Oxidative Enolate Coupling in Total Synthesis

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Appointment
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Education
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Awards
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• ACS Award in Pure Chemistry, 2010
• Sackler Prize, 2009
• National Fresenius Award, ACS, 2007
• Novartis Lecturer, 2007 – 2008
• Hirata Gold Medal, 2007
• Pfizer Award for Creativity in Organic Synthesis, 2006
• Beckman Foundation Fellow, 2006 – 2008
• Alfred P. Sloan Foundation Fellow, 2006 – 2008
• BMS Unrestricted “Freedom to Discover” Grant, 2006 – 2010
• NSF CAREER Award, 2006 – 2010
• Eli Lilly Young Investigator Award, 2005 – 2006
• AstraZeneca Excellence in Chemistry Award, 2005
• DuPont Young Professor Award, 2005
• Roche Excellence in Chemistry Award, 2005
• Amgen Young Investigator Award, 2005
• Searle Scholar Award, 2005
• GlaxoSmithKline Chemistry Scholar Award, 2005 – 2006

Contents:

1. Intermolecular enolate heterocoupling
A: Introduction

The **2,3-disubstituted-1,4-dicarbonyl moiety** is ubiquitous within natrural products and medicinal compounds. To achieve target-oriented syntheses concisely and efficiently is a longstanding dream of organic chemists.

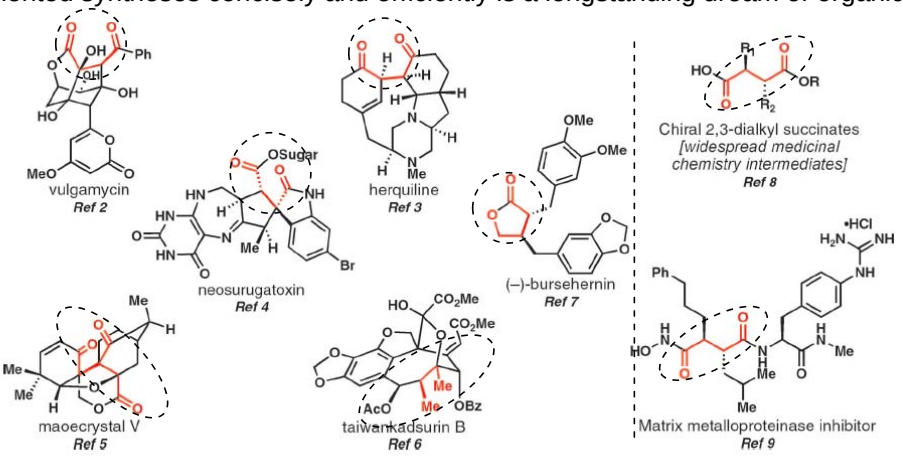


Figure 1. Selected natural products containing 1,4-dicarbonyl moieties.

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 are depicted in Figure 2. Multistep sequences or prefunctionalization of one or both of the monomers were necessary in most cases.

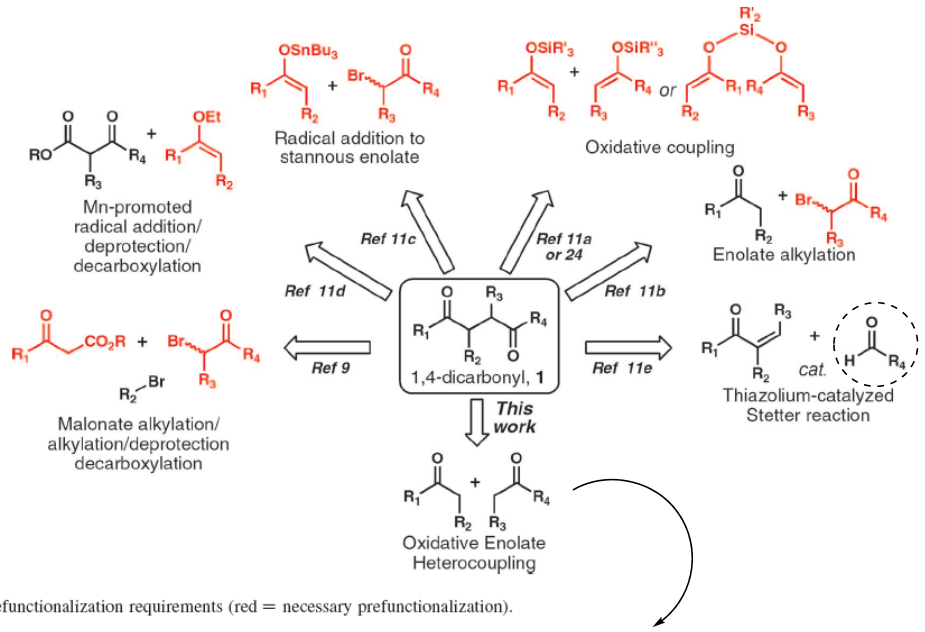


Figure 2. Prefunctionalization requirements (red = necessary prefunctionalization).

The oxidative enolate heterocoupling could directly join two different sp3-hybridized carbon centers in a single step without requiring prefunctionalization of the corresponding monomers.

Possible side products:

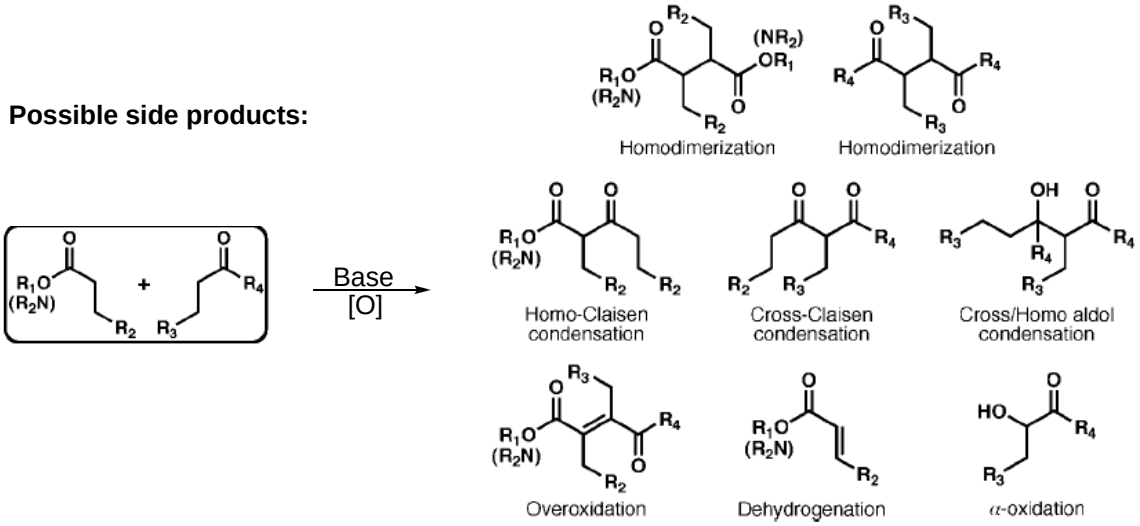


Figure 4. Possible reactions to compete with heterocoupling.

B : Background

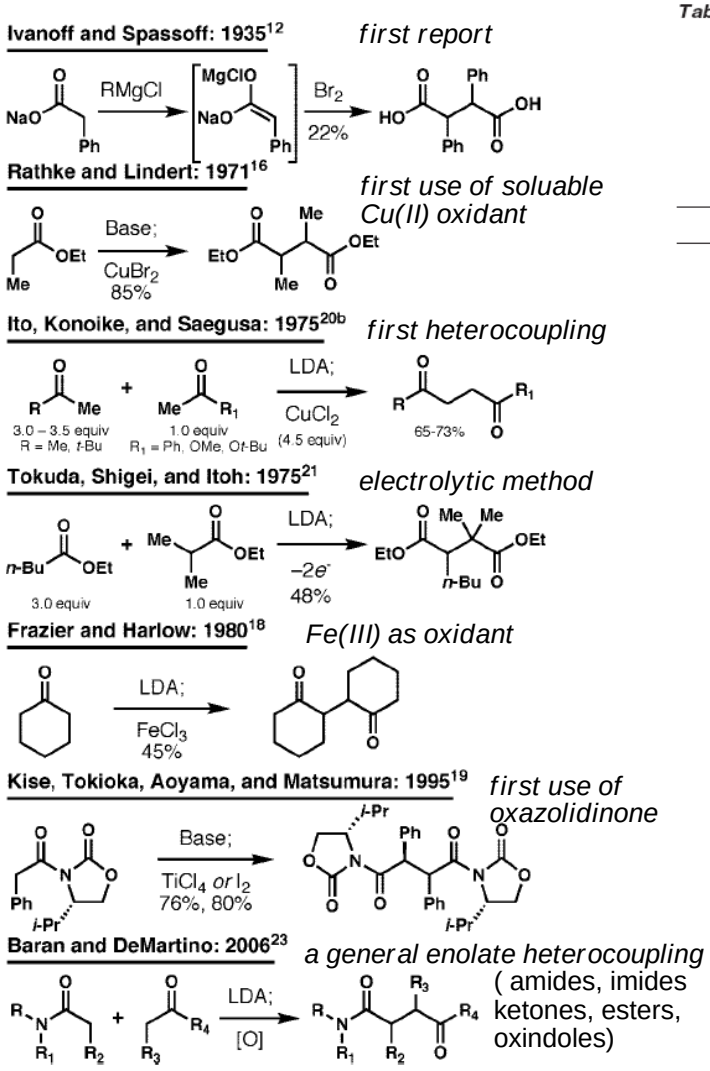
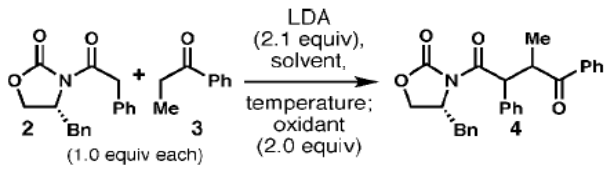


Figure 3. Pertinent intermolecular oxidative enolate coupling timeline.

C: Discovery and Optimization

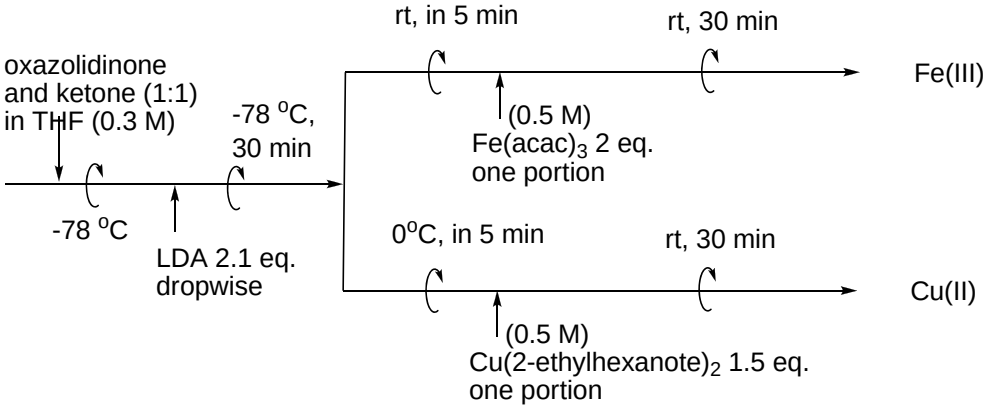
Table 1. Oxazolidinone–Propiophenone Coupling Optimization[a]



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

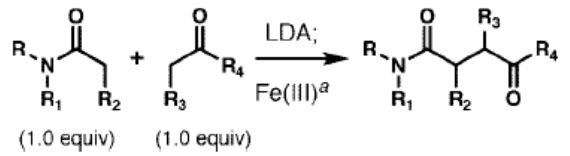
[a] Diastereomeric ratios determined by ^{1}H NMR integration. Diastereomeric ratios (for the methyl-bearing carbon) did not change with altered reaction conditions: Fe(III) entries, 1.8:1.0; Cu(II) entries, 1.0:1.6.

Procedure:

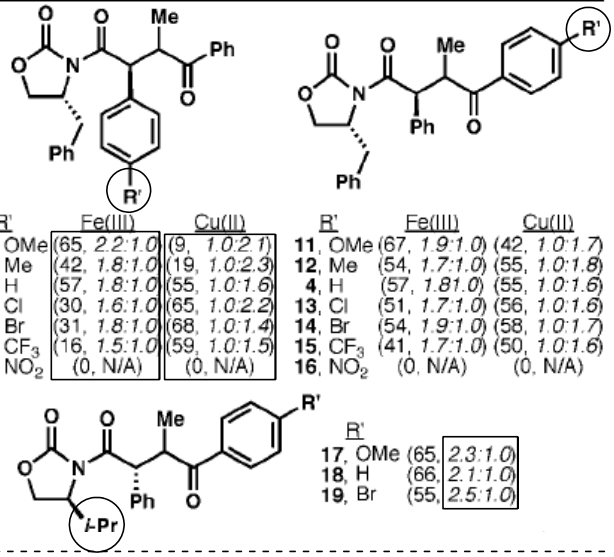


D: Scope

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



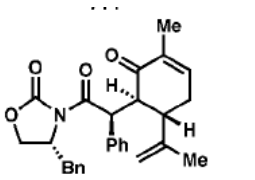
Cross-coupled products (yield %,[b] *d.r.*[c])



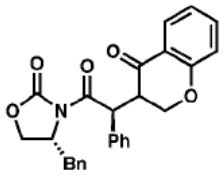
R'	Fe(III)	Cu(II)
5, OMe	(65, *2.2:1.0*)	(9, *1.0:2.1*)
6, Me	(42, *1.8:1.0*)	(19, *1.0:2.3*)
4, H	(57, *1.8:1.0*)	(55, *1.0:1.6*)
7, Cl	(30, *1.6:1.0*)	(65, *1.0:2.2*)
8, Br	(31, *1.8:1.0*)	(68, *1.0:1.4*)
9, CF_3	(16, *1.5:1.0*)	(59, *1.0:1.5*)
10, NO_2	(0, N/A)	(0, N/A)

R'	Fe(III)	Cu(II)
11, OMe	(67, *1.9:1.0*)	(42, *1.0:1.7*)
12, Me	(54, *1.7:1.0*)	(55, *1.0:1.8*)
4, H	(57, *1.81.0*)	(55, *1.0:1.6*)
13, Cl	(51, *1.7:1.0*)	(56, *1.0:1.6*)
14, Br	(54, *1.9:1.0*)	(58, *1.0:1.7*)
15, CF_3	(41, *1.7:1.0*)	(50, *1.0:1.6*)
16, NO_2	(0, N/A)	(0, N/A)

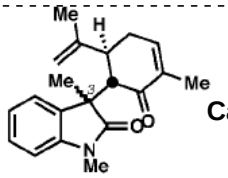
R'		
17, OMe	(65, *2.3:1.0*)	
18, H	(66, *2.1:1.0*)	
19, Br	(55, *2.5:1.0*)	



20 (52, *2.7:1.0*)

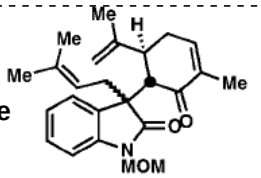


21 (59, *2.8:1.0*)
(60, *2.6:1.0*)
[gram scale]



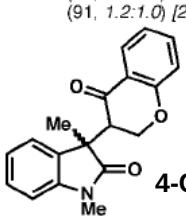
22 (60, *1.2:1.0*)
(91, *1.2:1.0*) *[2 equiv carvone]*

Carvone



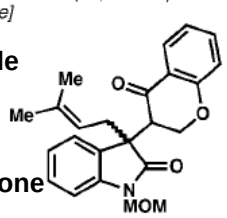
23 (54, *1.0:1.0*)

Oxindole



24 (72, *2.6:1.0*)

4-Chromanone



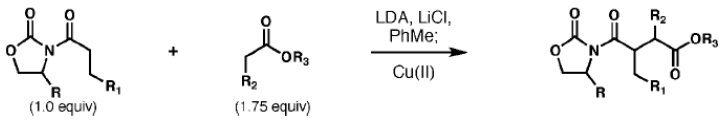
25 (73, *2.0:1.0*)

quaternary carbon center

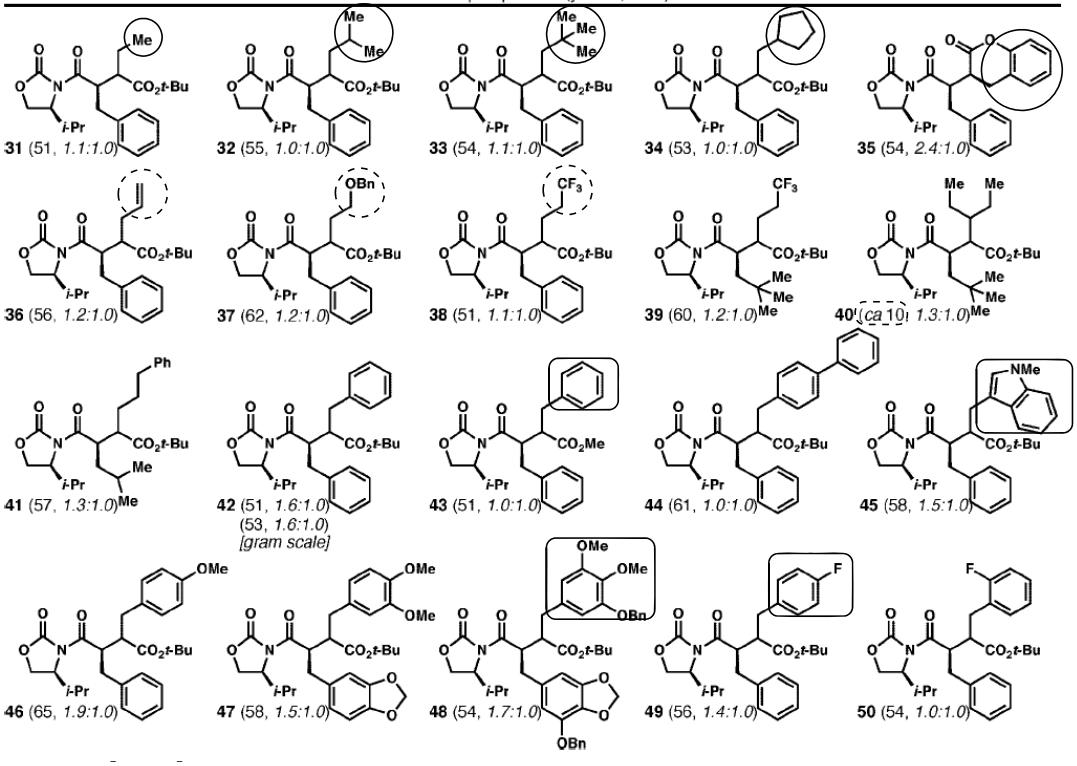
[a] $Fe(acac)_3$ used as oxidant unless otherwise stated. [b] Isolated yield. [c] Diastereomeric ratios determined by ^1H NMR integration.

1. 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.
2. 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.
3. the bulkier auxiliary modestly improving the diastereoselectivity (**17-21**).
4.The oxindoles were also cross-coupled with carvone (**22,23**) and cyclic aryl ketone 4-chromanone (**24,25**) affording complex compouds containing quaternary carbon center in good yield.

Table 3. Scope of 2,3-Dialkylsuccinate Couplings



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



31 (51, *1.1:1.0*)
32 (55, *1.0:1.0*)
33 (54, *1.1:1.0*)
34 (53, *1.0:1.0*)
35 (54, *2.4:1.0*)
36 (56, *1.2:1.0*)
37 (62, *1.2:1.0*)
38 (51, *1.1:1.0*)
39 (60, *1.2:1.0*)
40 (*ca* 10, *1.3:1.0*)
41 (57, *1.3:1.0*)
42 (51, *1.6:1.0*)
(53, *1.6:1.0*)
[gram scale]
43 (51, *1.0:1.0*)
44 (61, *1.0:1.0*)
45 (58, *1.5:1.0*)
46 (65, *1.9:1.0*)
47 (58, *1.5:1.0*)
48 (54, *1.7:1.0*)
49 (56, *1.4:1.0*)
50 (54, *1.0:1.0*)

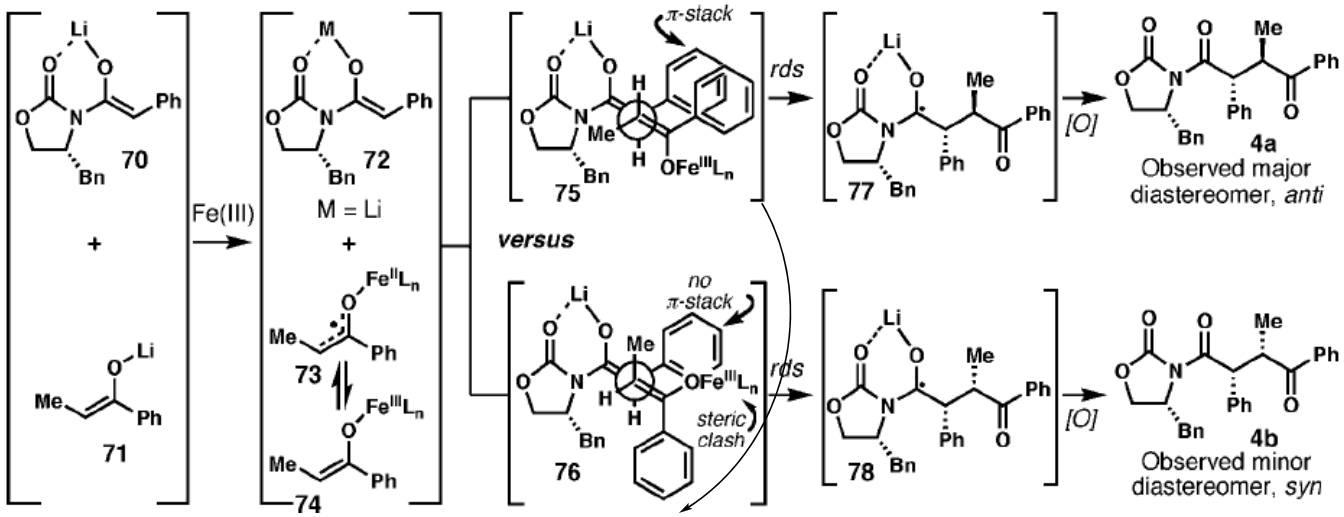
comments:

1. both steric environments (**31-35**) and functional group (**36-39**) are tolerated.

2. Electron-rich (**45-48**), -neutral (**41-44**), and -deficient aromatic units **(49,50)** are tolerated.

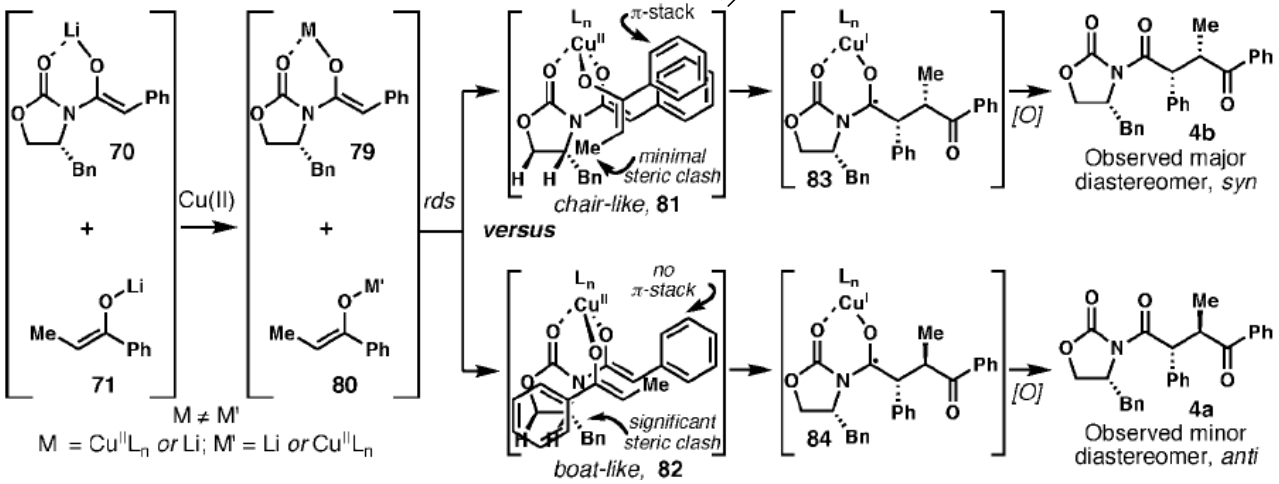
E: Mechanism

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



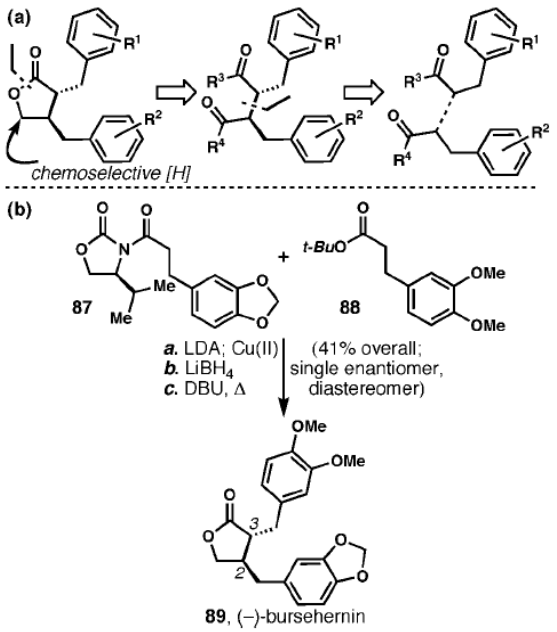
Scheme 12. Proposed $Cu(2\text{-ethylhexanoate})_2$ Mechanism

Cu(II)-Chelated Transition States



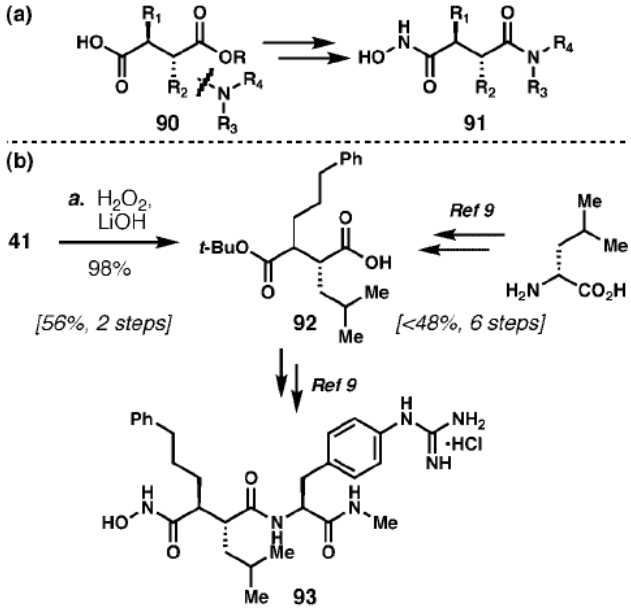
F: Application

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 $Cu(2\text{-ethylhexanoate})_2$, −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.

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

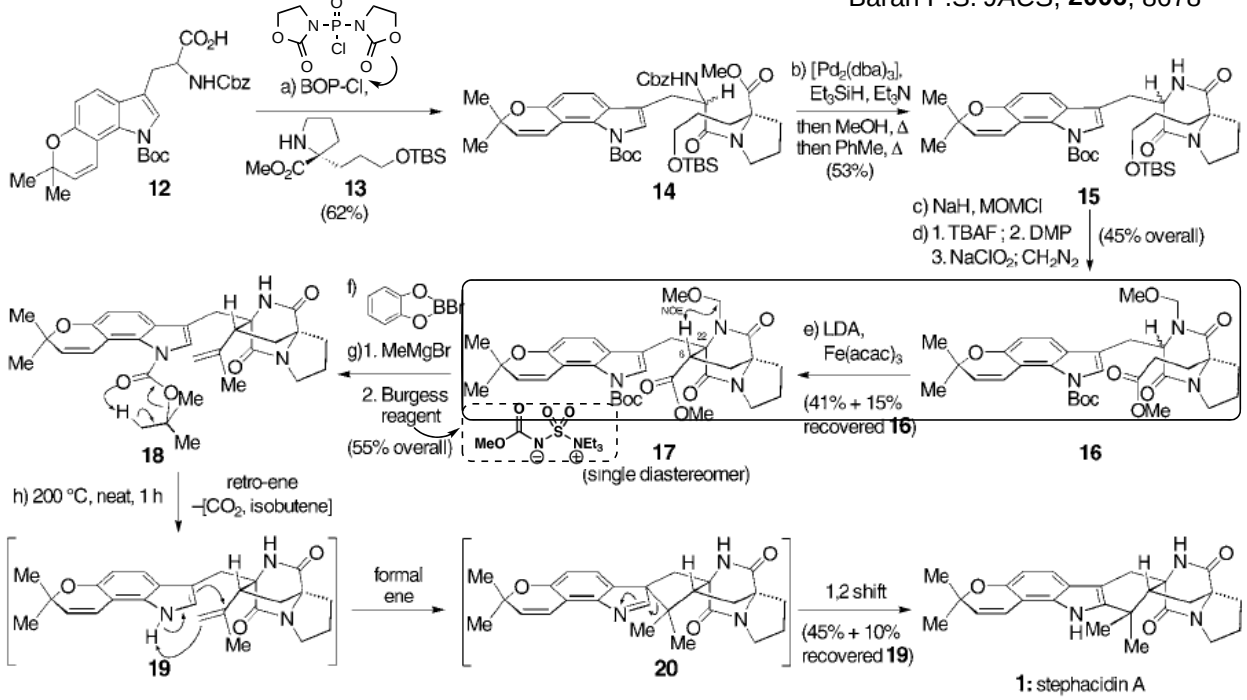


[a] Reagents and conditions: (a) H_2O_2 (10 equiv), LiOH (5 equiv), THF/H_2O (3:1), 0 to 25 °C, 36 h.

2. Intramolecular enolate coupling

A: The first total synthesis of Stephacidin A

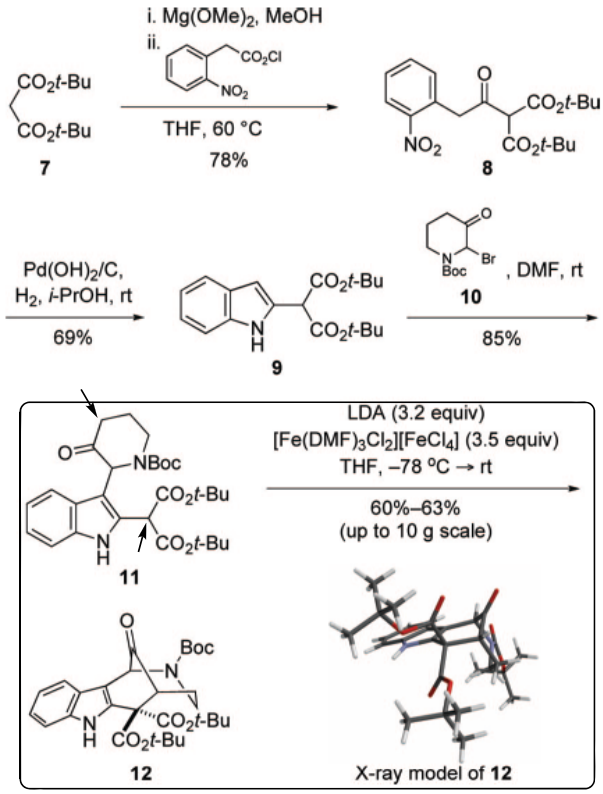
Baran P.S. *Angew*, **2005**, 606
Baran P.S. *Angew*, **2005**, 3892
Baran P.S. *JACS*, **2006**, 8678



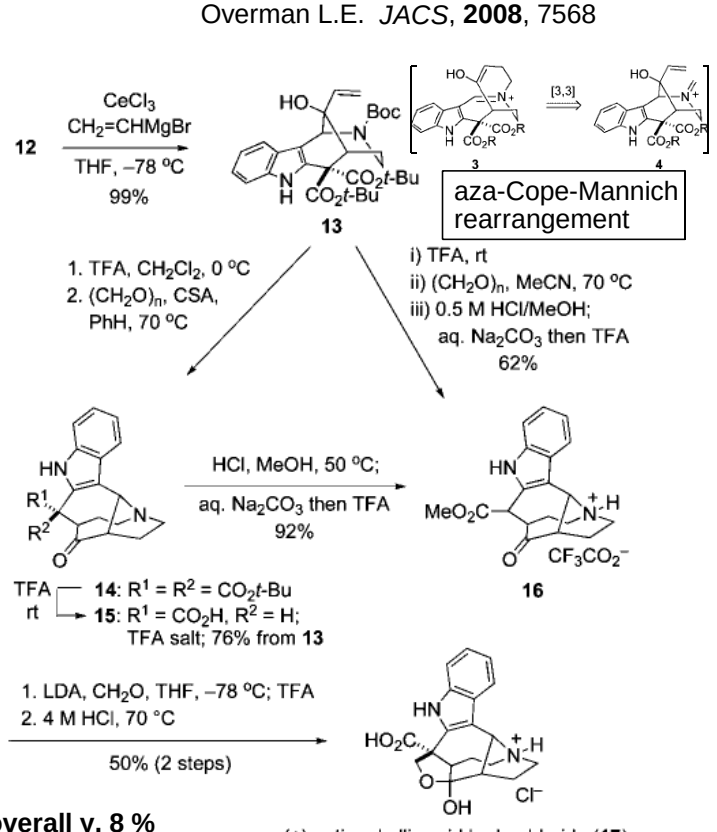
Scheme 3. Enantioselective total synthesis of stephacidin A (**1**). Reagents and conditions: a) **13** (1.5 equiv), BOPCl (1.1 equiv), *i*Pr$_2$EtN (1.1 equiv), CH_2Cl_2, 0→25 °C, 10 h, 62%; b) [Pd$_2$(dba)$_3$] (0.2 equiv), Et_3SiH (40 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 25 °C, 4 h; then MeOH, reflux, 30 min; then toluene, reflux, 2 h, 53% overall; c) NaH (1.2 equiv), MOMCl (1.1 equiv), DMF, 0 °C, 1 h, 65%; d) TBAF (3.0 equiv), THF, 25 °C, 1 h; then DMP (1.5 equiv), CH_2Cl_2, 25 °C, 2 h; then 2-methyl-2-butene (20 equiv), $NaH_2PO_4 \cdot H_2O$ (3.0 equiv), $NaClO_2$ (2.8 equiv), THF, H_2O, 20 min; then CH_2N_2 in Et_2O, MeOH, 5 min, 69% overall; e) LDA (2.2 equiv), THF, −78 °C, 5 min then [Fe(acac)$_3$] (2.2 equiv), THF, −78→25 °C, 1 h, 41% **17** with 15% recovered **16**; f) *B*-bromocatecholborane (1.5 equiv), CH_2Cl_2, 0 °C, 1.5 h, 63%; g) MeMgBr (6.0 equiv), toluene, 25 °C, 1 h, then Burgess reagent (2.0 equiv), benzene, 50 °C, 30 min, 88% overall; h) 200 °C, 1 h, 45% **1** with 10% recovered **19**. BOP = bis(2-oxo-3-oxazlidinyl)phosphinic chloride; dba = *trans*,*trans*-dibenzylideneacetone; MOM = methoxymethyl; TBAF = tetra-*n*-butylammonium fluoride; DMP = Dess–Martin periodinane; LDA = lithium diisopropylamide; acac = acetylacetonate.

B: The first total synthesis of (+/-)- Actinophyllic Acid

Overman L.E. *JACS*, **2008**, 7568



an intramolecular oxidative coupling of ketone and malonate enolate



overall y. 8 %

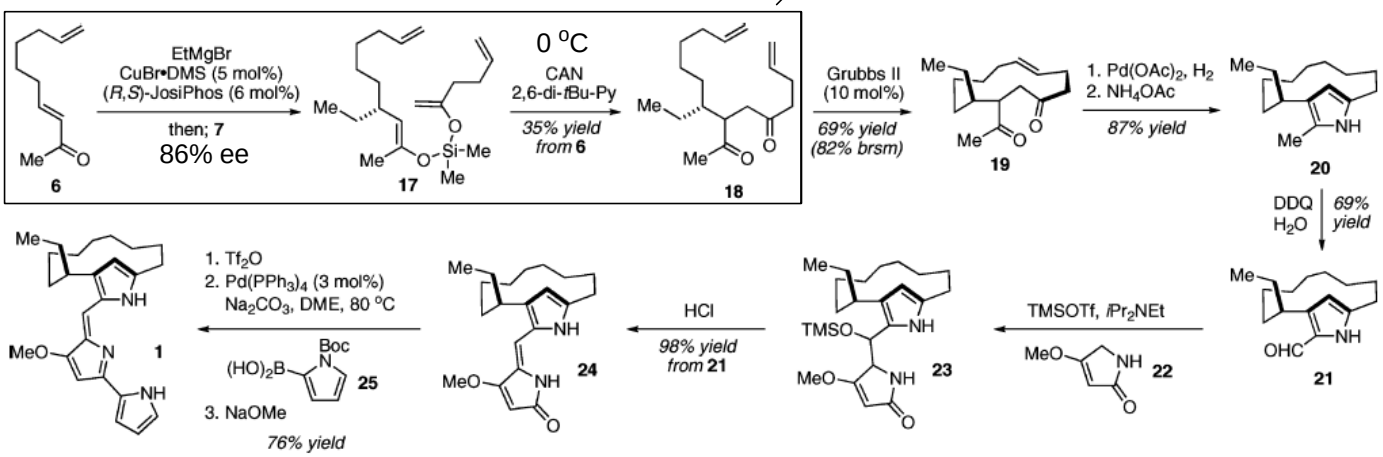
(±)-actinophyllic acid hydrochloride (**17**)

C: The first asymmetric total synthesis of Metacycloprodigiosin

Thomson R.J. *JACS*, **2009**, 14579

a Merged Conjugate Addition/Oxidative Coupling Sequence.

Scheme 2. Enantioselective Synthesis of Metacycloprodigiosin (**1**)

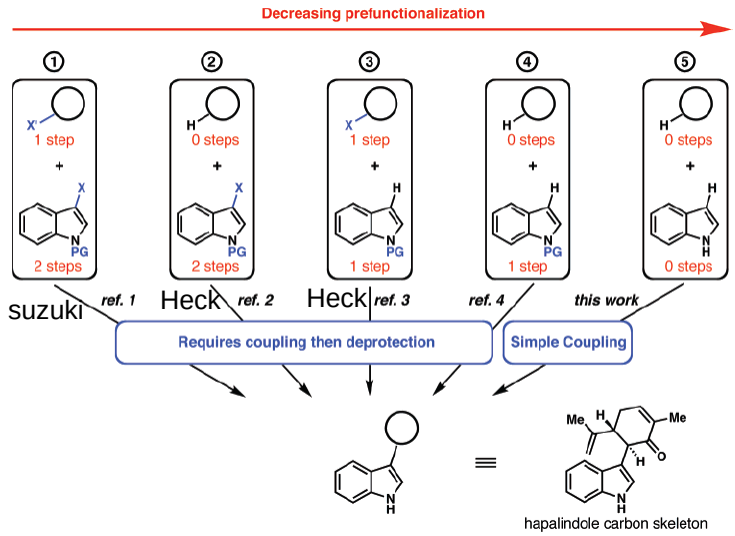


11 steps, 13 % overall yield.

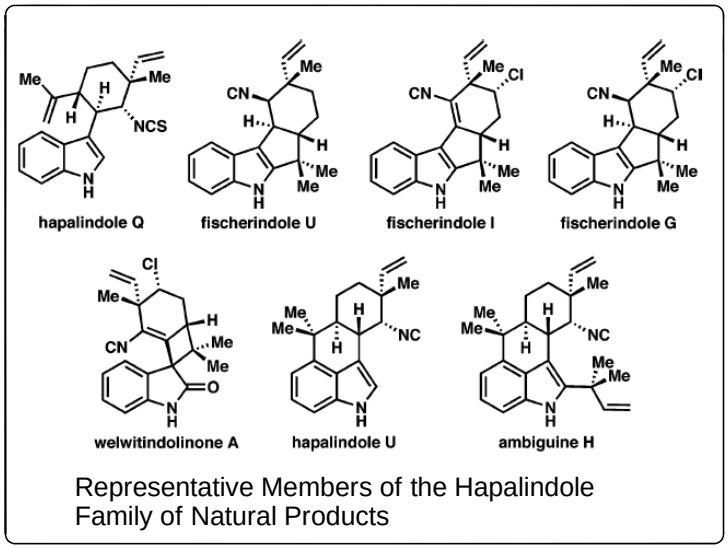
3. Direct oxidative coupling indoles and pyrroles with carbonyl compounds

A: Introduction

Cross-coupling paradigms:



"Chemoselectivity: The Mother of Invention in Total Synthesis"---Baran P.S.



Representative Members of the Hapalindole Family of Natural Products

B: Indole coupling

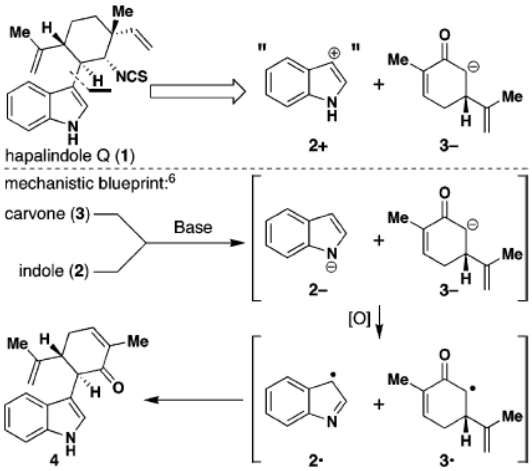
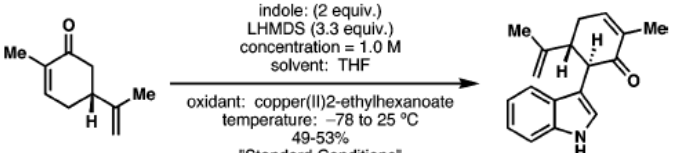


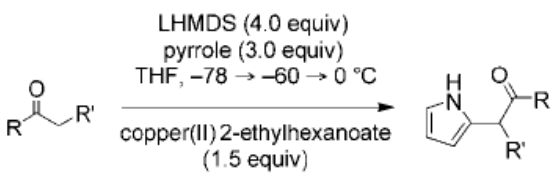
Figure 1. Retrosynthetic analysis of (+)-**1** leads to the invention of a direct coupling of indoles with carbonyl compounds.

Table 1. Indole–Carvone Coupling Optimizations



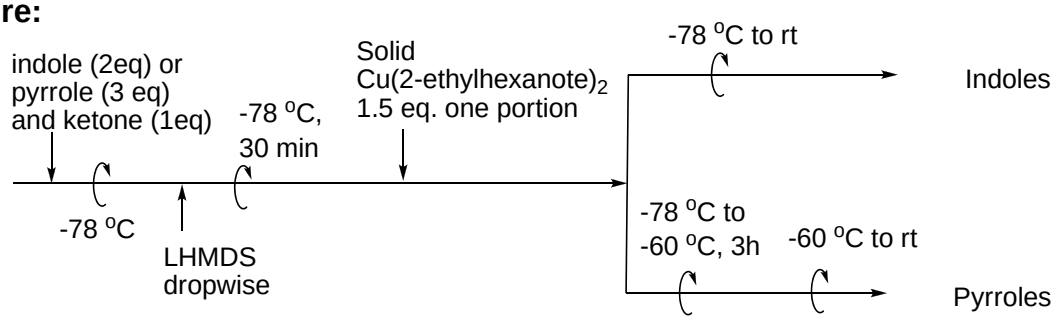
Baran P.S. *JACS*, **2004**, 7450

C: Pyrrole coupling



Baran P.S. *Angew*, **2005**, 609

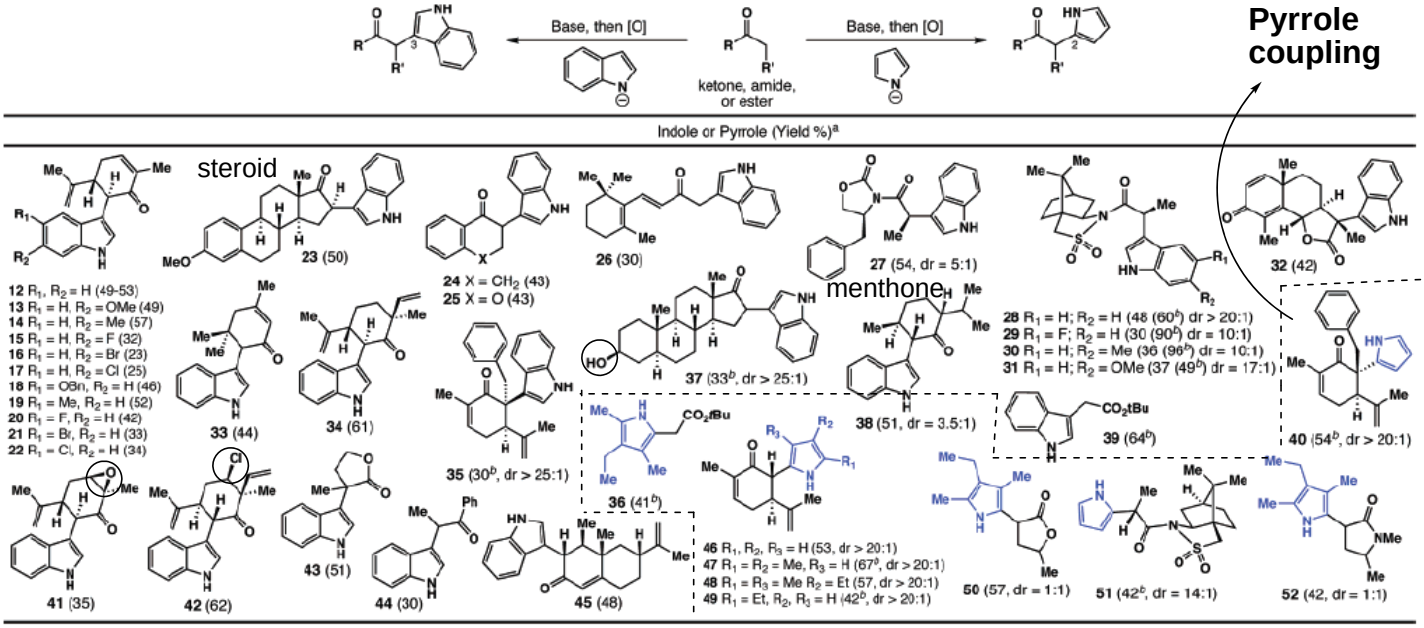
Procedure:



D: Scope

Baran P.S. *JACS*, **2007**, 12857

Table 2. Scope of the Indole and Pyrrole Coupling Reaction



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

Advantages:

1. The reactions allow tremendous complexity to be built into a target molecule using simple chemistry, which would otherwise require multiple steps to accomplish.
2. The coupling of unfunctionalized indoles and pyrroles with various carbonyl compounds such as esters, imides, lactones, lactams, ketones, and amides.
3. 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).
4. As a meaningful demonstration of its utility, the method has been applied effectively in total synthesis.

E: Mechanism study

(1) Dimerization of indole or pyrrole is never observed.

⇨ suggests that the ketone is oxidized first and then reacts with indole.

suggests that selective heterocouplings 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; the free N-H is required for the reaction to proceed.

⇨ suggests that the reaction is not proceeding via oxidation to a discrete α-radical on the carbonyl compound (which could react with the N-protected heterocycles) but instead supports a chelated transition state.

(3) Moderate to excellent diastereoselectivity was observed.

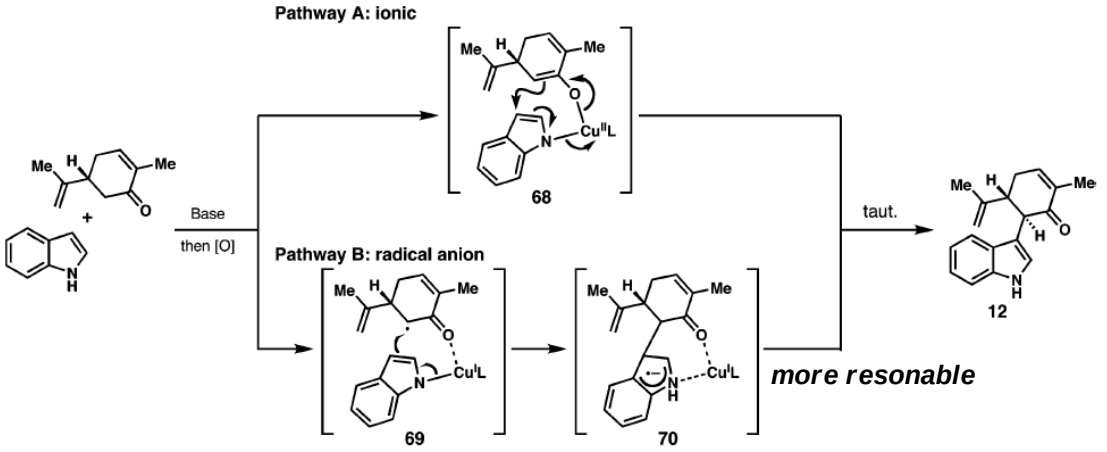
⇨ supports a chelated transition state.

(4) Only 1 equiv of oxidant, relative to the ketone, is necessary for the reaction to proceed.

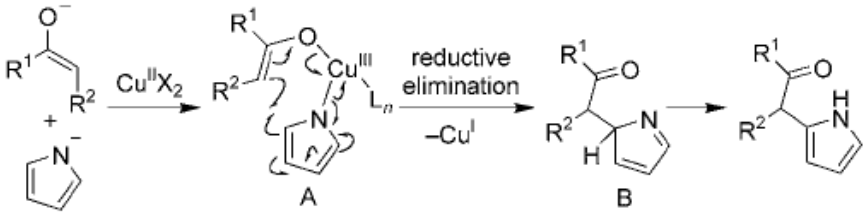
⇨ suggests that the reaction is proceeding by preferential oxidation of the carbonyl compound, which react with the indole or pyrrole anion, providing a radical anion intermediate. This radical anion could then be further oxidized by the remaining copper(I).

Mechanism for indole coupling

Scheme 7. Possible Mechanistic Pathways



Mechanism for pyrrole coupling



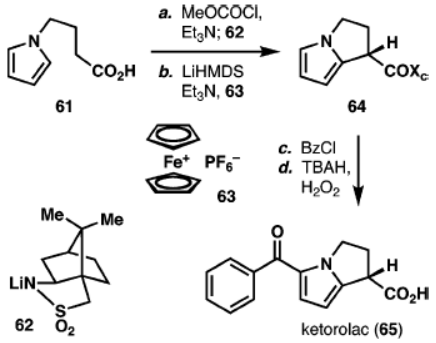
the characteristic red-brown color of copper(I) salts is often observed at the end of the reaction

Figure 2. Proposed mechanism for the direct coupling of pyrroles with carbonyl compounds by using Cu^{II}.

F. Application:

1) Total synthesis of Ketorolac

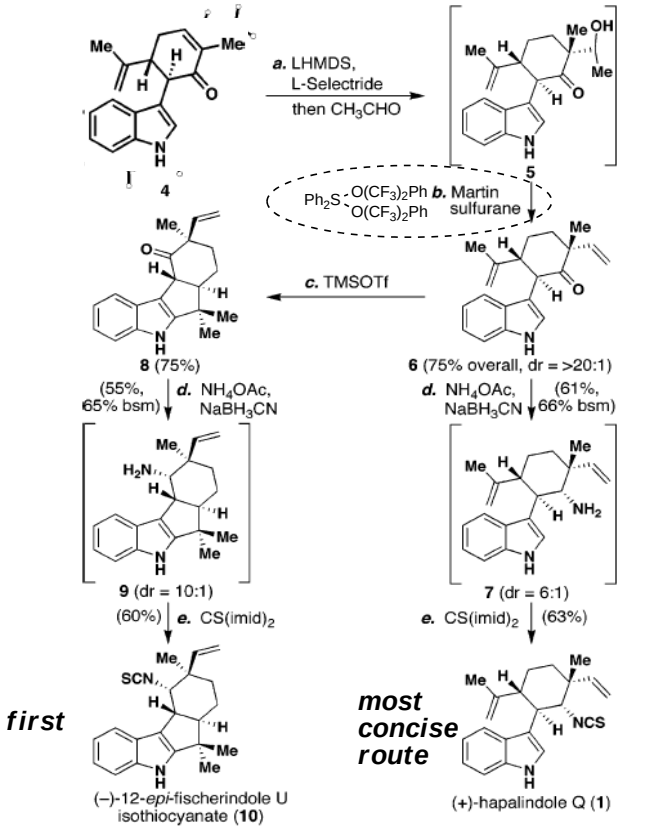
Scheme 6. Total Synthesis of Ketorolac[a]



[a] Reagents and conditions: (a) Et_3N (1.1 equiv), MeOCOCl (1.0 equiv), THF, 0 °C, 1 h; then **62**, 100%; (b) LHMDS (1.2 equiv), Et_3N (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), H_2O_2 (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 =

2) Enantioselective total synthesis of (+)-Hapalindole Q and (-)-Fisherindole U

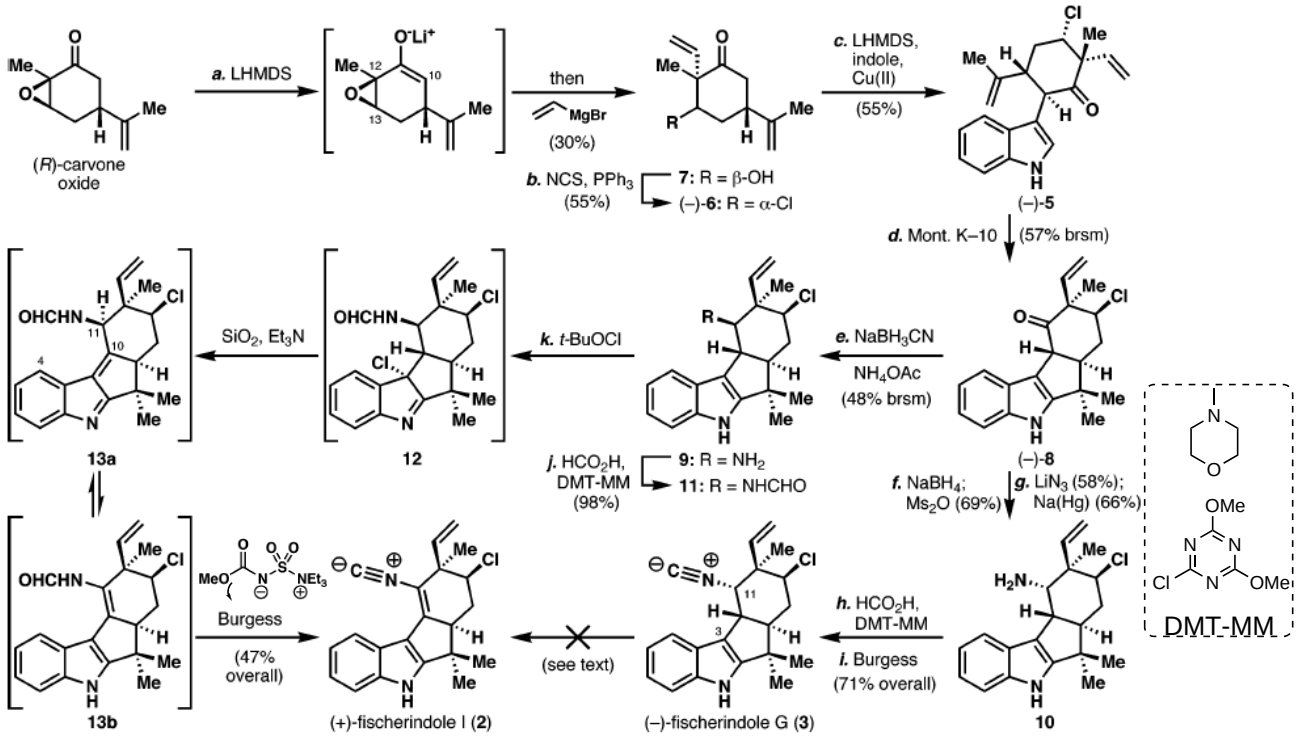
Scheme 1. Enantioselective Total Syntheses of (+)-**1** and (−)-**10**[a]



[a] Reagents and conditions: (a) LHMDS (1.5 equiv), THF, −78 °C, 20 min then L-Selectride (1.05 equiv), 1 h, then CH_3CHO (6.0 equiv), −78→23 °C, 2 h; (b) Martin sulfurane (1.1 equiv), $CHCl_3$, 10 min, 75% overall; (c) TMSOTf (3.0 equiv), MeOH (1.1 equiv), CH_2Cl_2, 0 °C, 1 h, 75% bsm; (d) $NaBH_3CN$ (10 equiv), NH_4OAc (40 equiv), MeOH, THF, 150 °C, 2 min, 61% (**7**); for **9**: same reagents, 23 °C, 48 h, 55%; (e) $CS(imid)_2$ (1.1 equiv), CH_2Cl_2, 0→23 °C, 3 h, 63% (**1**), 60% (**10**).

3) Enantioselective total synthesis of (+)-Fisherindole I and (-)-Fisherindole G Baran P.S. *JACS*, **2005**, 15394

Scheme 1. Short, Enantioselective Total Syntheses of (+)-**2** and (−)-**3**[a]



[a] Reagents and conditions: (a) LHMDS (1.2 equiv), THF, − 78 °C, 30 min; −15 °C, $CH_2CHMgBr$ (2.0 equiv), 15 min, 30%; (b) THF, PPh_3 (1.0 equiv), NCS (1.0 equiv), 18 h, 55%; (c) indole (2.0 equiv), LHMDS (3.1 equiv), THF, −78 °C, 30 min, then Cu(II)2-ethylhexanoate (1.5 equiv), −78 to 23 °C, 15 min, 55%; (d) DCE, Montmorillonite K-10 clay (10 equiv), microwave irradiation, 120 °C, 6 min, filter, then repeat, 40% + 30% recovered **5**; (e) THF, MeOH, $NaCNBH_3$ (10 equiv), NH_4OAc (40 equiv), 7 days, 26% **9** + 46% **8**; (f) MeOH, $NaBH_4$ (1.5 equiv), 0 °C, 5 min; then Ms_2O (2.0 equiv), py, 23 °C, 30 min, 69% overall; (g) DMF, LiN_3 (3.0 equiv), 120 °C, 48 h; then EtOH, Na(Hg) (10 equiv), reflux, 4 h, 38% overall; (h) HCO_2H (1.3 equiv), CDMT (1.4 equiv), DMAP (cat.), NMM (1.4 equiv), CH_2Cl_2, 23 °C, 30 min, 87%; (i) PhH, Burgess reagent (2.0 equiv), 23 °C, 30 min, 82%; (j) same as (h), 98%; (k) THF, TEA (1.0 equiv), *t*-BuOCl (1.5 equiv), 0 °C, 10 min, then SiO_2/Et_3N (PTLC), then PhH, Burgess reagent (2.0 equiv), 23 °C, 30 min, 47% overall. CDMT = 2-Chloro-4,6-dimethoxy-1,3,5-triazine; DCE = 1,2-dichloroethane; DMF = *N*,*N*-dimethylformamide; DMAP = 4-(dimethylamino)pyridine; IBX = *o*-iodoxybenzoic acid; LHMDS = lithium hexamethyldisilazide; Ms = methanesulfonyl; NCS = *N*-chlorosuccinimide; NMM = *N*-methylmorpholine.

4) Protecting-group-free synthesis of (+)-ambiguine H and (-)-hapalindole U Baran P.S. *Nature*, **2007**, 404

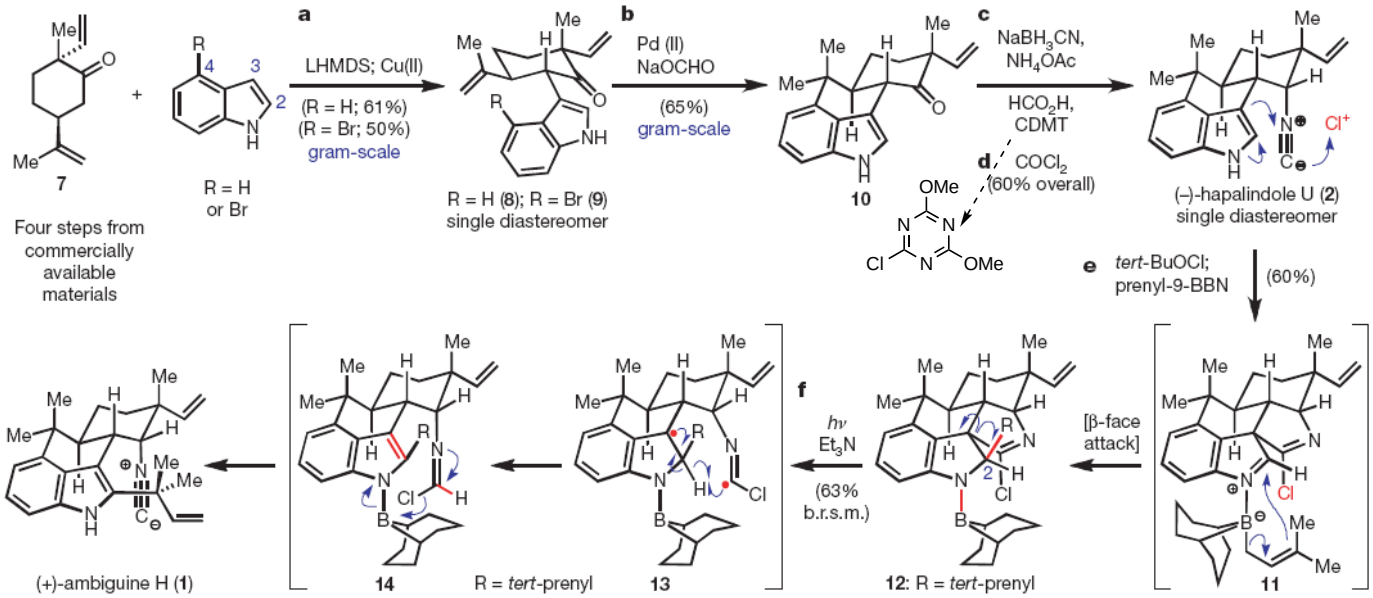


Figure 3 | Protecting-group-free synthesis of ambiguine H (1) and hapalindole U (2). Reagents and conditions as follows. **a**, Indole (1.9 equiv.), ketone **7** (1.0 equiv.), LHMDS (3.4 equiv.), Cu(II)-2-ethylhexanoate (1.5 equiv.), THF, starting temperature −78 °C, 5 min to 25 °C, yield is 61%; or 4-bromoindole (2.8 equiv.), ketone **7** (1.0 equiv.), LHMDS (4.4 equiv.), Cu(II)-2-ethylhexanoate (2.0 equiv.), THF, –78 °C, 5 min to 25 °C, 50%. **b**, $[Pd(P(o\text{-}tol)_3OAc]_2$ (0.05 equiv.), NaOCHO (1.25 equiv.), TBAB (2.0 equiv.), Et_3N (2.2 equiv.), DMF, 80 °C, slow addition of Pd over 5 h, 65%. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (9.3 equiv.), MeOH/THF, microwave irradiation at 150 °C, 2.5 min; then HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.05 equiv.), NMM (2.2 equiv.), DCM, 2 h, 25 °C. **d**, $COCl_2$ (2.0 equiv.), Et_3N (17.5 equiv.), DCM, 0 °C, 60% over two steps. **e**, *tert*-BuOCl (1.15 equiv), DCM, –78 °C, 12 min; then prenyl-9-BBN (2.0 equiv), −78 °C, 30 min, 60%. **f**, Et_3N (5.0 equiv.), benzene, *hv*, 5 h, 63% b.r.s.m. (based on recovered starting material). LHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran; TBAB, *tetra*-*n*-butyl ammonium bromide; Et_3N, triethylamine; DMF, *N*,*N*-dimethylformamide; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; DMAP, 4-*N*-dimethylaminopyridine; NMM, *N*-methylmorpholine; DCM, dichloromethane; 9-BBN, 9-borabicyclo-nonane. For selected physical data for compounds **1**, **2**, **7**–**10** and **12**, see the Supplementary Information. Compounds **2**, **12** and **1** were verified by X-ray crystallography.

5) Protecting-group-free synthesis of (-)-fisherindole I and (+)-welwitindolinone A

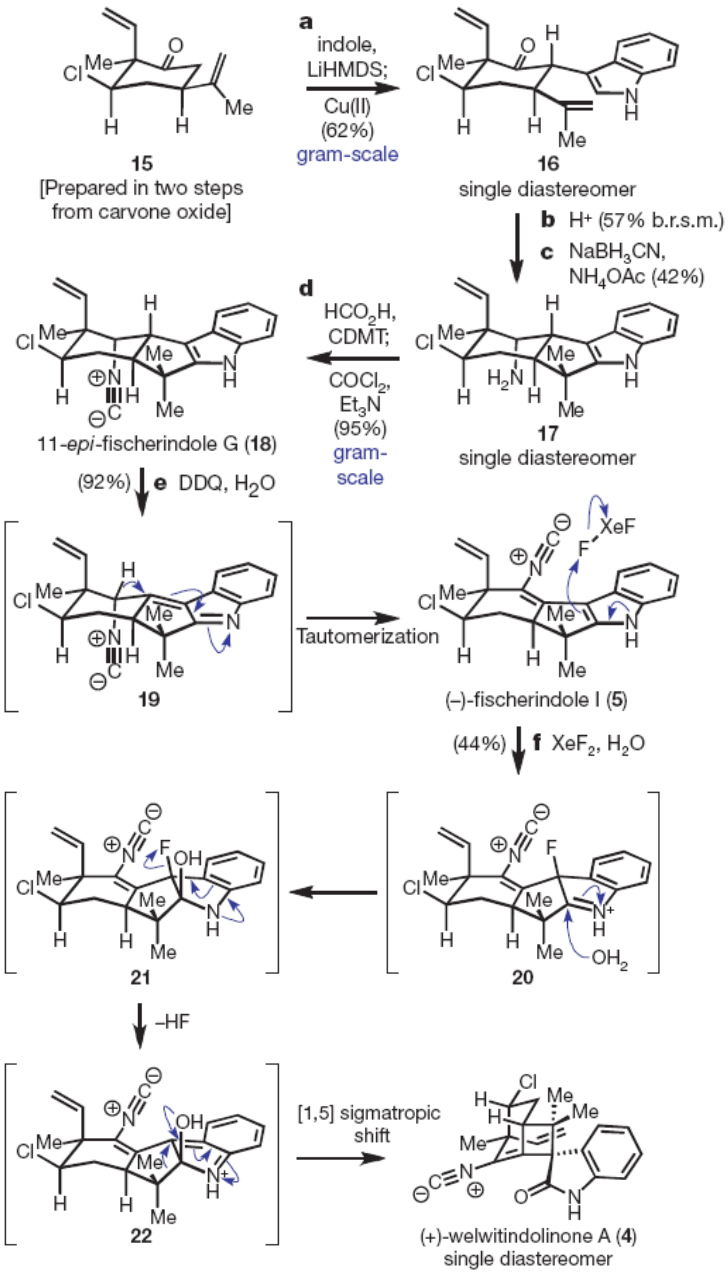


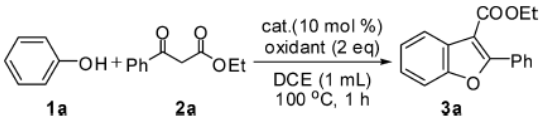
Figure 4 | Protecting-group-free total synthesis of fischerindole I (5) and welwitindolinone A (4). Reagents and conditions as follows. **a**, Indole (2.0 equiv.), LiHMDS (3.3 equiv.), THF, −78 °C, 30 min, copper(II)-2-ethylhexanoate (1.5 equiv.), −78 to 23 °C, 20 min, 62%. **b**, Montmorillonite K-10 clay, microwave irradiation at 120 °C, 6 min, 57% b.r.s.m. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (7.5 equiv.), 3 Å molecular sieves, MeOH/THF, sonication, 18 h, 42%. **d**, HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.1 equiv.), NMM (2.2 equiv.), DCM, 23 °C, 30 min; Et_3N (17.5 equiv.), $COCl_2$ (2.0 equiv.), DCM, 0 °C, 10 min, 95%. **e**, DDQ (2.5 equiv.), H_2O, THF, 0 °C, 30 min, 92%. **f**, XeF_2, H_2O, MeCN, 23 °C, 5 min; 44%. DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; MeCN, acetonitrile. For selected

4. Direct oxidative coupling phenols with β-keto esters

Iron-Catalyzed Tandem Oxidative Coupling and Annulation: An Efficient Approach to Construct Polysubstituted Benzofurans

Li Z.P. *JACS*, **2009**, 17387

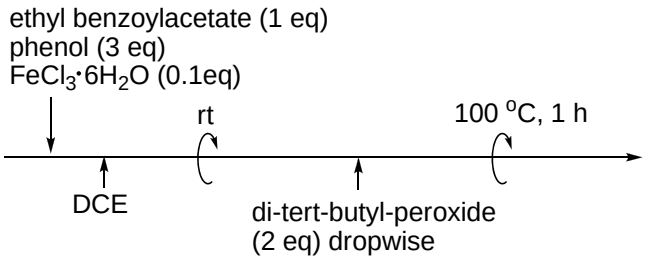
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	1a (equiv)	oxidant	yield (%)[b]
1	$FeCl_2$	1	$(t\text{-BuO})_2$	8
2	$FeBr_2$	1	$(t\text{-BuO})_2$	9
3	$FeCl_3$	1	$(t\text{-BuO})_2$	30
4	$FeCl_3 \cdot 6H_2O$	1	$(t\text{-BuO})_2$	46
5	$Fe(ClO_4)_3 \cdot xH_2O$	1	$(t\text{-BuO})_2$	16
6	$Fe(ClO_4)_2 \cdot xH_2O$	1	$(t\text{-BuO})_2$	47
7	$FeCl_3 \cdot 6H_2O$	3	$(t\text{-BuO})_2$	75
8	$FeCl_3 \cdot 6H_2O$	3	$(t\text{-BuO})_2$	N.D.[c,d]
9	$FeCl_3 \cdot 6H_2O$	3	*t*-BuOOH	11
10	$FeCl_3 \cdot 6H_2O$	3	PhCOOO-*t*-Bu	8
11	–	3	$(t\text{-BuO})_2$	N.D.
12	$FeCl_3 \cdot 6H_2O$	3	–	22[e]

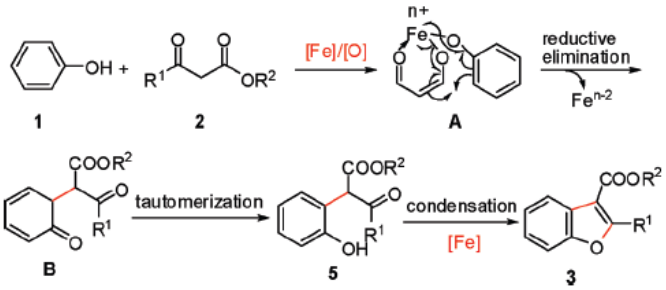
[a] Conditions: **2a** (0.5 mmol), $FeCl_3$ (0.05 mmol), peroxide (1.0 mmol) and DCE (1.0 mL), 100 °C, 1 h; unless otherwise noted; DCE = dichloroethane. [b] NMR yields are determined by ^1H NMR using mesitylene as an internal standard. [c] Not detected by ^1H NMR. [d] 4 Å molecular sieve (25 mg) was added. [e] $FeCl_3 \cdot 6H_2O$ (0.5 mmol) was used.

Procedure:



Mechanism:

Scheme 4. Tentative Mechanism of Iron-Catalyzed Oxidative Reaction of **1** and **2**



5. Perspectives

A: Catalytic asymmetric oxidative enolate coupling

1) The proposed metal-chelated transition state mechanisms make "metal-catalytzed" and "asymmetric induction" (ligand control) possible.

2) Using molecular O_2 as oxidant is the final goal.

B: To find new application in total synthsis.