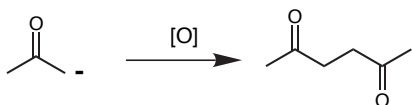


The Oxidative Coupling of Enolates and Enol Derivatives

Evans Research Seminars
March 14, 1995



An underappreciated umpolung of enolates

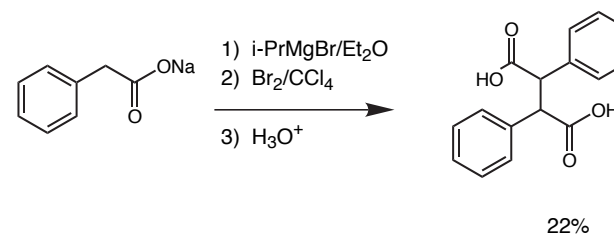
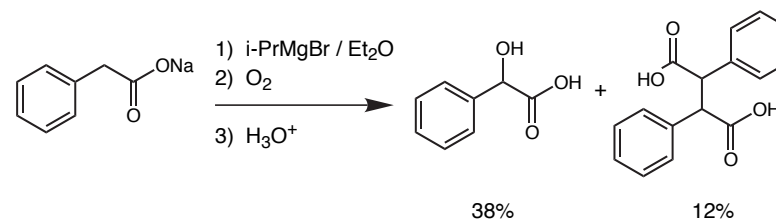
1. Ketone Enolates
2. Ester Enolates
3. Carboxylic Acid Dianions
4. Silyl Enolate Derivates
5. Applications to Organic Synthesis

Leading Papers:
Saegusa, T. *JACS*, **1977**, 99, 1487
Fox, M.A. *JOC*, **1988**, 53, 3745
Narasaka, K. *Chem. Letters*, **1992**, 2099

Chuck Scales

Reaction Background

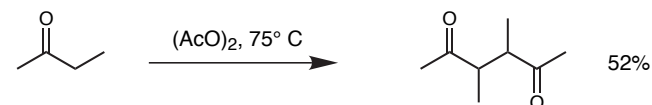
Synthesis of 3,4-diphenyl succinic acid



- Also obtained a "high" yield of α -bromophenylacetic acid
- Proposed radical dimerization as mechanism for production of β -diphenylsuccinic acid.

Ivanoff, *Bull. Soc. Chem. Fr.*, **1935**, 2, 76

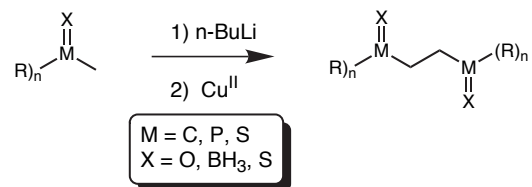
Synthesis of 1,4 Diketones



Kharasch, M.S., McBay, H.C., and Urry, W.H., *JACS*, **1948**, 70, 1269

Reaction Background

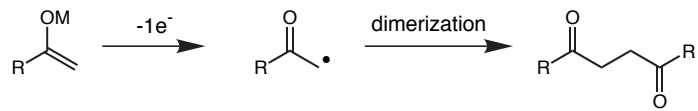
Coupling of Stabilized Anions



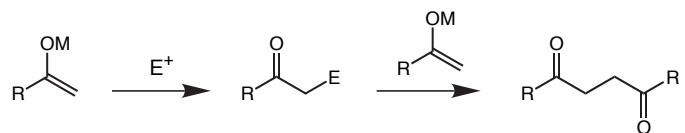
Mislow, K. *JACS*, **1973**, *95*, 5839
 Tamaru, Y. *JACS*, **1978**, *100*, 1923
 A. Muci and K. Campos, unpublished results

Anion Coupling Models

- Type 1 Oxidants

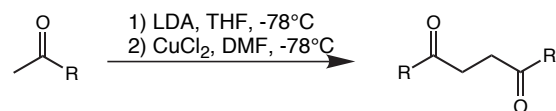



- Type 2 Oxidants



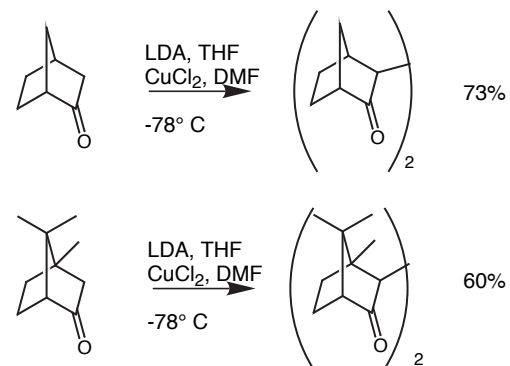
Synthesis of 1,4-Diketones

Methyl Ketone Dimerization



| R | Yield |
|---|-------|
| phenyl | 95% |
| ferrocenyl | 78% |
| furanyl | 41% |
| cyclopropyl | 46% |
| -C(CH ₂) ₂ CO ₂ Et | 64% |
| -CH=CH-  | 82% |

α-Substituted Ketone Dimerization

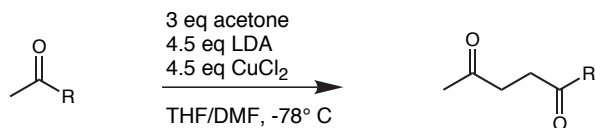


- Product mixture of exo-exo, exo-endo, and endo-endo isomers

Saegusa, *JACS* **1977**, *99*, 1487

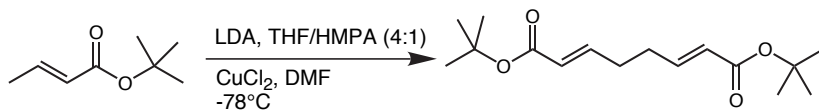
Synthesis of 1,4-Diketones

Cross-Coupling of Methyl Ketones

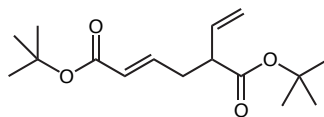


| R | Yield | |
|---|--------------|-------|
| | Cross-couple | Dimer |
| | 68% | 1% |
| | 53% | 1% |
| | 59% | 4% |
| | 65% | 2% |

γ Coupling of α,β -unsaturated ketones



33% γ,γ coupling product



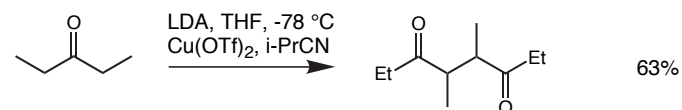
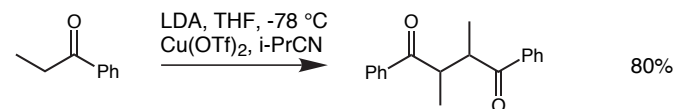
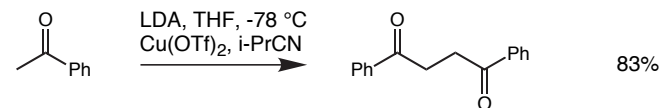
32% α,γ coupling product

- No α,α coupling product seen
- γ,γ couple not produced from thermal rearrangement of α,α product

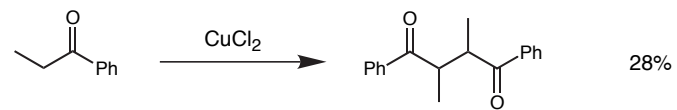
Saegusa, T. et al. *JACS* **1977**, *99*, 1487

1,4-Diketones with Copper (II) Triflate

From enolates



Anions Make a Difference

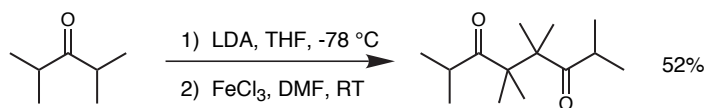


- Yield difference may be due to lability of triflate versus chloride ions

Kobayashi, et al. *TL*, **18**, 3741 (1977)
Kobayashi, et al. *Chem. Pharm. Bull.*, **28**, 262 (1980)

Coupling of Ketone Enolates

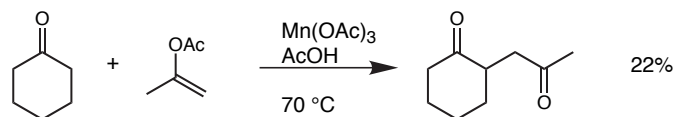
Oxidative Coupling with Ferric Chloride



- Dimers obtained from hindered enolates in moderate yields (40-60%)
- Prepared from kinetic and thermodynamic enolates

Frazier, R.H. et al. *JOC*, **1980**, 45, 5408

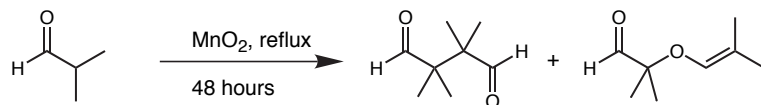
Oxidation with Manganic Acetate



- Proposed radical coupling mechanism for transformation

Dessau, R.M. et al. *JOC*, **1974**, 39, 3457

Oxidative Dimerization of Aldehydes

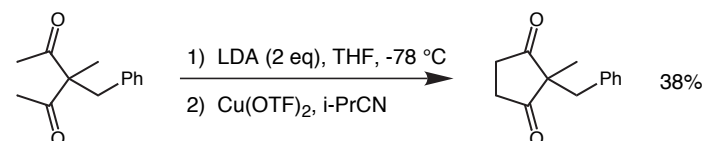


- All examples produced ca 80% yield of dimer in 45:55 ratio (C-C:C-O).

Leffingwell, J.C. *JCS Chem. Comm.*, **1970**, 357

Intramolecular Coupling

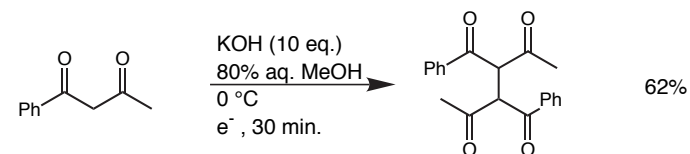
Ketone cyclization



- Generally poor yields; spirocyclic examples included.

Kobayashi, et al. *TL*, **1978**, 19, 3555

Tetraketone Synthesis



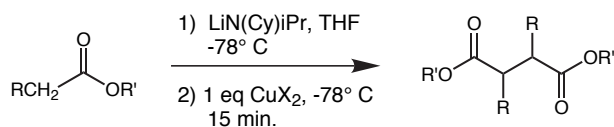
- Synthesized various aryl substituted 3,4-aryl-2,5-hexanediones
- Observed that EDG favor oxidation and EWG disfavor oxidation (correlated to Hammett plot)

Hammett Plot Here

Lacan, M. et al. *Croat. Chem. Acta*, **1973**, 45, 465

Ester Enolate Coupling

Synthesis of Succinate Esters



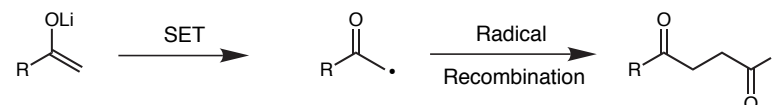
| R | R' | Yield | |
|------------------|-------|-------------------|--|
| | | CuBr ₂ | Cu(O ₂ C ₅ H ₉) ₂ |
| -H | -t-Bu | 85 | 95 |
| -Me | -Et | 81 | 50 |
| -n-Bu | -Et | 63 | ---- |
| -Me ₂ | -Et | 25 | 20 |
| -i-Pr | -Et | 20 | 20 |
| -Ph | -Et | 75 | 60 |
| | -Et | | |

- Increasing alkyl substitution decreases yield of dimer
- Yield of α-bromoester increased with increasing alkyl substitution when copper (II) bromide used as oxidizing agent
- Yield of dimer not increased with copper (II) valerate
- Product obtained as an unspecified mixture of stereoisomers

Rathke, *J. Am. Chem. Soc.* **1971**, 93, 4605

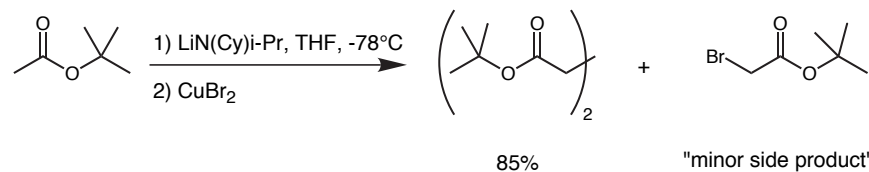
Oxidative Coupling Mechanism

Proposed Mechanism

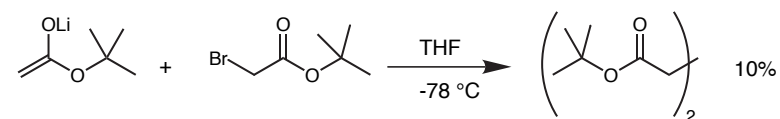


- Radical may be associated with oxidizing agent

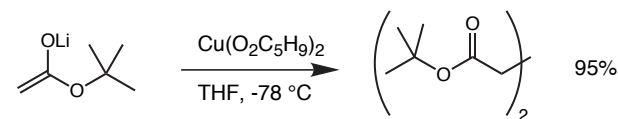
Evidence for Radical Mechanism



- Investigation of possible S_N2 mechanism



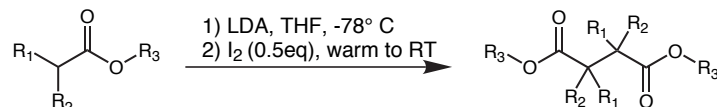
- Exclusion of bromide source also leads to product



Rathke, *J. Am. Chem. Soc.* **1971**, 93, 4605

Succinate Esters with Other Oxidants

Oxidation with Iodine

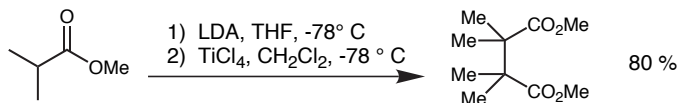


| R ₁ | R ₂ | R ₃ | Yield |
|----------------|----------------|----------------|-------|
| H | H | t-Bu | 97% |
| Me | H | t-Bu | 80% |
| Me | Me | Me | 90% |
| Me | Me | Et | 85% |

- Authors propose an S_N2 mechanism for this transformation

Brocksom, T.J., et al. *Synthesis* **1987**, 396

Oxidation with TiCl₄

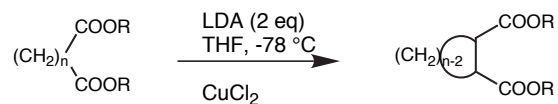


- Excellent yields with α-substituted esters (i-Pr, BnO)
- Other Lewis acids (BF₃·OEt₂, SnCl₄) do not promote oxidation
- ZrCl₄ resulted in Claisen condensation products
- Not applicable for ketones or amides

Ojima, et al. *Chem. Letters* **1992**, 1591

Intramolecular Coupling

Ester cyclization



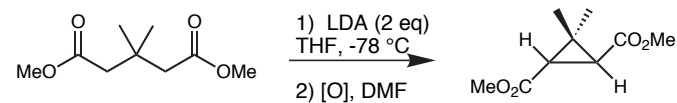
| n | R | Yield |
|---|------|---|
| 3 | Me | 88% (3:1 cis:trans) ^a |
| 4 | t-Bu | 20% (undetermined mixture of stereoisomers) ^b |
| 5 | t-Bu | >50% (undetermined mixture of stereoisomers) ^b |
| 6 | Me | 93% (0.6:1 cis:trans) ^a |

- Equilibration between cis and trans isomers noted for all reactions.
- Dimethyl adipate and dimethyl pimelate gave exclusively Dieckmann cyclization under the reaction conditions.

^aChung, S.K. et al. *JOC*, **1983**, 48, 1125

^bBabler, J.H. et al. *JOC*, **1987**, 52, 3462

Oxidation of dimethyl β,β-dimethylglutarate



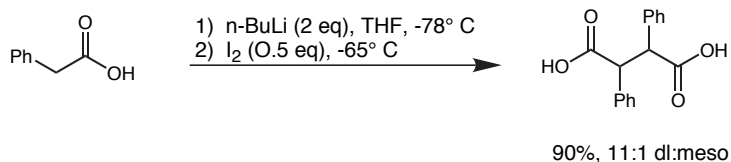
| Oxidant | Temp. | Yield | cis:trans |
|-------------------|-------|-------|-----------|
| CuCl ₂ | -78 | 71% | 57:43 |
| CuCl ₂ | 0 | 83% | 68:32 |
| I ₂ | -78 | 76% | 19:81 |
| AgCl | -78 | 81% | 80:20 |

- No attempt to rationalize stereochemical outcome of reaction

Babler, J.H. et al. *Synth. Comm.*, **1983**, 13, 905

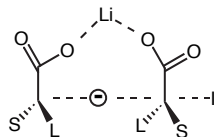
Carboxylic Acid Dianion Coupling

Coupling of Acid Dianions



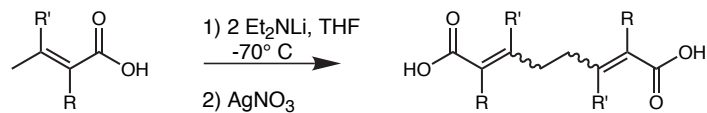
- Yields increased with dianion salt isolation

Stereochemical Model

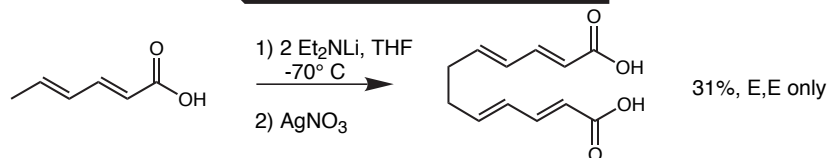


Belletire, J.L. et al. *TL*, **1984**, *25*, 5969

γ Coupling of α,β -Unsaturated Carboxylic Acids



| R | R' | Yield | E,E:E,Z:Z,Z |
|----|----|-------|-------------|
| H | H | 49 | 1:0:0 |
| Me | H | 63% | 1:0:0 |
| H | Me | 38% | 1:1:1 |
| Me | Me | 61% | 7:3:0 |

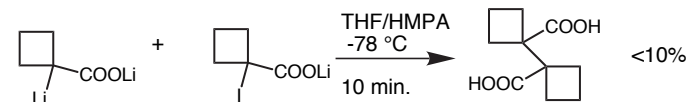
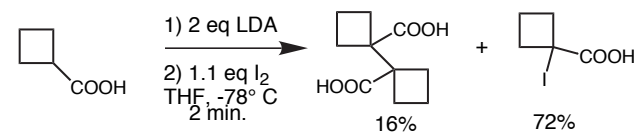


- No rationale for observed stereochemistry
- Also observed unspecified yields of γ,α coupled product

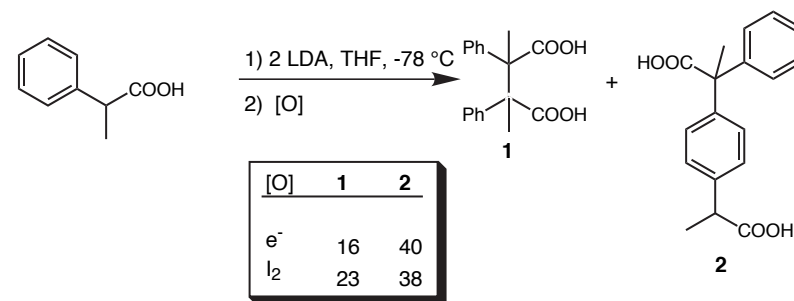
Mestres, R. *TL*, **1988**, *29*, 6181

Iodine Oxidation Mechanism

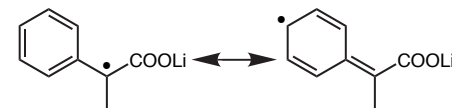
Mechanistic Investigations



- "Dimerization reaction is much faster than nucleophilic substitution under the reaction conditions."



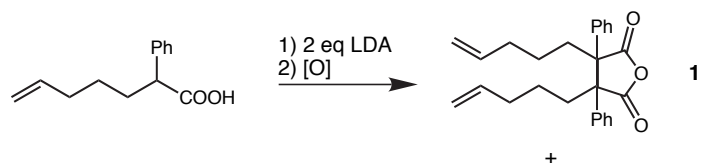
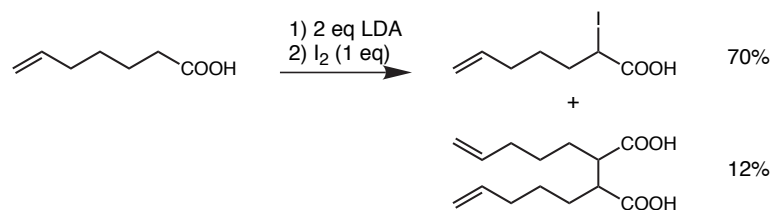
- Formation of α,para coupling product **2** supports radical anion intermediate



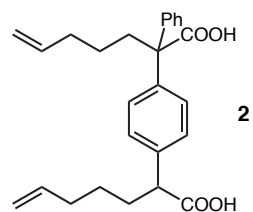
Fox, M.A. et al. *JACS* **1988**, *53*, 3745

Iodine Oxidation Mechanism

5-Hexenyl Radical Trap



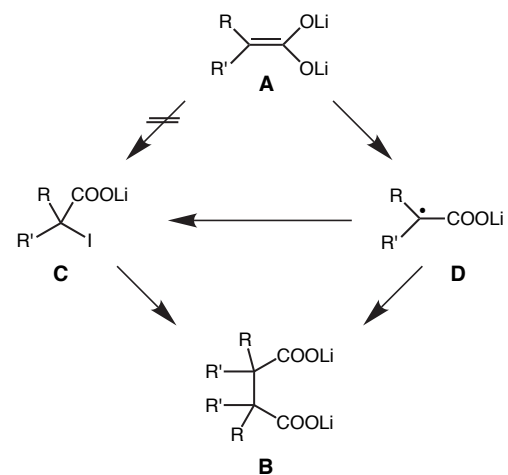
| | 1 | 2 |
|----------------|-----|-----|
| [O] | | |
| I ₂ | 26% | 32% |
| e ⁻ | 8% | 36% |



No cyclopentylmethyl products seen!

Fox, M.A. et al. *JACS* **1988**, 53, 3745

Mechanism for Iodine Promoted Coupling

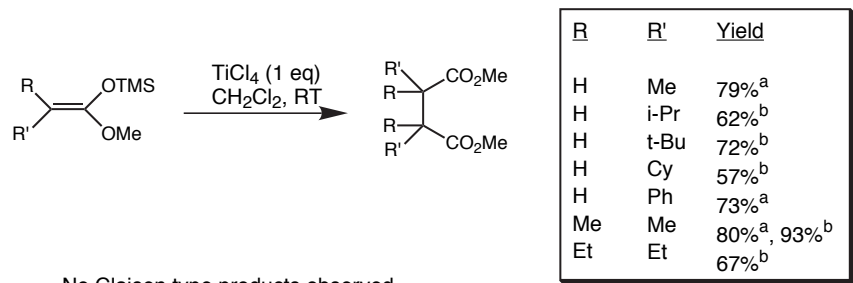


- Proposed initial step is SET to form radical anion (**D**).
- Radical anion (**D**) may iodinate, then form dimer (**B**) via S_N2 reaction
- Radical anion may form dimer directly, especially if R and R' are large (>H)
- Direct iodination of dianion neither supported or excluded by experiments

Fox, M.A. et al. *JACS* **1988**, 53, 3745

Silyl Ketene Acetal Dimerization

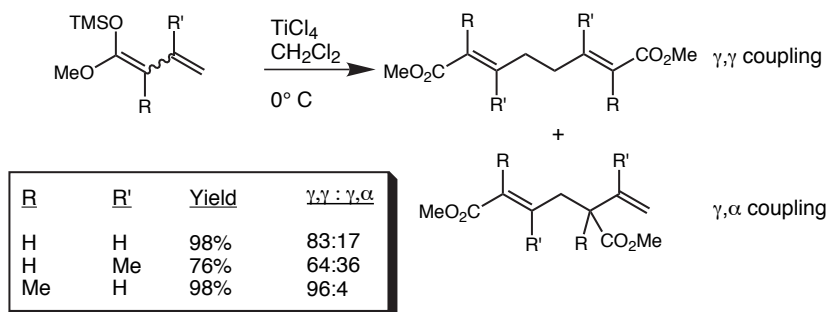
Silyl Ketene Acetals



- No Claisen type products observed
- SET (Ti^{IV} → Ti^{III}) followed by radical coupling mechanism proposed by both authors
- Other reagents (Cu^{II} salts, FeCl₃) ineffective for coupling reaction.

^a Ojima, I. et al. *TL* **1977**, *18*, 2009
^b Rhodes, Y.E. et al. *Synth. Comm.* **1985**, *15*, 301

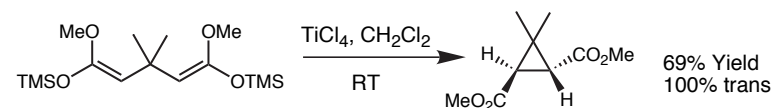
Vinyl Ketene Silyl Acetal Coupling



Ojima, I. et al. *TL* **1983**, *24*, 785

Silyl Ketene Acetal Coupling

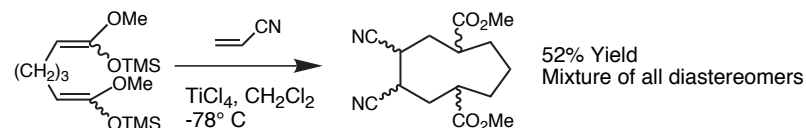
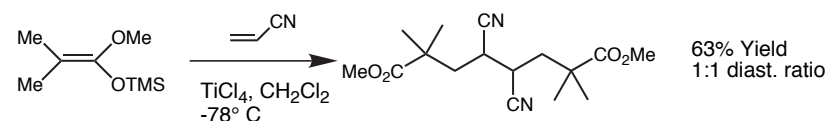
Carbocycle Synthesis



- Stereochemical course under thermodynamic control
- No coupling from ketone-derived enol silyl ethers
- Generally poor yields; exclusively 1,3-trans product.

Chan, T.H. *Tetrahedron*, **1983**, *39*, 847

Acrylonitrile Trapping

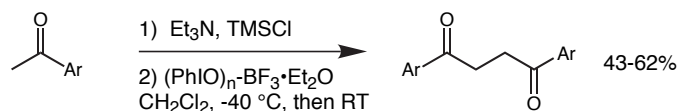


- Authors propose enoxyradical trapping by acrylonitrile, followed by dimerization
- Reactions with methacrylonitrile gave poor yields.
- Attempts to trap putative radical intermediate with FeCl₃, CCl₄, CBr₄, and tributyltin hydride failed.

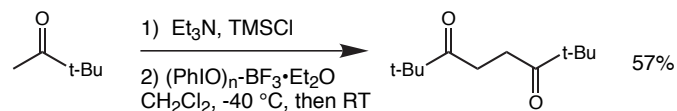
Rousseau, G. *Tetrahedron*, **1990**, *46*, 7011

Silyl Enol Ether Dimerization

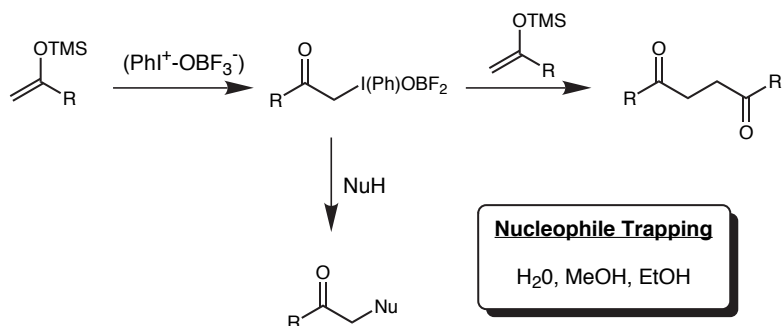
Hypervalent Iodine Oxidants



Ar = Ph, p-HOC₆H₄, p-MeOC₆H₄, p-ClC₆H₄, p-MeC₆H₄



Proposed Mechanism

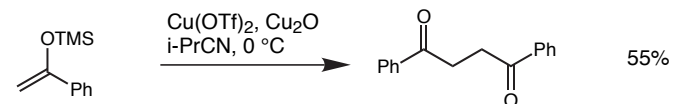


- Nucleophile trapping accomplished in "good yields."

Moriarty, R., et al. *JCS Chem. Comm.*, 420 (1985)
Moriarty, R., et al. *J. Chem. Soc. Perk. Trans. I*, 559 (1987)
Caple, R., et al. *JOC*, 54, 2609 (1989)

Silyl Enol Ether Dimerization

Metal Oxidants



| Oxidant | # eq | Solvent | Temp.(°C) | Time (hr) | Yield | Ref. |
|---|------|--|---------------|-----------|-------|------|
| Cu(OTf) ₂ /Cu ₂ O | 1,4 | i-PrCN | 0 | 2 | 55% | a |
| Ag ₂ O | 1 | DMSO | 65 | 2 | 73% | b |
| Pb(OAc) ₄ | 0.5 | 2:1 CH ₂ Cl ₂ :THF | -78, then 23 | 1.5;1 | 45% | c |
| VO(OEt)Cl ₂ | 2 | CH ₂ Cl ₂ | -75, then -40 | 3;4 | 30% | d |

- All authors also reported yields for non-styrenyl silyl enol ethers.
- Yields are extremely substrate dependent.
- Generally, increasing steric hindrance decreases yields.
- All authors propose oxidation to cation radical, followed by loss of trimethylsilyl cation and radical coupling.

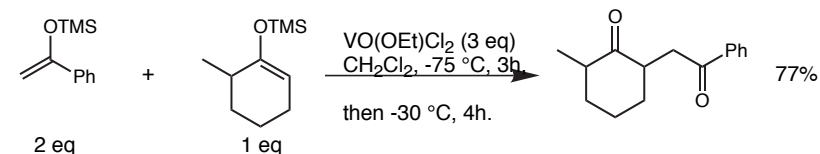
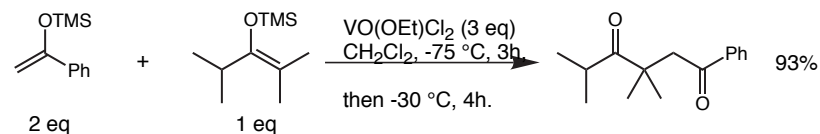
^aKobayashi, Y. et al. *Chem. Pharm. Bull.*, 1980, 28, 262

^bSaegusa, T. et al. *JACS* 1975, 97, 649

^cMoriarty, R.M. et al. *JL* 1987, 28, 873

^dOhshiro, Y. et al. *JL* 1992, 33, 5823

Cross Coupling Experiments

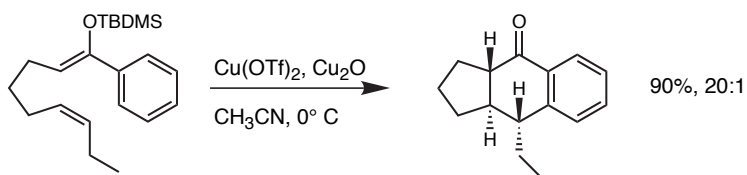


- Less reactive substrate added first, followed by more reactive substrate.
- In all cases, trace amounts of dimers isolated.

Ohshiro, Y. et al. *ibid.*

Silyl Enol Ether Coupling

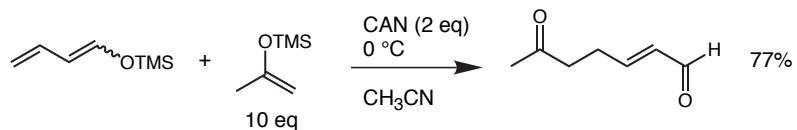
Alkene Trapping



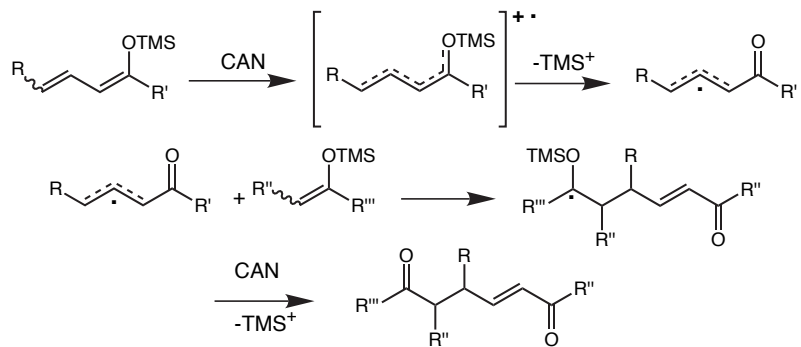
- Also observed for δ,ϵ olefins.
- Kinetic product can be isomerized in KOH/MeOH.

Snider, et al. *JOC*, 1990, 55, 4786

6-Oxo- α,β -Unsaturated Carbonyl Compounds



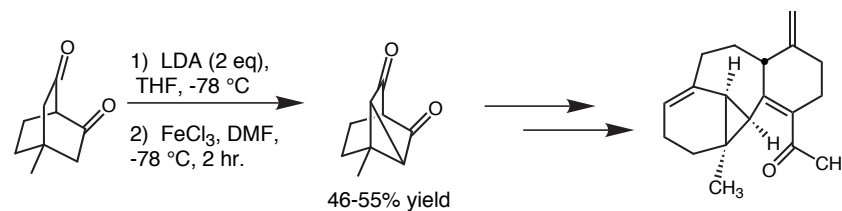
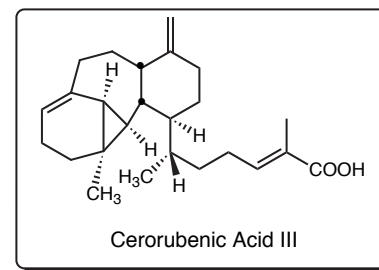
Proposed Mechanism



Ruzziconi, R. et al. *TL* 1993, 34, 721

Application: Ketone Enolates

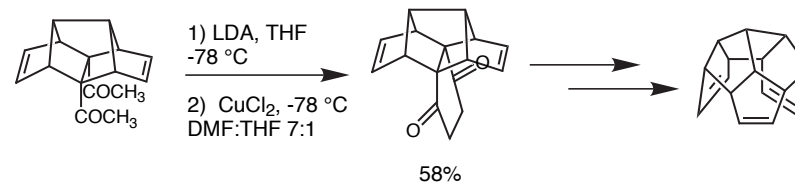
Cerorubenic Acid III: Construction of the Tetracyclic Core



- Other oxidants (CuCl_2 , $\text{Cu}(\text{OTf})_2$) coupled with poor yields

Paquette, L.A. *JOC*, 1993, 58, 4245

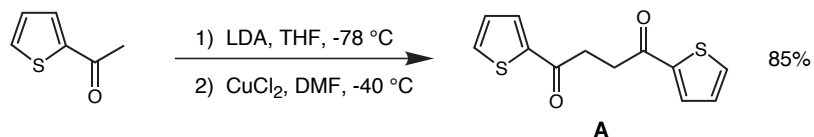
C₁₆ Hexaquinacene



Paquette, L.A. et al. *JACS*, 1978, 100, 1600

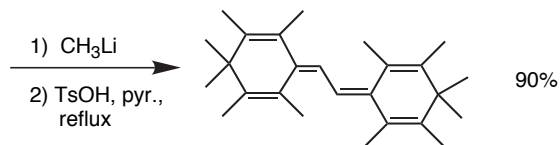
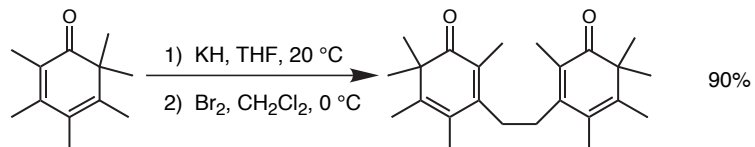
Ketone Enolate Applications II

Coupling of 2-acetylthiophene



Kagan, J. et al *Heterocycles*, **1983**, 20, 1941

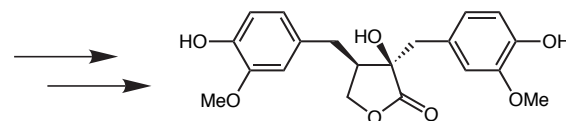
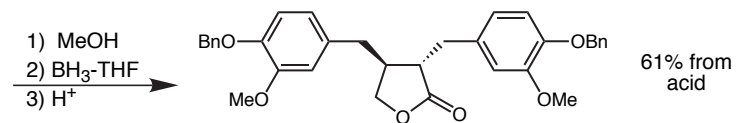
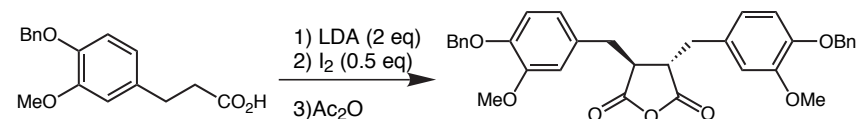
γ-Coupling of Ketone Enolates



Hart, H. et al. *JL*, **1977**, 18, 2307

Application: Carboxylic Acid Dianions

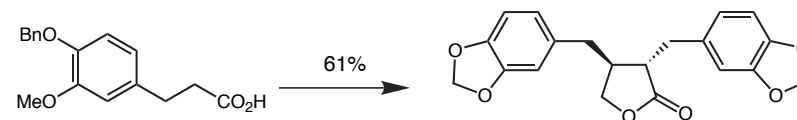
Total Synthesis of Racemic Wikstromol



Belletire, J.L. et al, *JOC*, **1988**, 53, 4724

- Anhydride "obtained as a single diastereomer by NMR analysis."

Total Synthesis of Racemic Hinokinin

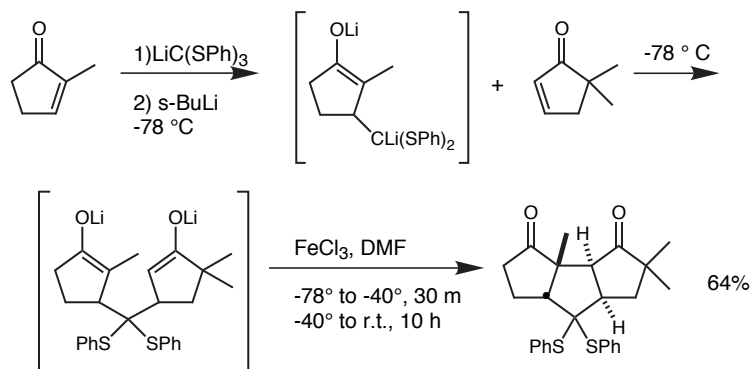


- Mixture of erythro and threo acids; anhydride exclusively threo.

Belletire, J.L. et al, *JOC*, **1987**, 52, 2549

Applications: Ketone Enolates and Silyl Enol Ethers

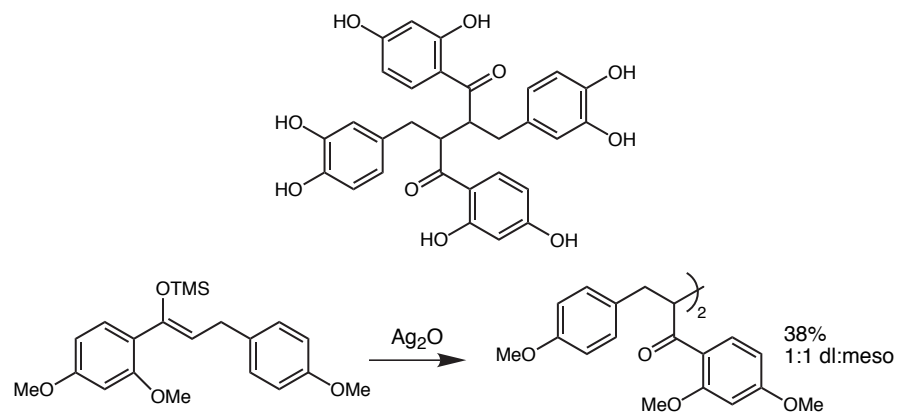
Synthesis of Racemic Hirsutene



- Isolated as a single diastereomer; proof by conversion to hirsutene.

Cohen, T. *JOC*, **1992**, 57, 1968

Studies Toward the Synthesis of Brackenin

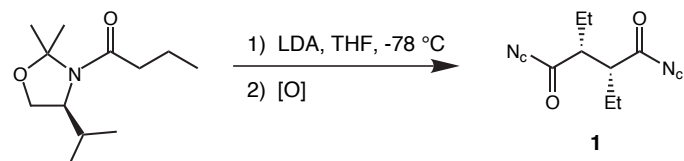


- "Use of Li enolates [for coupling] proved to be unsatisfactory."

Drewes, S.E. *JCS Perkin Trans 1*, **1989**, 1585

Stereoselective Synthesis of Succinamides

Oxazolidine Auxiliary Experiments

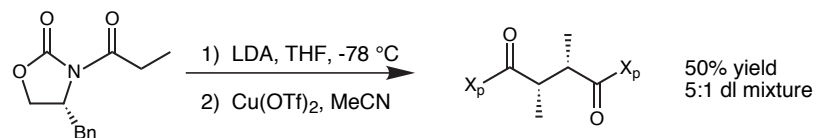


| Oxidant | Yield | 1:Σ_others |
|-------------------|--------|------------|
| I ₂ | 40-50% | 92:8 |
| CuCl ₂ | 50-55% | 98:2 |

- No model for induction proposed

Porter, N.A. et al. *JL*, 1993, 34, 4457

Oxazolidinone Auxiliary Experiments

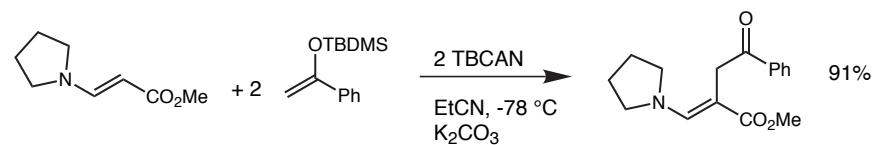
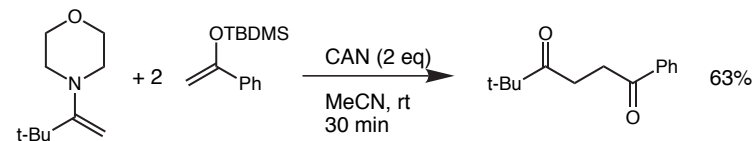


- Also obtained ca. 30% yield of meso dimer

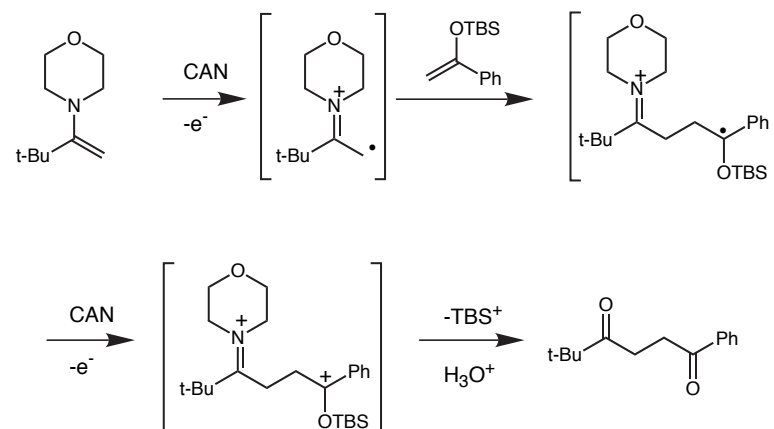
J. Ellman and M. Dart, unpublished results

Oxidative Coupling of Enamines

Silyl Enol Ether Trapping



Proposed Mechanism



Narasaka, K. et al. *Chem. Letters* 1992, 2099