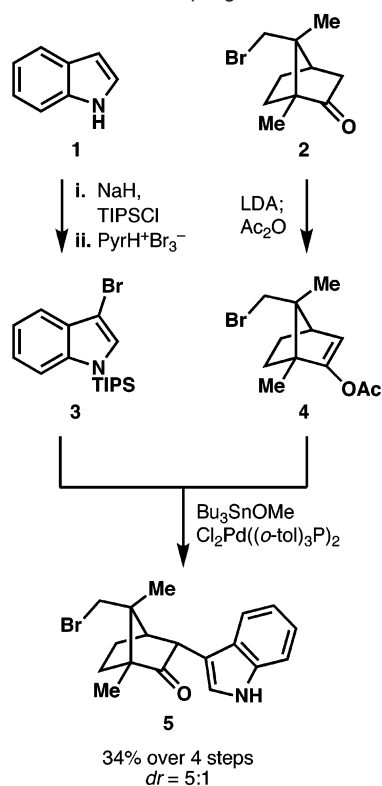
(11) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125–3126.

(12) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499–3502.

(13) The coupling of the enol acetate of carvone with 3-bromo-*N*-TIPS-indole has been attempted using Albizati’s conditions, and none of the desired product was obtained.

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Scheme 1. Albizati's Indole Coupling Reaction

form the coupled adduct **9**. Subsequent tautomerization, hemiketalization, and elimination of water directly furnished usnic acid (**11**) in one synthetic operation (Scheme 2).

One of the most impressive aspects of Barton's synthesis resides in the selective formation of a coupling product that arises from the heterodimerization of *ortho*- and *para*- localized radicals (**7** and **8**). This precedent led to a simple hypothesis: if heterocoupling of two radicals was truly occurring in the usnic acid synthesis, then an analogous reaction might occur between indole and a carbonyl containing entity (Scheme 3). Theoretically, if an appropriate oxidant was found that could simultaneously oxidize the carvone enolate to the radical and the indole anion to the radical, then perhaps a heterocoupling could be achieved between the two species. For the indole anion, the HOMO coefficient is largest on C-3, which causes indole to be nucleophilic at this position. In light of this knowledge, our hopes for successfully accomplishing the desired coupling were further bolstered by the fact that the same orbital is invoked for the radical species (SOMO). It therefore seemed reasonable to assume that the indole radical should also react at C-3.¹⁶ However, there were still several potential pitfalls to this proposed transformation: (1) securing an oxidant that could simultaneously oxidize both species, (2) avoiding a statistical product distribution in the intermolecular coupling to obtain a good yield of the heterodimer without requiring prohibitive excesses of reagents or starting materials, (3) overoxidation of the indole partner, and (4) controlling the diastereoselectivity of the coupling due to the intermediacy of a radical species.

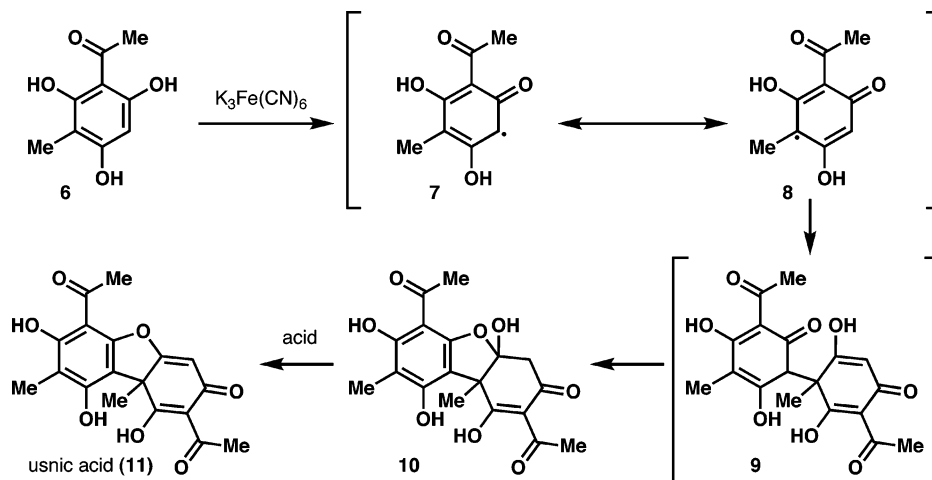
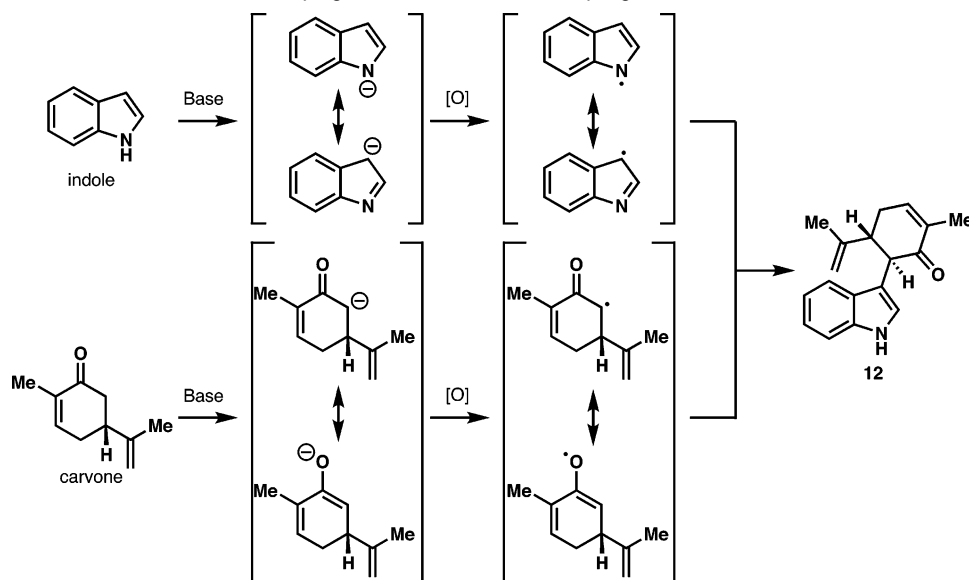
There is a myriad of chemical literature concerning the radical reactions of ketones, specifically the oxidation and subsequent dimerization of ketone enolates. It is instructive at this juncture

to review a brief history of the development of this C–C bond forming reaction, in an effort to convey the context in which these current investigations were undertaken. The prototypical oxidative enolate coupling was first reported over 70 years ago in 1934, when Ivanoff and Spassoff treated the magnesium chloride enolate of sodium phenylacetate with molecular bromine and observed a 22% yield of the dimer.¹⁷ The authors posited that the reaction occurs through a radical intermediate; however, it was many years before any formal mechanistic insights were gained.¹⁸

This observation by Ivanoff subsequently lay dormant for several decades. During these intervening years, little was truly known about the reaction or substrate scope; in fact, to this day, many questions remain unanswered concerning this intriguing reaction. In 1968, Kauffmann reported the first example of an oxidative dimerization of a ketone enolate, namely acetophenone, using copper(I) salts, albeit in modest yields.¹⁹ Following this publication, Rathke reported the first use of a soluble copper(II) oxidant [copper(II) valerate] in the oxidative dimerization of ester enolates in moderate to excellent yields.²⁰ Saegusa subsequently demonstrated efficient, high-yielding dimerizations of ketone enolates, using a variety of copper(II) based oxidants.²¹ He also described the heterocoupling of two different ketone enolates, which required 3 equiv or more of one of the coupling partners to furnish acceptable yields of the *heterocoupled* product. Many reports have appeared that use a wide variety of oxidants to effect the couplings, including copper salts,^{18b,c,19–22,23c,d,24m,25,26d} iron salts,^{18d,23,37d,e} iodine,^{18a,c,23d,24,28b,33,37a–c} *N*-iodosuccinimide,²⁵ hypervalent iodine-based reagents,²⁶ silver salts,^{18b,27} titanium salts,^{26d,28} potassium permanganate,²⁹ direct electrochemical oxidation,^{18a,30} short chain alkyl polyhalides,³¹ and bromine.^{17,32} A few studies involving the dimerization of enolates conjugated throughout an aromatic system have been reported,^{29,33} which show the versatility of this coupling reaction in the formation of a wide variety of dimerized compounds. Several reports exist that elicit the coupling of other stabilized anions, such as phosphine oxides,³⁴ sulfoxides/sulfones,³⁴ and methylpyridines^{36b} under

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Scheme 2. Barton's Classic Synthesis of Usnic Acid (11)**Scheme 3.** Initial Mechanistic Rationale in Developing the Oxidative Indole Coupling Reaction

similar conditions. Oxidative dimerizations of indoles have been reported using hypervalent iodine in the context of a biomimetic calycanthaceous alkaloid synthesis.³⁵ Asymmetric dimerizations can be performed using a variety of chiral auxiliaries,^{18c,22i,23d,24m,25,26c,d,28b,d} and there is even one report that oxidizes a chiral titanium enolate to achieve modest asymmetric induction.^{23g} Several groups have shown that intramolecular couplings can proceed in impressive yields.^{18b,d,22c–f,i,23b,25,37d,e} However, the inability to extend such

successes to intermolecular reactions is both disappointing and expected due to the assumed mechanistic explanation.

Given the extensive history of oxidative enolate coupling chemistry,³⁶ it was clear that the homodimerization of two enolates to form a symmetrical diketone was straightforward using a wide range of oxidants. The use of intramolecular oxidative coupling to selectively form a heterocoupled product

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without a prohibitive excess of one of the coupling partners remained a far more daunting task. In fact, the technology was so limited in scope that it had been scarcely utilized in total syntheses,^{18d,23b,d,26d,37} mainly in the construction of various symmetrical lignans.

In order to address the selectivity problem (homocoupling vs heterocoupling) in intermolecular couplings, a few potential solutions have been put forth. In these reports, selective homo- or heterocouplings are performed by first converting one or both coupling partners into either the enol ethers or silyl enol ethers and reacting those with either ketones or other silyl enol ethers to give coupled products in reasonable yields. A similar reaction manifold has been observed for the coupling of enamines with various nucleophilic π -systems.³⁸ A variety of oxidants have been utilized in such couplings including Mn(OAc)₃,³⁹ Ag₂O,⁴⁰ TiCl₄,⁴¹ Cu(OTf)₂,^{22f} CAN,⁴² direct electrochemical oxidation,⁴³ (EtO)VOCl₂,⁴⁴ and Fe(phen)₃(PF₆)₃.⁴⁵ Using vanadium oxidants, it was discovered that selective heterocouplings could be performed by exploiting the differing rates of oxidation of sterically dissimilar enol silanes.⁴⁴ Silicon or titanium tethers can be employed to ensure that a heterocoupling will occur between two distinct carbonyl compounds.⁴⁵ Similarly, it was shown that two different esters could be heterocoupled by constructing the mixed diester of BINOL.^{28e} The selective reaction of silyl enol ethers with furans has also been reported.⁴⁶ Unfortunately, these studies stopped short of achieving a selective heterocoupling of two free carbonyl compounds *without* resorting to prefunctionalization of one or more of the substrates. It is likely that enolate-type couplings would find more widespread use if this were possible.

Given the aforementioned considerations and the somewhat daunting precedent, success of an oxidative coupling to forge the key bond in the hapalindoles seemed unlikely. Experimental studies were therefore initiated in the hope that a greater understanding of the process could be realized and perhaps the

methodology could be rendered more synthetically useful. Indeed, when a mixture of carvone enolate and indole anion were treated with FeCl₃ as oxidant, a minor amount (8%) of the desired coupled product (**12**) was obtained as a single diastereomer (Table 1, entry 15).

Optimization

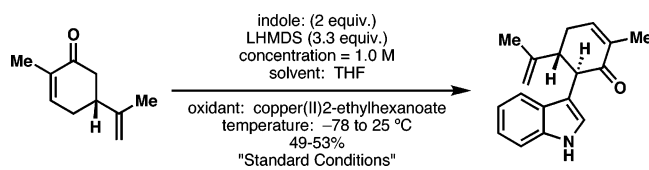
Given the initial success, a more detailed study and optimization of the direct indole coupling reaction was undertaken. It was initially reasoned that the oxidant played a major role in the efficiency of the reaction, so a variety of oxidants were screened that were known (*vide supra*), or predicted, to promote the direct coupling reaction (Table 1). It was quickly discovered that FeCl₃ did not have to be used as a DMF solution (as is commonly reported in enolate oxidation)^{23a} but could simply be added to the reaction as a solid, a finding that facilitated the screening of the remaining oxidants. In addition to the technical simplicity, the reactions were much cleaner in the absence of DMF. While many common oxidants [I₂, K₃Fe(CN)₆, Mn(OAc)₃] failed to furnish any of the desired coupled product, success was realized when copper-based oxidants were explored. A screen of several readily available soluble copper salts led to the selection of copper(II) 2-ethylhexanoate as the optimum oxidant for the desired coupling reaction, in part due to its high solubility in organic solvents. It should also be noted that these reactions were extremely “clean” as monitored by TLC; only **12**, indole, and two diastereomeric carvone dimers were observed.

In addition to the “standard” oxidants preceded in the literature for these coupling reactions, several other oxidants should be mentioned, since they unexpectedly provided product. For example, ceric ammonium nitrate (CAN) cleanly provided the desired product in 16% yield, even though it was not soluble in THF and had never before been used in an oxidative enolate coupling (however, it has been used in enol silane couplings, *vide supra*). Interestingly, if CAN was added as a solution in DMF, no product was observed. Surprisingly, Pb(OAc)₄ also gave a 17% yield of the product when used as a solution in DMF, even though it too had never been employed in an oxidative enolate coupling. It was also discovered that by changing the ligand environment (and therefore tuning the oxidation potential of the metal center), the outcome of the coupling could be modulated [i.e., Mn(acac)₃ versus Mn(OAc)₃]. Also worthy of note is that stoichiometric palladium(II) provided no detectable product.⁴⁷

Once the proper oxidant was selected, a systematic screen of the other reaction parameters was undertaken, beginning with a search for the optimum solvent (Table 1). A screen of common solvents revealed that DCM and THF provided identical results, so THF was selected for its ease of use with various bases. A study of an assortment of bases showed that LHMDs was

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Table 1. Indole–Carvone Coupling Optimizations


entry	change from standard conditions	yield
1	oxidant = iodine	0%
2	oxidant = potassium ferricyanide	0%
3	oxidant = vanadyl acetylacetonate	0%
4	oxidant = cobalt(II) acetylacetonate	0%
5	oxidant = silver(I) trifluoromethanesulfonate	0%
6	oxidant = chromium(VI) oxide	0%
7	oxidant = palladium(II) acetate	0%
8	oxidant = ferrocenium hexafluorophosphate	0%
9	oxidant = carbon tetrachloride	0%
10	oxidant = manganese(III) acetate	0%
11	oxidant = cobalt(II) acetate	0%
12	oxidant = iodobenzene bistrifluoroacetate	trace
13	oxidant = xenon difluoride	trace
14	oxidant = lead tetraacetate	trace (17%) ^a
15	oxidant = iron(III) chloride	8% (8%) ^a
16	oxidant = iron(III) acetylacetonate	13%
17	oxidant = titanium tetrachloride	14%
18	oxidant = manganese(III) acetylacetonate	15%
19	oxidant = ceric ammonium nitrate	16% (trace) ^a
20	oxidant = copper(II) 3,5-diisopropylsalicylate	20%
21	oxidant = copper(II) chloride	25% (8%) ^a
22	oxidant = copper(II) 2-pyrazinecarboxylate	30%
23	oxidant = copper(II) acetate	30%
24	oxidant = copper(II) trifluoromethanesulfonate	46%
25	oxidant = copper(II) acetylacetonate	47%
26	oxidant = copper(II) trifluoroacetylacetonate	48%
27	oxidant = copper(II) 2-ethylhexanoate	49–53%
28	solvent = DME	18%
29	solvent = Et ₂ O	37%
30	solvent = CPME	ca. 40%
31	solvent = DCE	45%
32	solvent = DCM	49%
33	solvent = THF	49–53%
34	concentration = 0.01 M	43%
35	concentration = 0.1 M	44%
36	concentration = 1.0 M	49–53%
37	concentration = neat	43%
38	temperature = –78 °C	0%
39	temperature = –78 to –43 °C	11%
40	temperature = –78 to –20 °C	47%
41	temperature = –78 to 0 °C	45%
42	temperature = –78 to 23 °C	40%
43	indole equiv = 1	27%
44	indole equiv = 3	60%
45	indole equiv = 4	66%
46	indole equiv = 5	77%

^a When added as a solution in DMF.

optimal, but LDA provided similar results. Changing the cation (i.e., Na, K) only proved detrimental to the yield. It was also found that the optimum concentration was 1.0 M in THF as shown in Table 1. There was a subtle trend toward higher yields with increasing concentration, but this was limited by the solubility of the copper oxidants. Various methods of adding the oxidant were also investigated, and the highest yield was observed when the copper salt was added as a solid (instead of in solution) presumably due to increased reaction concentration.

Next, a temperature screen (Table 1) revealed that the ideal temperature for oxidant addition was –20 °C.⁴⁸ However,

(48) The experimental procedure involved immediately transferring the flask containing the reaction mixture and the oxidant at –78 °C into a bath of the desired temperature (i.e., –20 °C in this entry) and allowing the reaction to stir for 10 min before quenching.

adding the oxidant at –78 °C, removing the cooling bath, and allowing the reaction to naturally warm to ambient temperature before quenching provided a slightly higher yield than that of the corresponding reaction at –20 °C. The effect on the yield with varying equivalents of indole was also examined, and not surprisingly, as the amount of indole was increased, the yield also increased proportionately (Table 1). However, limiting the loading to 2 equiv provides an appropriate balance between yield and amount of oxidant.

Perhaps the most mechanistically revealing of all the optimization studies undertaken was that of oxidant stoichiometry. As is clearly evident from the graphical depiction in Figure 2, a full stoichiometric amount of oxidant was not required to drive the reaction to completion. In fact, only 0.5 equiv, relative to both coupling partners, was required to completely consume the carvone, and any excess oxidant only caused minor fluctuations in yield. The short-term lesson learned is that less oxidant was needed to obtain the same yield, thus simplifying the procedure. The mechanistic implications of this finding will be discussed shortly (*vide infra*).

The optimizations delineated above led to the following simple procedure: To a solution of carbonyl compound (1 equiv) and indole (2 equiv) in THF (1.0 M) at –78 °C in a flame-dried flask under a nitrogen atmosphere was added a 1.0 M solution of LHMDs (3.3 equiv). After stirring for 30 min at –78 °C, the septum was removed, solid copper(II) 2-ethylhexanoate (1.5 equiv) was rapidly added in one portion, and the septum was quickly replaced.⁴⁹ The flask was then removed from the cooling bath and allowed to warm to ambient temperature, and then the reaction was quenched. Using this procedure, the reaction was found to be efficient and practical, even on a large scale, with no diminution in yield.⁵⁰

Scope

Table 2 summarizes the range of couplings that were examined in both the initial communication of this work and a wide variety of new substrates that have since been investigated. Most simple ketones couple efficiently including carvone (**12**), chromanone (**25**), tetralone (**24**), and menthone (**38**). Ketones that are much smaller (coupling at a terminal methyl group) are more prone to homodimerization, which explains the lower yield with substrates such as propiophenone (**44**). More highly substituted carbonyl compounds such as chloroketone **42**, vinyl ketone **34**, steroid **23**, and decalin **45** proceed as well, if not better than, simpler ketones. Such reactions allow tremendous complexity to be built into a target molecule using simple chemistry, which would otherwise require multiple steps to accomplish.

As already alluded to (*vide supra*), functional group tolerance was an important parameter to consider while developing the oxidative indole coupling reaction. Several noteworthy examples include unprotected or reactive functional groups that could potentially undergo competing side reactions. For example, chloroketone **42** is unreactive toward the radical-generating reaction conditions. Steroid **37** proceeds without requiring

(49) It was found that opening the reaction flask to the ambient atmosphere for the time required for addition was not detrimental to the reaction yield. Comparison studies were performed in which the reaction was performed under meticulous Schlenk technique (degassed, rigorously dry, and the oxidant was added as a solution in THF) and an identical yield of the product was obtained.

(50) See Supporting Information for a detailed general procedure.

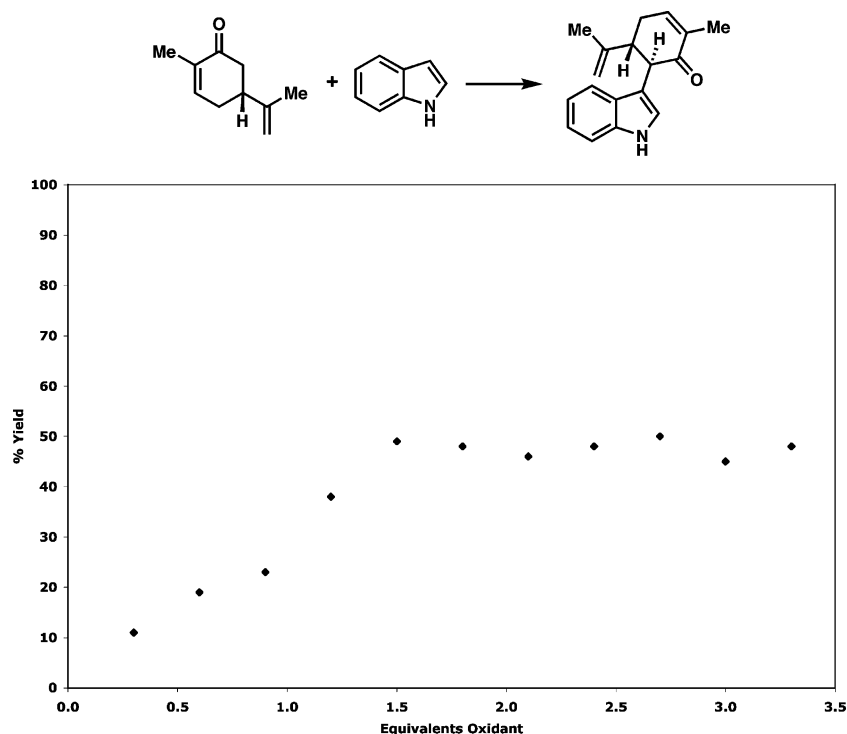
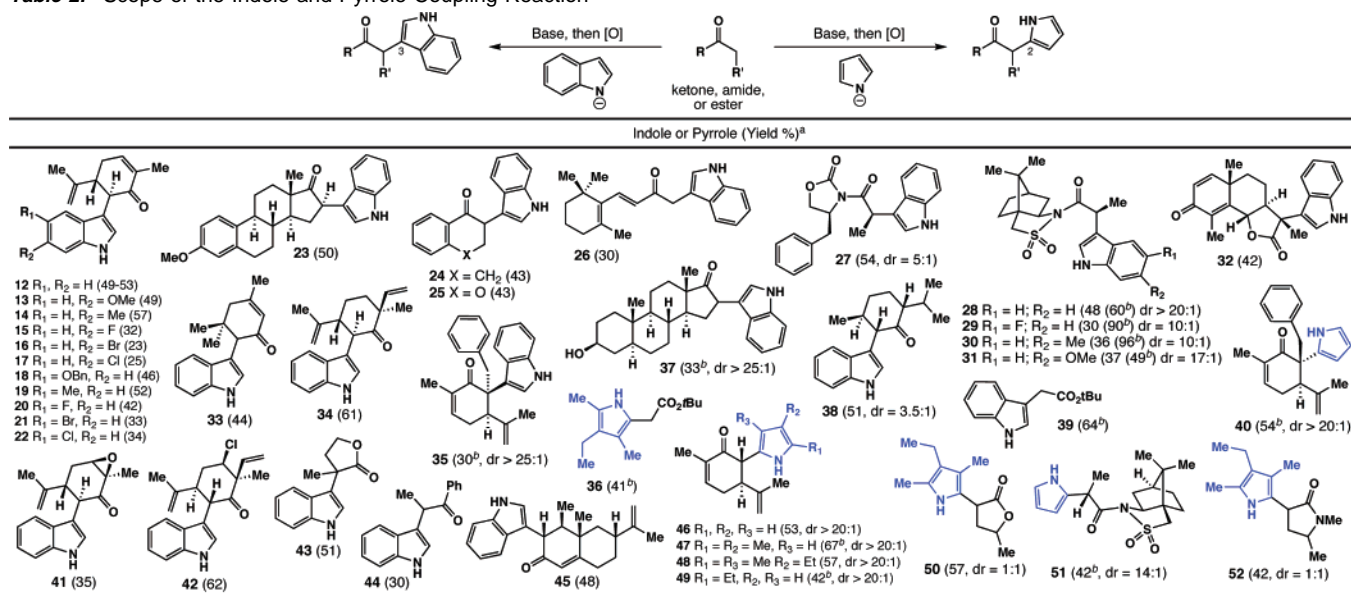


Figure 2. Optimum equivalents of oxidant selection.

Table 2. Scope of the Indole and Pyrrole Coupling Reaction



^a Isolated yield. ^b Yield based on recovered starting material.

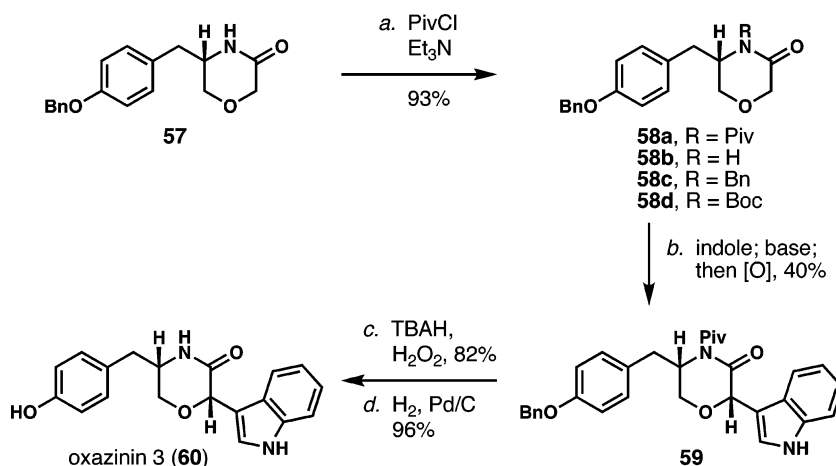
protection of the secondary hydroxyl group; an extra equivalent of base was added to deprotonate this potentially troublesome functional group. Epoxide **41** is obtained in acceptable yield, even though multiple side reactions could be envisioned in the presence of this reactive moiety. Quaternary centers can be formed in moderate (benzylcarvone **40**) to good (tricycle **32** and lactone **43**) yields, and coupling can even occur at hindered neopentyl centers such as that of isophorone (**33**). The reaction is amenable to asymmetric synthesis with either the Evans (**27**) or Oppolzer (**28–31**) chiral auxiliaries in good to excellent diastereoselectivities and yields. The coupling of β -ionone (**26**) is especially noteworthy, in spite of the moderate yield, because this represents the first ketone that was selectively coupled at a

methyl group using the standard conditions, even though these types of compounds are extremely prone to homodimerization. Finally, the reaction can be performed on a myriad of carbonyl compounds including esters (**39**), lactones (**43**), amides (**27–31**), and ketones, and a wide variety of substitution patterns are tolerated on the indole (**13–22**, **29–31**).⁵¹

Application to Total Synthesis

The direct indole coupling reaction is a useful method for the synthesis of complex natural products as has already been

(51) Several of the adducts listed in Table 2 would be difficult or nearly impossible to obtain so quickly in any other fashion.

Scheme 5. Total Synthesis of Oxazinin 3^a

^a Reagents and conditions: (a) Et₃N (2 equiv), THF; PivCl (1.1 equiv), 2 h, 93%; (b) indole (3 equiv); LHMDS (4.4 equiv), -78 °C, 30 min; copper(II) 2-ethylhexanoate (1.5 equiv), -78 to 25 °C, 10 min, 40%; (c) TBAH (2 equiv), H₂O₂ (2 equiv), DME, 0 °C, 2 h, 82%; (d) Pd/C (0.1 equiv), MeOH, H₂, 15 h, 96%; THF = tetrahydrofuran, PivCl = pivaloyl chloride, LHMDS = lithium hexamethyldisilazide, TBAH = tetrabutylammonium hydroxide, DME = dimethoxyethane.

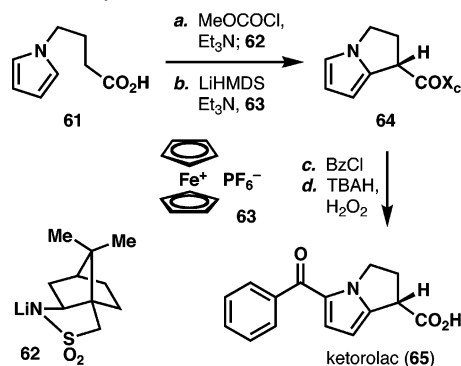
Success was finally realized when the pivaloyl group was introduced, which provided an appropriate balance between electron density, base stability, and ease of removal.

Extension to Other Heterocycles

Indoles are the most ubiquitous heterocycle found in naturally occurring substances and medicinal agents.⁶¹ However, other heterocycles also feature prominently in natural products and medicinal chemistry. So could the direct indole coupling developed above be extended to the construction of other complex heterocyclic scaffolds?

Initial studies centered around those heterocycles most predominant in either natural products or medicinal chemistry: specifically pyridine, pyrimidine, pyrazole, indazole, furan, thiophene, imidazole, and pyrrole. It was quickly discovered that pyridine, pyrimidine, furan, and thiophene could not participate in the direct coupling reaction using the developed conditions, presumably because they lacked the requisite free N–H bond (*vide infra* for mechanistic reasoning). Furthermore, pyrazole and indazole did not work, likely due to the decreased electron density on the aromatic heterocycle. Similarly, imidazole was not a competent coupling partner, perhaps because of the extremely high metal chelating ability of this heterocycle.

A successful coupling was realized with pyrrole under the developed conditions to furnish products that are the result of pyrrole coupling at C-2 with the α -carbon of carbonyl compounds (see Table 2). Pyrrole is more reactive and less stable than indole, requiring the reaction conditions to be slightly modified to allow for a more efficient process.⁶² In fact, due to pyrrole's propensity to polymerize *via* both radical and acidic mechanisms, extra care and celerity were required during purification, otherwise significant product decomposition was observed (unless the heterocycle was deactivated with either electron-deficient groups or by blocking the open positions of the ring). Pyrroles are also versatile heterocyclic intermediates because they can be converted into pyridines,⁶³ pyrrolinone,⁶⁴

Scheme 6. Total Synthesis of Ketorolac^a

^a Reagents and conditions: (a) Et₃N (1.1 equiv), MeOCOCI (1.0 equiv), THF, 0 °C, 1 h; then **62**, 100%; (b) LHMDS (1.2 equiv), Et₃N (2.0 equiv), THF, -78 °C, 30 min; then 12 °C, **63** (0.75 equiv), 5 min, dr = 4.5:1, extremely unstable; (c) BzCl, 70 °C, 4 h, 27% BRSM; (d) TBAH (2.0 equiv), H₂O₂ (2.0 equiv), 2-methylbut-2-ene (3.0 equiv), DME, -10 °C, 3 h, 58%; X_C = Chiral Auxiliary, THF = tetrahydrofuran, LHMDS = lithium hexamethyldisilazide, brsm = based on recovered starting material, BzCl = benzoyl chloride, TBAH = tetrabutylammonium hydroxide, DME = dimethoxyethane.

and pyrrolidines.⁶⁵ A broad substrate scope was observed in the direct pyrrole coupling reaction, as shown in Table 2. Ketones (**40**, **46–49**), esters (**36**), amides (**51**), lactams (**52**), and lactones (**50**) all participated in couplings, tolerating a range of functional groups. As with indoles, quaternary centers could be forged in reasonable yield (**40**) and the reaction could also be applied to asymmetric synthesis using the Oppolzer sultam (**51**). A range of substitution patterns around the pyrrole nucleus are tolerated, which can provide highly complex heterocyclic scaffolds in good yields (**47–49**).

Pyrrole is also found in a wide variety of medicinal compounds, so as a further testament to the utility of the direct pyrrole coupling reaction, the method was showcased in a synthesis of the nonsteroidal anti-inflammatory drug ketorolac (**65**).⁶⁶ It was known that the (*S*)-enantiomer is significantly more active than the (*R*)-antipode,⁶⁷ and therefore an asymmetric

(61) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Malden, MA, 2004.

(62) See Supporting Information for a detailed general procedure.

(63) (a) Closs, G. L.; Schwartz, G. M. *J. Org. Chem.* **1961**, *26*, 2609. (b) Jones, R. L.; Rees, C. W. *J. Chem. Soc. C* **1969**, 2249–2251.

(64) Chen, Q.; Wang, T.; Zhang, Y.; Wang, Q.; Ma, J. *Synth. Commun.* **2002**, *32*, 1031–1040.

(65) Denmark, S. E.; Matsushashi, H. *J. Org. Chem.* **2002**, *67*, 3479–3486.

6-Series Hammett Plot

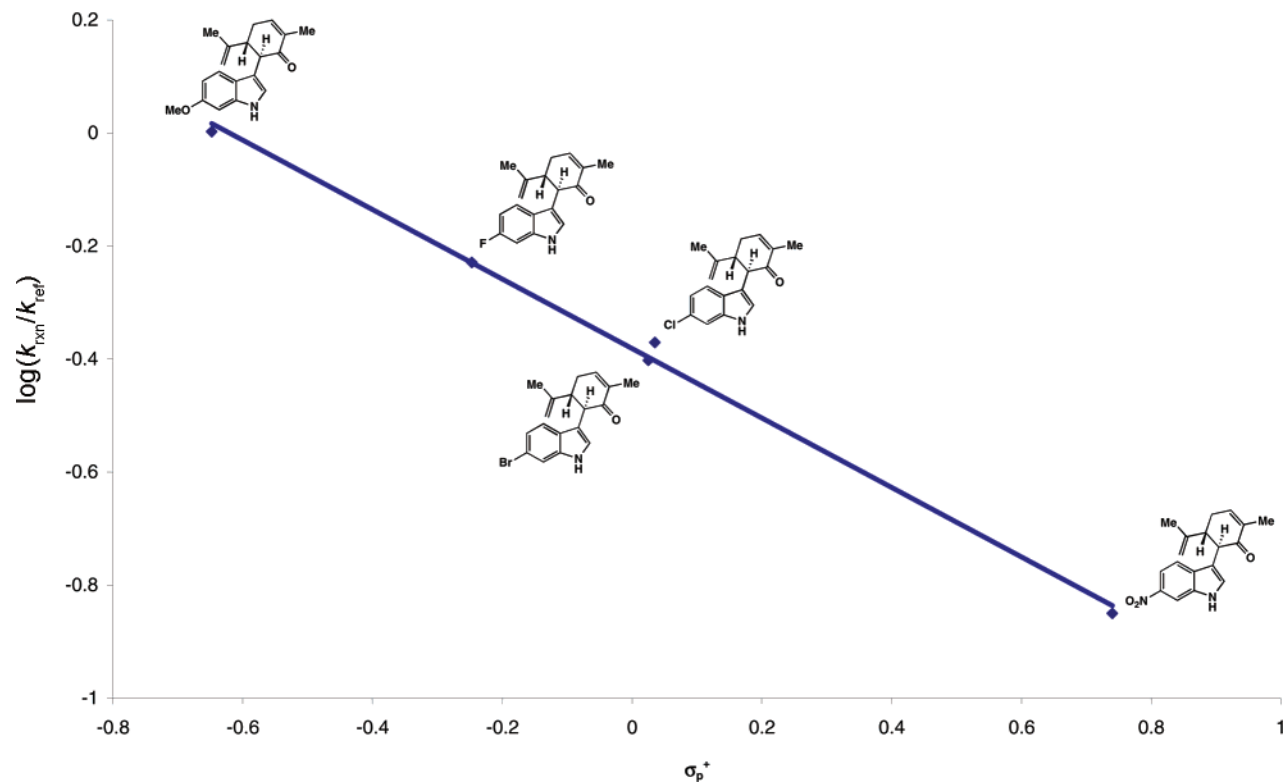


Figure 4. Hammett plot for C-6 substituted indoles.

synthesis was preferred.⁶⁸ The pioneering syntheses by Muchowski and co-workers at Syntex (now Hoffman-LaRoche) served as inspiration in developing a route based upon the oxidative pyrrole coupling. Any new synthesis would be hard-pressed to improve upon Syntex's original route (*ca* 45% yield from pyrrole, racemic) but would at least serve as a proving ground for the versatility of the pyrrole coupling reaction in a discovery-scale setting.

The synthesis commenced by installing the appropriate Oppolzer sultam as a chiral auxiliary on the known⁶⁹ pyrrole acid **61** (Scheme 6). Unexpectedly, even after extensive experimentation, the intramolecular coupling could not be accomplished using a wide variety of oxidants [including both copper(II) and iron(III) salts] to forge the bicyclic core of ketorolac. This result was quite surprising, because the oxidative coupling literature has consistently invoked oxidation of an enolate to an α -radical (*vide supra*). Were this mechanism operable, this electrophilic radical should be attacked by the electron-rich heterocyclic system, yielding the desired product. Success was finally realized when ferrocenium hexafluorophosphate (**63**)⁷⁰ was used as the oxidant, providing the annulated product (**64**), where no other attempted oxidants were successful. This particular oxidant has been unambiguously shown by Jahn and co-workers to oxidize enolates to discrete radicals, which can react with a wide variety of olefinic partners.⁶⁸ The unique

success of this iron-based oxidant implies that copper-based reactions are not proceeding *via* oxidation to the discrete radical. Also of note is the fact that ferrocenium hexafluorophosphate is not a competent oxidant for the intermolecular pyrrole or indole coupling reactions.

Once annulated, the pyrrole product (**64**) was extremely unstable, requiring that the material be immediately⁷¹ benzoylated to procure the full carbon skeleton.⁷² Hydrolysis of the chiral auxiliary without epimerization of the final product initially proved problematic; however, optimized conditions were found using tetrabutylammonium hydroxide and hydrogen peroxide,⁷³ giving ketorolac (**65**) in good yield and enantiopurity. Highlights of this route include the avoidance of protecting groups, conservation of oxidation state, and the stereochemical induction observed in the key coupling reaction.

Mechanistic Analysis

A Hammett analysis was performed to probe the nature of the rate-limiting step of this intriguing reaction and, perhaps, oxidative enolate couplings in general. A series of couplings were executed between carvone and C-5 and C-6 substituted indoles, from which a set of Hammett plots was derived. As can be observed from the plot for C-6 substituted indoles (Figure

(66) (a) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109–135. (b) Harrington, P. J.; Khatri, H. N.; Schloemer, G. C. U.S. Patent 6197976, 2001, and references therein.

(67) Guzmán, A.; Yuste, F.; Toscano, R. A.; Young, J. M.; Van Horn, A. R.; Muchowski, J. M. *J. Med. Chem.* **1986**, *29*, 589–591.

(68) Ketorolac is still marketed as a racemate, despite the fact that one enantiomer is known to be more active than the other.

(69) Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1993**, *58*, 516–519.

(70) (a) Jahn, U.; Hartmann, P. *Chem. Commun.* **1998**, 209–210. (b) Jahn, U. *J. Org. Chem.* **1998**, *63*, 7130–7131. (c) Jahn, U.; Müller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212–5213. (d) Jahn, U.; Hartmann, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2277–2282. (e) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333–3355. (f) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2002**, 718–735.

(71) Benzoylation effectively removes electron density from and, thereby, stabilizes the pyrrole.

(72) Muchowski, J. M.; et. al. *J. Med. Chem.* **1985**, *28*, 1037–1049.

5-Series Hammett Plot

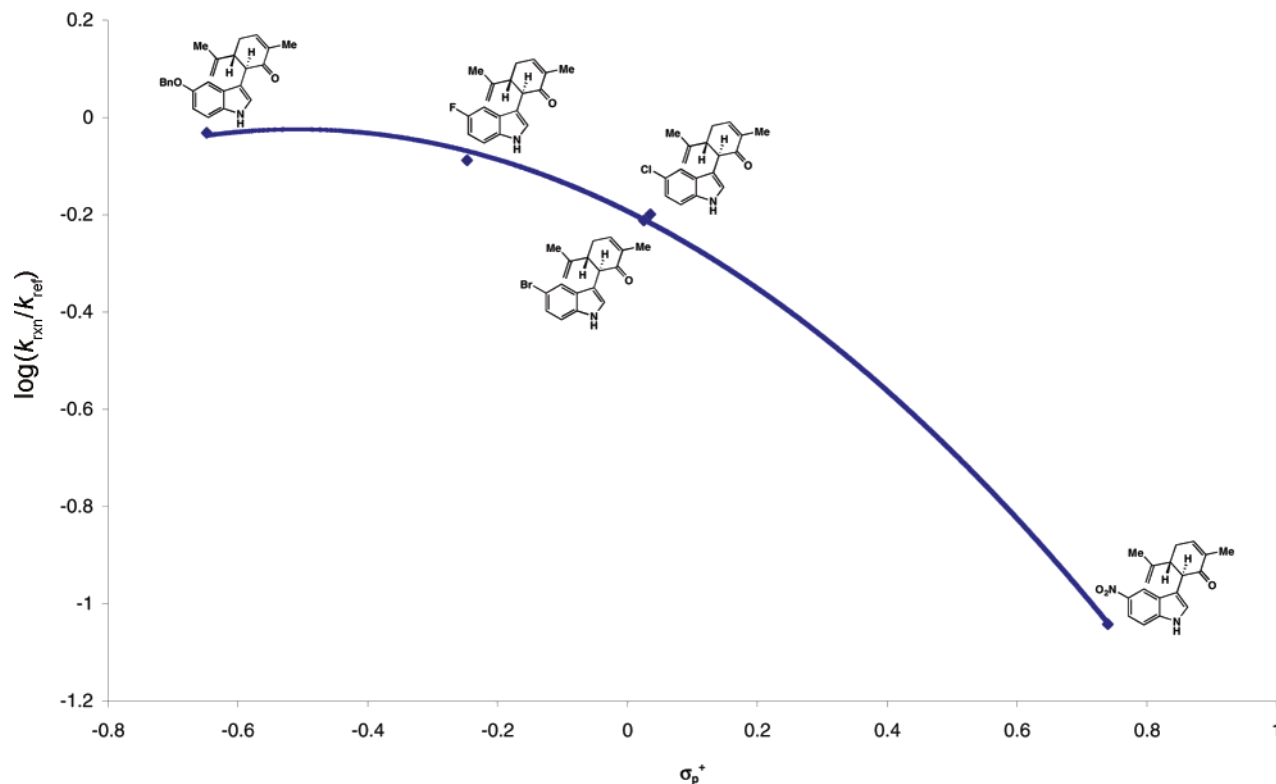
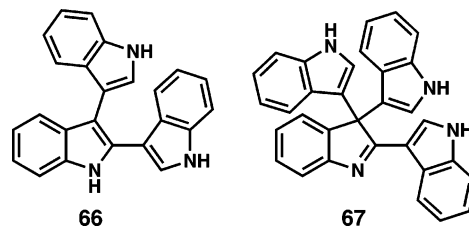


Figure 5. Hammett plot for C-5 substituted indoles.

4), a linear correlation between the ratio of reaction rates ($k_{\text{txn}}/k_{\text{ref}}$)⁷⁴ and the substituent parameter (σ_p^+)⁷⁵ was obtained, which provided a small, negative reaction constant ($\rho = -0.61$, $R^2 = 0.996$). This relatively small ρ value correlates to a slight dependence of the reaction on the polarizing influence of the aromatic substituents, which is indicative of a radical-based mechanism.¹⁶ Were the rate-determining step proceeding through an ionic pathway, a much larger ρ -value would be expected, with a larger dependence on the electronic nature of the aromatic ring. Additionally, the negative sign of ρ suggests an electron-deficient transition state of the reaction relative to the ground state. In other words, negative charge is lost during the transition state, which could be explained by a radical-based coupling in which C-3 might transform from a stabilized anion into a tetrasubstituted center bearing no charge.

In contrast, the Hammett plot for C-5 substituted indoles does not exhibit a linear relationship (Figure 5) between the ratio of reaction rates ($k_{\text{txn}}/k_{\text{ref}}$) and the substituent parameter (σ_p^+). A gradual curve is instead observed, indicating increased charge localization at the activated center during the course of the reaction but that the transition state does not change significantly as a consequence of this charge development. This suggests that negative charge is increased at N-1 during the course of the reaction, even though this center is not

Chart 2. Indole Trimer and Tetramer



participating in the rate-limiting step. This data would be consistent with nucleophilic attack of the indole anion onto an electrophilic α -keto radical, resulting in a radical anion at N-1, which would be less resonance stabilized, and therefore more localized, than the initial anion located at the same position (i.e., the anion can also reside at C-3, whereas the radical anion cannot).

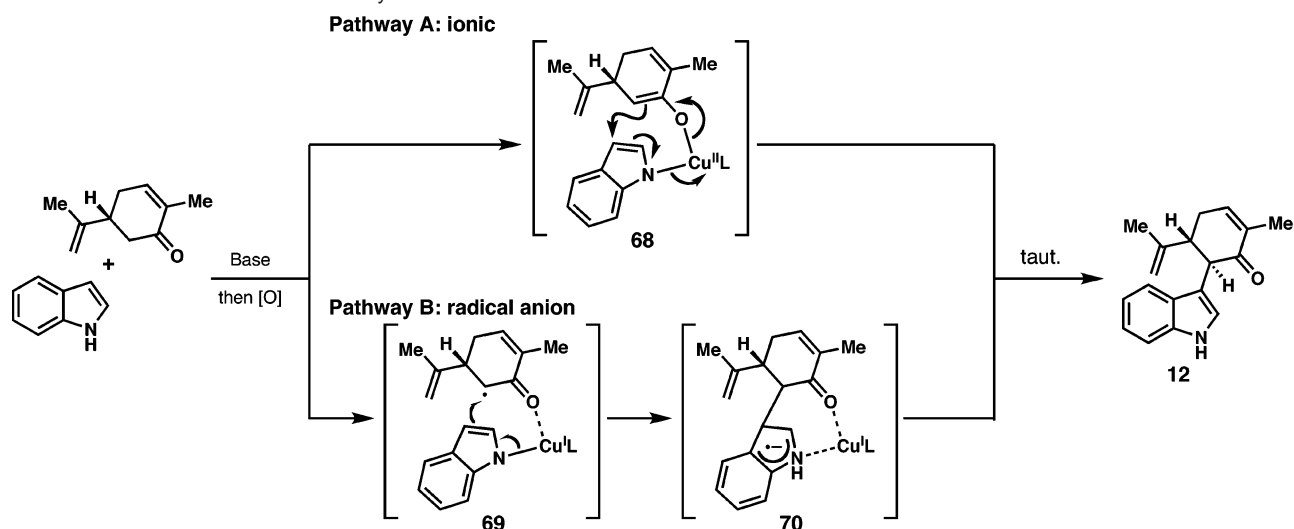
In addition to the above Hammett analysis, several observations have been made over the course of these and other studies involving oxidative enolate couplings in this laboratory, providing further clues to the mechanism of the oxidative coupling reaction. (1) Dimerization of indole is never observed, unless a ketone is either not present or cannot be oxidized under the reaction conditions, in which case the trimer (**66**) and tetramer (**67**, verified by X-ray crystallography) are obtained (Chart 2). This suggests that the ketone is oxidized first and then reacts with indole. This also provides evidence that selective hetero-couplings can be designed by tuning the oxidation potential of the oxidant to react preferentially with one coupling partner over the other. (2) N-Protected indoles or pyrroles are unreactive; in fact, the free N-H is required for the reaction to proceed. This suggests that the reaction is not proceeding *via* oxidation to a

(73) Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 882–884.

(74) k_{ref} = rate constant of the reaction of indole with carvone; k_{txn} = rate constant of the reaction of substituted indoles with carvone. For the determination of r , the following expression was used: $k_{\text{txn}}/k_{\text{ref}} = \log[1 - x_p/x_r]/\log[1 - y_p/y_r]$; r = reaction constant; x_p = mmol product formed from substituted indole; x_r = mmol starting carvone placed in the reaction; y_p = mmol product formed from unsubstituted indole; y_r = mmol starting carvone placed in the reaction.

(75) Swain, C. G.; Lupton, E. C., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4328–4337.

Scheme 7. Possible Mechanistic Pathways



discrete α -radical on the carbonyl compound (which could react with the N-protected heterocycles)⁸ but instead supports a chelated transition state. (3) Ferrocenium hexafluorophosphate is not a competent oxidant for the intermolecular couplings, and copper(II) does not effect the annulation. This provides evidence against the intermediacy of a discrete α -radical on the carbonyl compound. There is also limited evidence in the literature that questions the widely accepted view that this reaction proceeds *via* the dimerization of two carbonyl α -radicals.^{18c,d} (4) Only 1 equiv of oxidant, relative to the ketone, is necessary for the reaction to proceed (1.5 equiv provides a slightly improved yield). This suggests that the reaction is proceeding by preferential oxidation of the carbonyl compound, which theoretically could react with the indole or pyrrole anion, providing a radical anion intermediate. This radical anion could then be further oxidized by the remaining copper(I). (5) Excellent diastereoselectivity is observed in the intramolecular coupling of an amide and an ester during the stephacidin B synthesis to form two adjacent stereocenters, one of which is quaternary (regardless of the oxidant used).⁷⁶ In an intermolecular setting, moderate to low diastereoselectivity is observed using the Evans chiral auxiliary.⁶⁰ These results can be explained by invoking a chelated transition state; however, substrate control cannot be excluded based on these findings. Thus, the extent of metal complexation in the transition state of the coupling is unclear. It should be noted that a chelated transition state in oxidative enolate couplings has been implicated in the literature based on observed diastereoselectivities.^{18b}

The mechanistic evidence delineated above is suggestive of two plausible mechanistic interpretations (Scheme 7). Both invoke a metal-chelated transition state and involve reduction of the copper species to copper(0). In pathway A, an enolate and an indole anion initially coordinate to the copper(II) center, giving the chelated intermediate (**68**). This intermediate could undergo a net two-electron reductive elimination of the metal center to give **12** after tautomerization.

While this mechanism cannot be ruled out based on the above evidence, pathway B is certainly more compelling. In this pathway, the same chelate **68** can undergo single-electron transfer to form the chelated α -keto radical **69**. Due to its proximity to the indole anion, the radical can suffer attack by this nucleophilic species, resulting in radical anion **70**. This high-energy intermediate can then be further oxidized by the proximal copper(I) center, expelling, after tautomerization, the coupled product and copper(0). In light of the fact that copper(I) is a viable oxidant for the oxidative coupling reaction^{22a} and that the radical anion would be prone to oxidation by the coordinated, albeit weakly oxidizing, copper(I) species, this mechanistic interpretation is certainly reasonable. It should also be clearly noted that alternative mechanisms could easily be drawn that do not invoke a chelated transition state or the eventual reduction to copper(0), but given the evidence presented herein, pathway B is certainly preferred.

Conclusions

This research program was initiated with the structures of the hapalindole family in mind and with a conscious effort to eliminate prefunctionalization steps that are often found in cross-coupling chemistry (Figure 1). Inspired by Barton's landmark total synthesis of usnic acid (Scheme 2), a method was devised for the direct oxidative coupling of indoles and pyrroles to a range of carbonyl compounds. Viewed within proper historical context, this method represents an important advance in the field of oxidative enolate coupling. Specifically, it has been shown that the heterocoupling of two different anionic species is a synthetically pragmatic process. Indeed, work from this laboratory has shown that this reaction paradigm is not limited to cross-coupling between heteroaromatic systems and carbonyl compounds, as two different carbonyl compounds can also be coupled in an intermolecular setting. Exploiting the innate reactivity of the coupling partners has led, in part, to such selectivity. Aside from the rapid increase in complexity associated with convergent synthetic strategies, this type of transformation carries with it several additional benefits such as high levels of chemoselectivity, regioselectivity, predictable stereoselectivity (substrate control), and practicality (easily scalable). While the reaction demonstrates admirable scope and generality for a range of pyrrole and indole couplings, it has clear

(76) (a) Baran, P. S.; Guerrero, C. A.; Ambhaikar, N. A.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606–609. (b) Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892–3895. (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. A.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678–8693.

limitations. For instance, the reaction is not amenable to a wide range of heterocyclic scaffolds, electron-deficient indoles do not couple well, and methyl ketones are prone to homodimerization. However, despite these limitations, this method has already been shown to be an efficient and enabling technology in natural products synthesis^{7-9,36d} and many further applications are anticipated. Methods that rapidly generate meaningful complexity with exquisite chemoselectivity will not only benefit the science of synthesis as a whole but also find further applications in biology and medicine.

Acknowledgment. We thank Dr. D. H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance, and Dr. G. Siuzdak and Dr. R. Chadha for mass spectrometric and X-ray crystallographic assistance, respectively. We are grateful to the National Science Foundation for predoctoral fellowships (J.M.R. and D.W.L.). 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 (NGIMS).

Note Added after ASAP Publication: The y-axis labels for Figures 4 and 5 were absent due to production error in the version published on the Web September 27, 2007. The final Web version published September 28, 2007 and the print version are correct.

Supporting Information Available: Full characterization, including copies of ¹H and ¹³C NMR spectra, and experimental procedures for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA074392M