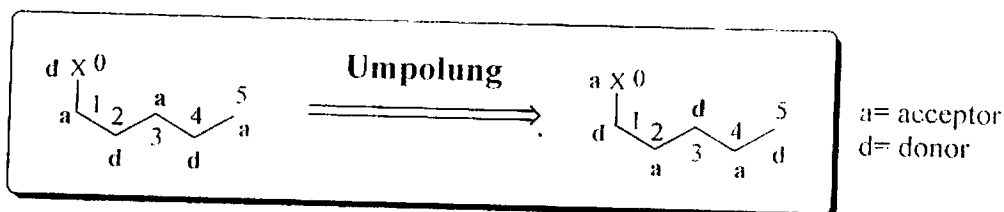


Direct Reactivity Umpolung

2007. Jul. 4th. Yohei Shimizu (M2)

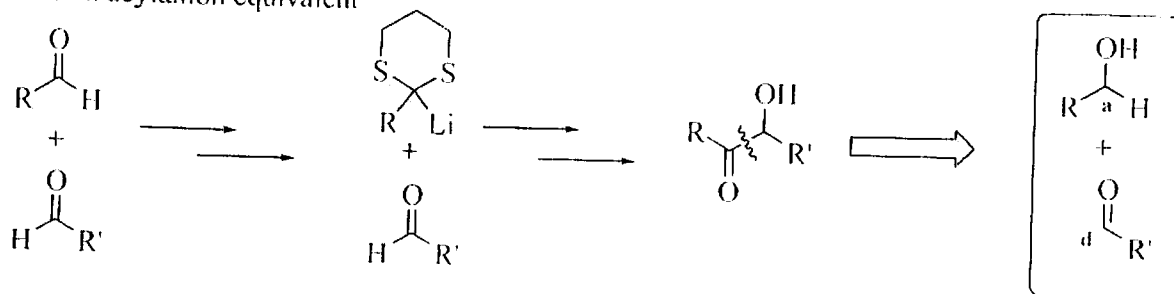
Umpolung is any process by which donor and acceptor reactivity of an atom are interchanged.



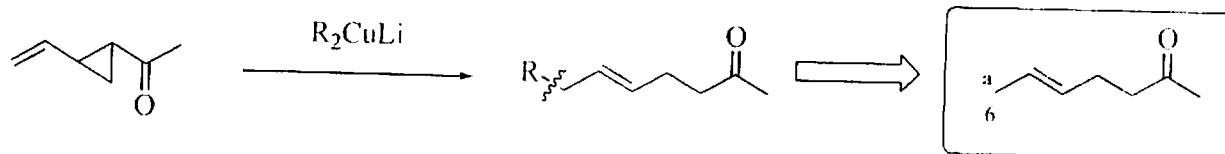
'usual' reactivity C_{2n} = donor, C_{2n+1} = acceptor
 umpolung reactivity C_{2n} = acceptor, C_{2n+1} = donor

Reactivity umpolung enables us to construct new bonds which is difficult to construct or cannot be achieved by "usual" reactivity.

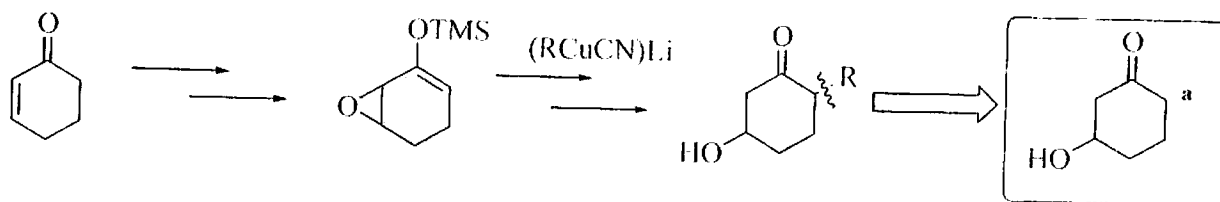
well known acylation equivalent



use of cyclopropanes to make C_{2n} acceptor



α -carbon as electrophiles by using epoxide



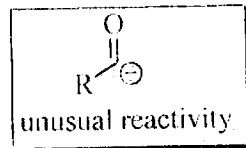
These examples need pre-functionalization to achieve reactivity umpolung. Of course they can be alternative synthetic approaches of 'usual' reactivity, but if we can omit pre-functionalization reactivity umpolung should be more useful tool in organic chemistry. Today I will focus on the direct reactivity umpolung methods.

Today's contents

1. Benzoin Condensation and Stetter Reaction
2. Allylation by Umpolung of π -Allylpalladium
3. Oxidative Coupling of Enolates

1. Benzoin Condensation and Stetter Reaction

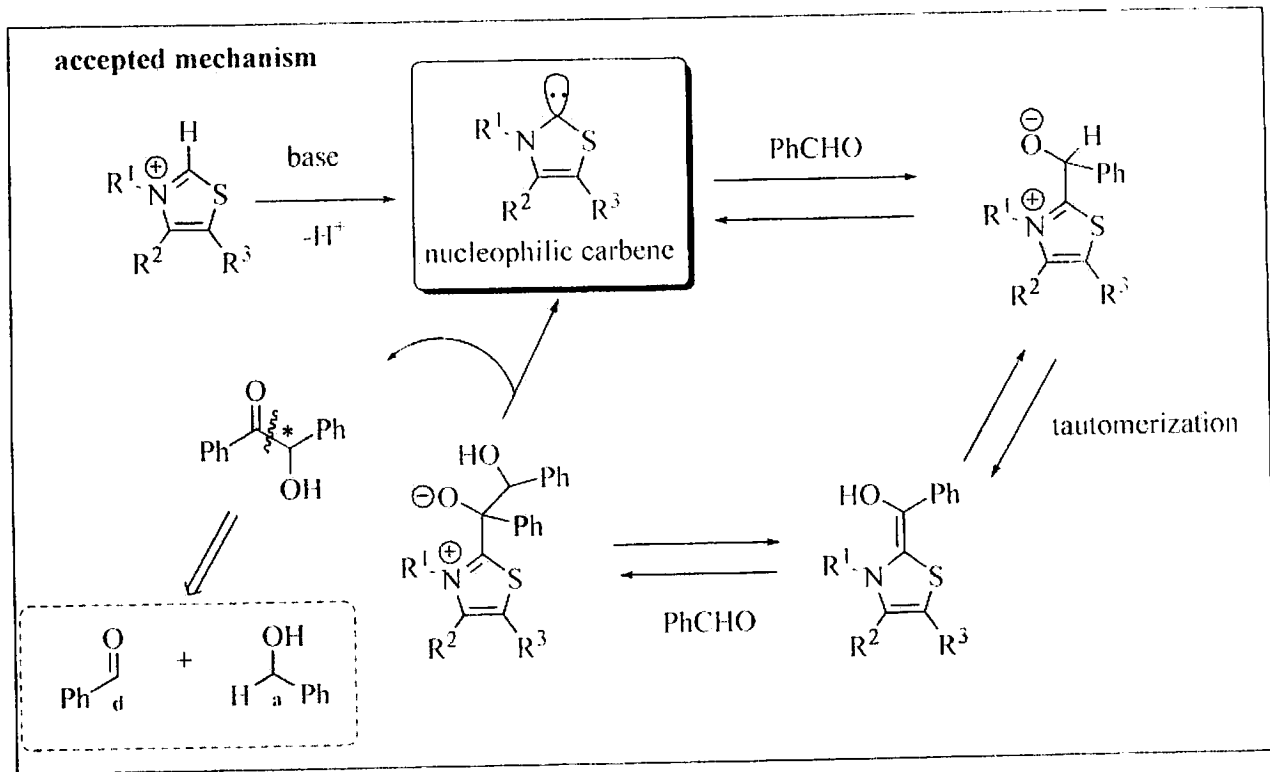
These reactions' feature is generation of acylanion equivalent by catalytic methods.



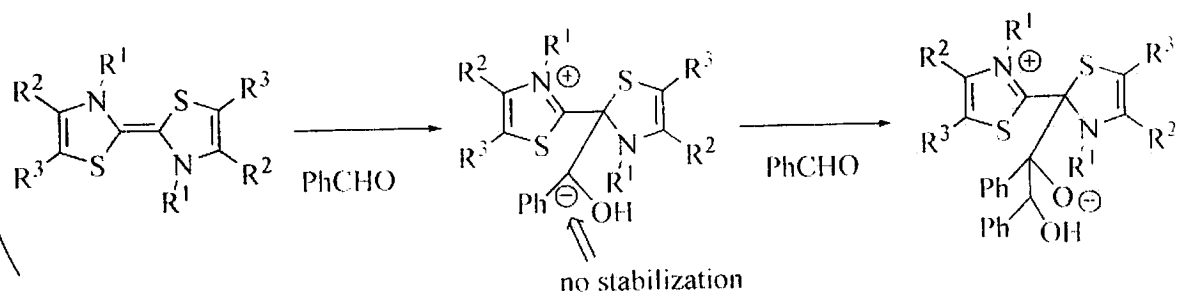
Conventional benzoin condensation was catalyzed by CN^- .

In 1943 Ukai et. al. found that thiazolium salts can be used as catalysts for benzoin condensation.

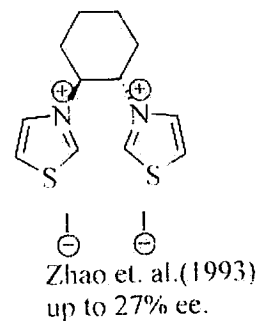
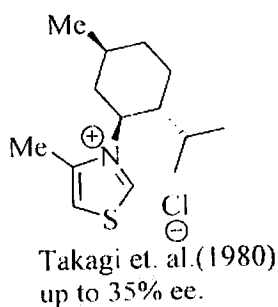
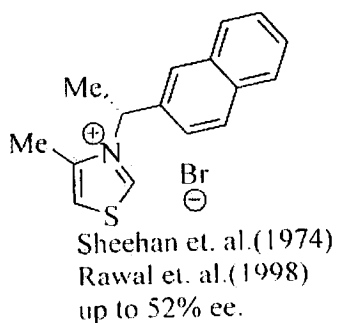
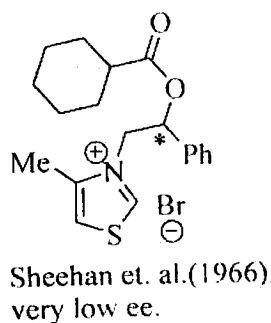
The mechanism was proposed by R. Breslow et. al. and accepted so far.



Some groups insisted that dimer of thiazolium ion was an actual catalyst. But this mechanism was ruled out by spectroscopic and kinetic studies (first-order in thiazoliumcat.).



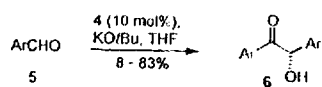
This type of nucleophilic carbene catalyzed reactions can be applicable for catalytic asymmetric C-C bond formation reaction.



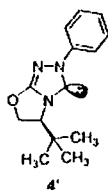
All these examples are far from satisfactory...

Great progress of this field was achieved by triazolium salt which was developed by Enders. Nucleophilic carbenes derived from triazolium salts are more stable than those derived from thiazolium salts.

D. Enders; U. Kallfass *Angew. Chem. Int. Ed.* 2002, 41, 1743



6	Ar	T [°C]	Yield [%]	ee [%] ^[d]
a	H	18	83	90
b	4-F ₂ C ₆ H ₃	18	81	83
b'	4-F ₃ C ₆ H ₂	0	61	91
c	4-Cl ₂ C ₆ H ₃	18	80	64
c'	4-Cl ₃ C ₆ H ₂	0	44	89
d	4-Br ₂ C ₆ H ₃	18	82	53
d'	4-Br ₃ C ₆ H ₂	0	59	91
e	3-Cl ₂ C ₆ H ₃	18	92	62
e'	3-Cl ₃ C ₆ H ₂	0	85	86
f	4-Me ₂ C ₆ H ₃	18	16	93
g	3-Me ₂ C ₆ H ₃	18	70	86
g'	3-Me ₃ C ₆ H ₂	0	36	91
h	4-MeOC ₆ H ₄	18	8	95
i	2-furyl ^[d]	0	100	64
i'	2-furyl	-78	41	88
j	2-naphthyl	18	69	80

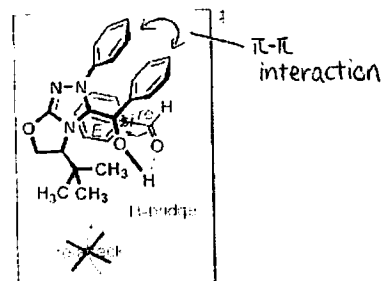


Electron-rich aromatic aldehydes gave better ee, but low reactivities.

π - π interaction increases ee??

Electron density at carbonyl carbon determines the reactivity??

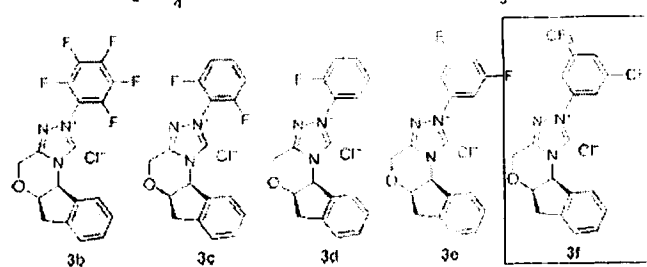
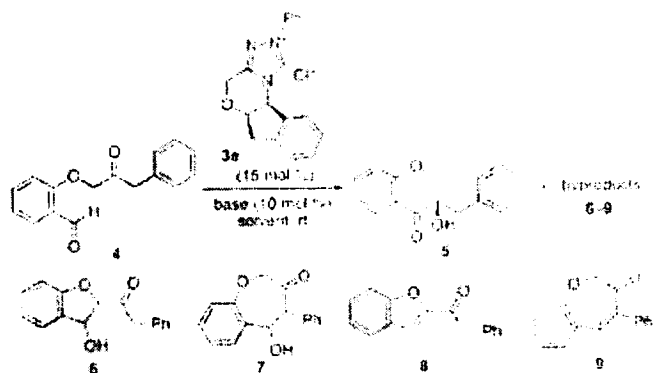
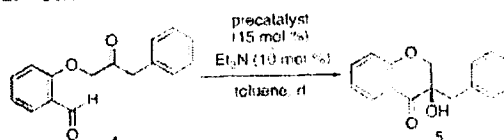
their proposed transition state



Recently Suzuki et. al. developed intramolecular cross benzoin condensation.

Takikawa, H.; Suzuki, K. *Org. Lett.* early view

Table 2. Reactions with Modified Triazolium Salts



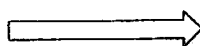
entry	base	solvent	time/h	α-ketol 5		byproducts 6-9
				yield/%	ee/%	yield/%
1	DBU	THF	3.5	10	93	78
2	Et ₃ N	THF	26	36	88	51
3	Et ₃ N	toluene	24	39	92	57
4	KHMDS	toluene	7	31	94	55

entry	precatalyst	time/h	α-ketol 5		byproducts 6-9
			yield/%	ee/%	yield/%
1	3b	2	93	68	0
2	3c	2	94	81	0
3	3d	5	67	88	32
4	3e	8	85	92	12
5	3f	5	87	94	11

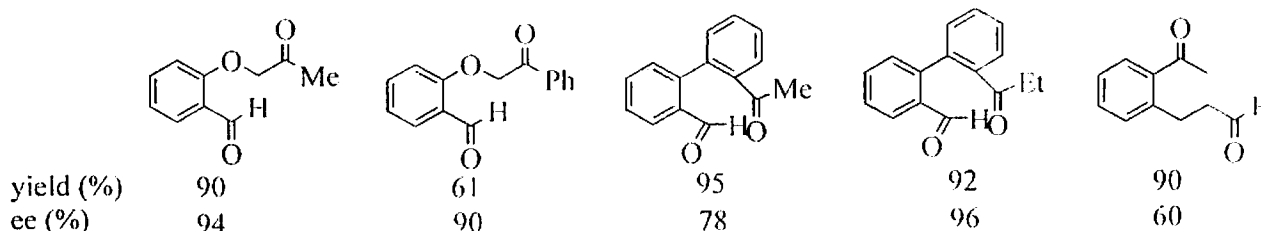
^a All reactions were performed on 1.0 mmol of 4 with a combination of precatalyst 3a (15 mol %) and base (10 mol %) at room temperature. Enantiomeric excess was assessed by HPLC analysis on CHIRALPAK AD-H. ^b Containing a small amount of unidentified byproducts. ^c Reaction was performed with prior generated carbene [by mixing 3a (15 mol %) with KHMDS (10 mol %) for 10 min; toluene, rt].

^a All reactions were performed with 1.0 mmol of 4 with a combination of precatalyst 3b-f (15 mol %) and Et₃N (10 mol %) at 0.5 M in toluene at room temperature. Enantiomeric excess was assessed by HPLC analysis on CHIRALPAK AD-H.

Competing intramolecular aldol reactions were problematic. Weaker base could suppress this side reaction a little, but still needed improvement.



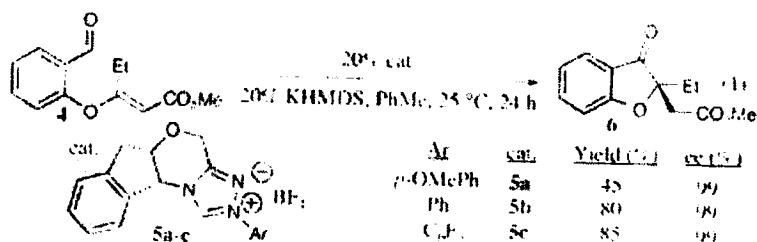
By changing the N-phenyl group to **electron-withdrawing group**, desired reaction proceeded dominantly.



Triazolium salts are applicable to asymmetric Stetter reaction which is 1,4-addition variant of the benzoin condensation.

Rovis et. al. studied this chemistry intensively, and excellent results have been reported.

Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876.



Similar to Suzuki's case, amino indanol derived catalysts showed its effectiveness and the character of N-aryl substituents change the reactivity without any loss of selectivity.

Table 1. Aromatic Substrates

Table 2. Aliphatic Substrates

Entry	Substrate	Product ^a	Yield (%)	ee (%) ^b	Entry	Substrate	Product ^c	Yield (%)	ee (%) ^d
1	X = H, 4	X = H, 6	96	97	1	Ar = 4-Ph, 17	Ar = 4-Ph, 18	97	96
2	X = Br, 7	X = Br, 8	92	89	2	Ar = p-NO ₂ -Ph, 19	Ar = p-NO ₂ -Ph, 20	99	95
3	9	10	95	92	3	R = Me, 21	R = Me, 22	91	95
4	11	12	95	99	4	R = CH ₂ -Ph, 23	R = CH ₂ -Ph, 24	60	99
5 ^e	13	14	55	99	5	R = Bu, 25	R = Bu, 26	71	98

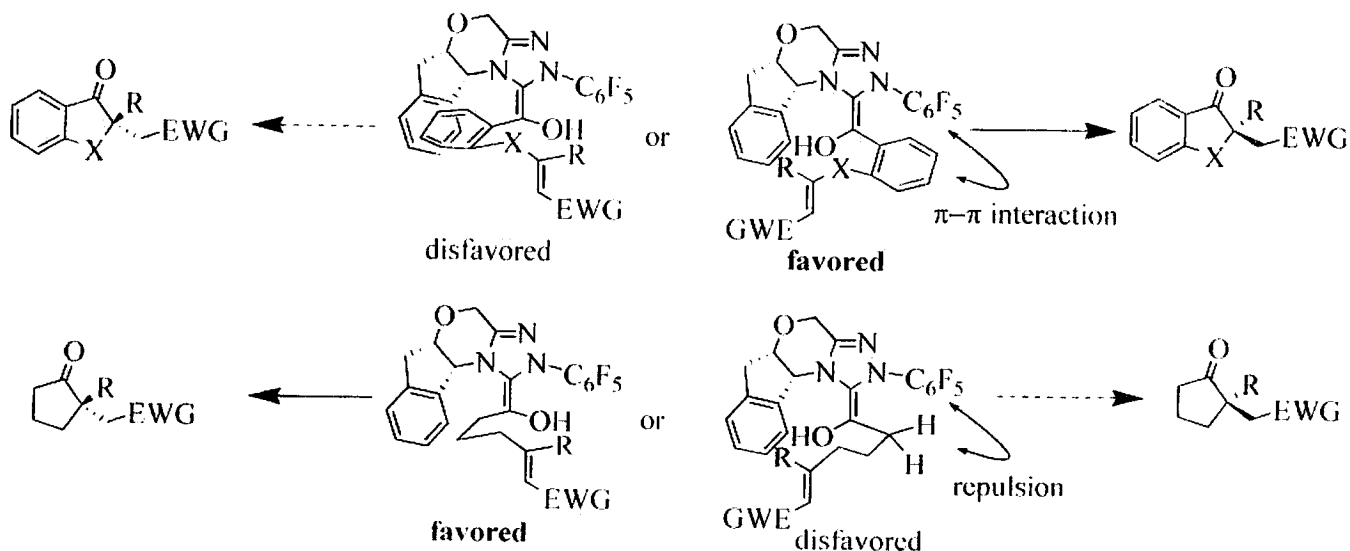
opposite stereochemistry

^a Absolute configuration assigned by analogy to 10. ^b Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. ^c Absolute configuration established by single-crystal X-ray analysis. ^d Catalyst added in two portions.

^a Absolute configuration assigned by analogy to 22. ^b Enantiomeric excess determined by GC or HPLC analysis on a chiral stationary phase (see Supporting Information for details). ^c Absolute configuration established by comparison of optical rotation to known compound (see Supporting Information for details).

Appropriate bases are required to give satisfactory yields and ee.

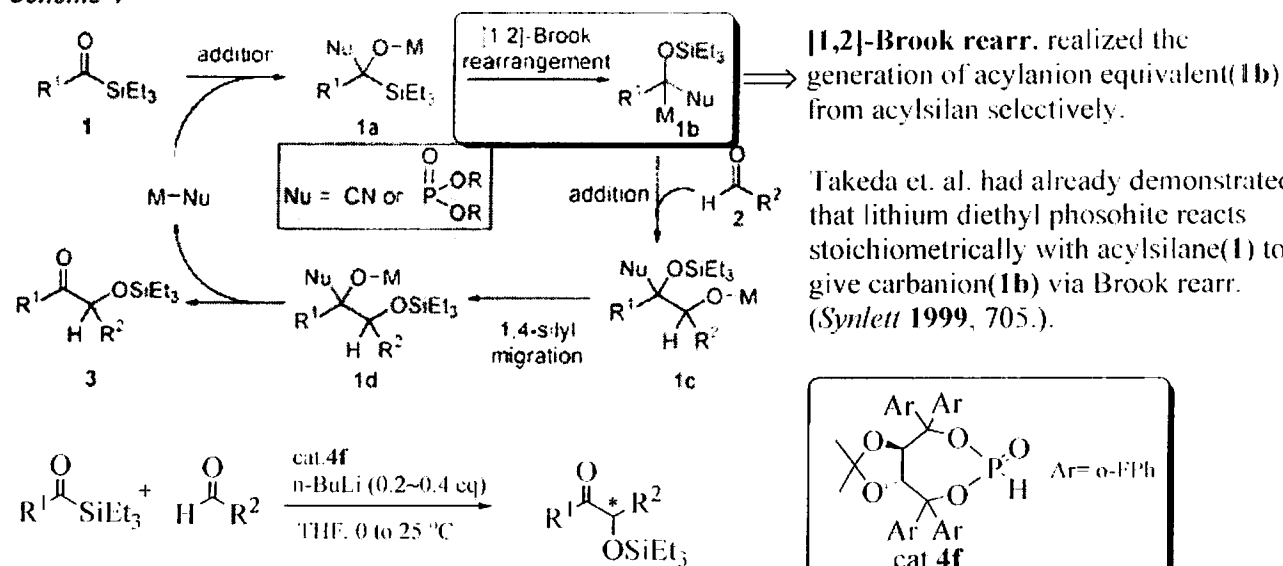
The reversal in stereoinduction between the aromatic and the aliphatic is unclear. A possible explanation is shown below.



Intermolecular cross benzoin condensation and Stetter reaction have been very difficult, but recently Johnson et. al. succeeded to provide intermolecular cross benzoin condensation products. Their strategy is the use of acylsilane as an acylanion equivalent.

X. Linghu; J. R. Potnick; J. S. Johnson *J. Am. Chem. Soc.* **2004**, *126*, 3070.

Scheme 1



entry	product ^b	cat. 4f (mol %)	% ee ^c	% yield ^d
1		7.5	82	84
2		7.5	82	75
3		7.5	87	82
4		5	91	87
5		7.5	88	83
6		7.5	90	83
7		10	83 ^e	79
8		5	81 ^e	80

9		12.5	86	86
10		7.5	85	68
11		15	73	78
12		20	41	88
13		20	67	72

^a R¹CO₂SiEt₃ (1.0 equiv), R²CHO (1.5 equiv), phosphite **4f** and *n*-BuLi (0.2–0.4 equiv) in THF from 0 to 25 °C. Reaction time 2–5 h. See Supporting Information for details. ^b The *S*-configurations of silyl benzoin **3a**, **3c**, **3d**, **3e**, and **3k** were assigned by chemical correlation to compounds of known absolute configuration. Other acyl-, aryl-, silyl benzoin products were assigned by analogy. ^c Product ratios determined by CSP-SFC using a Chiralpak-OD or Chiralcel OD column unless otherwise noted. ^d Isolate yield of analytically pure silyloxy ketones or hydroxy ketones. ^e Selectivity determined by CSP-SFC using a Chiralpak AS column after hydrolysis of the product TES ether.

Based on their concept, intermolecular cross benzoin reaction proceeded well.

While BINOL derived catalyst showed no catalytic activity, TADDOL derived phosphite (**4f**) worked and gave satisfactory results especially for aromatic substrates.

Synthetically useful level direct catalytic intermolecular benzoin condensation and Stetter reaction have not been developed.

To afford this challenging reaction, we should overcome some serious problems, such as

>>>selective generation of acylanion equivalent from the aldehyde

>>>suppress the self coupling

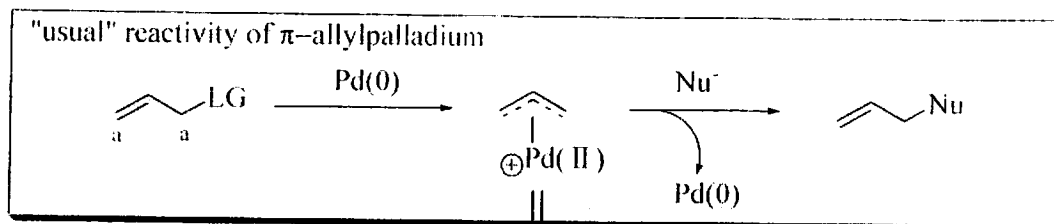
>>>for asymmetric reaction, epimerization at α -position should be suppressed

2. Allylation by Umpolung of π -Allylpalladium

π -allylpalladium chemistry has shown great utility, and became reliable synthetic tool.

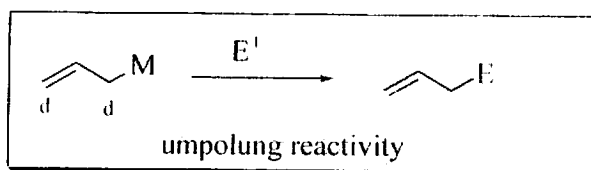
>>>easy preparation of π -allylpalladium

>>>relatively mild condition

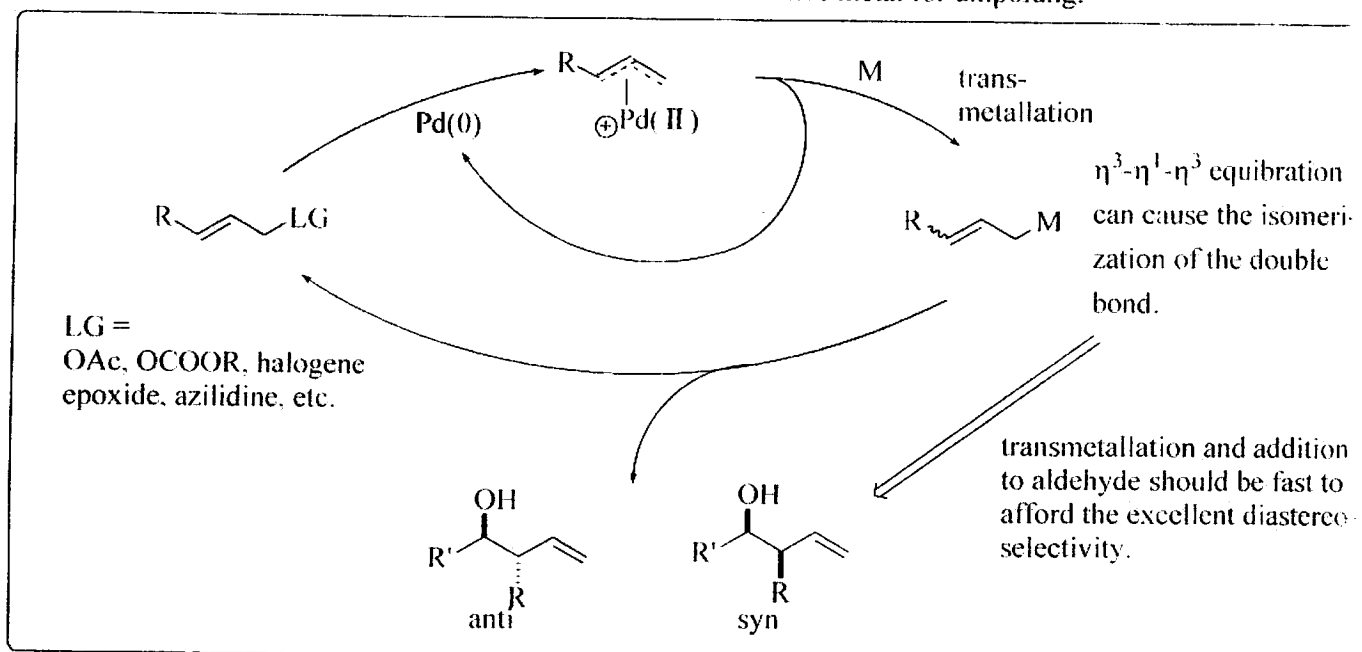


umpolung

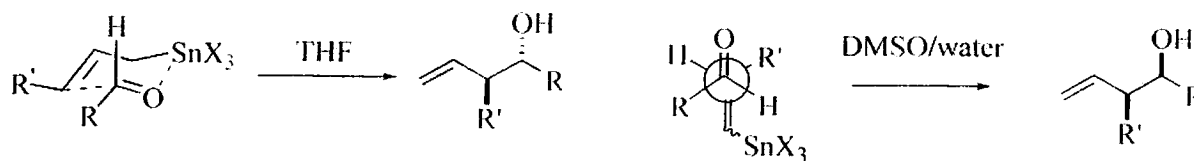
If π -allylpalladium could be used as nucleophile based on the concept of umpolung, nucleophilic allylic reagents are easily prepared under mild conditions.



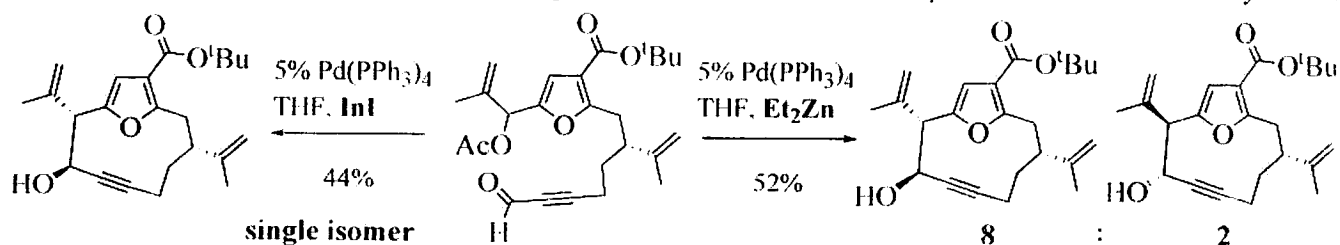
The strategy of transmetalation between palladium and more electropositive metal than palladium has been studied and revealed that Sn, In and Zn are effective metal for umpolung.



As shown above, the active species are allyl-tin, -indium or zinc, so the transition states are depending on the conditions and the metals.

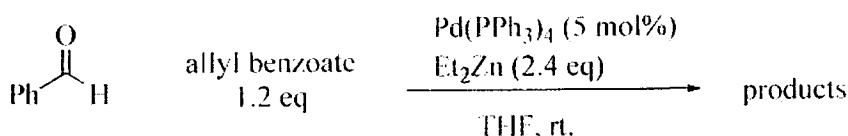


Strong coordination of DMSO to Sn prevent the formation of cyclic TS

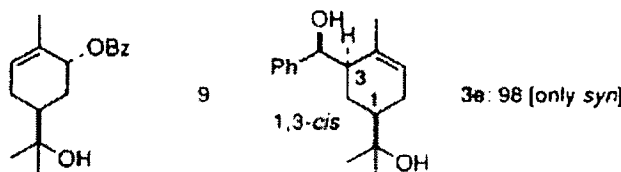
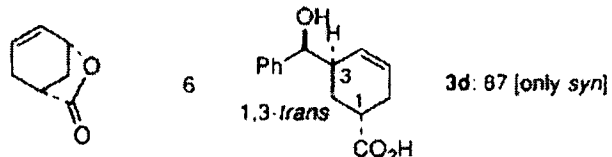
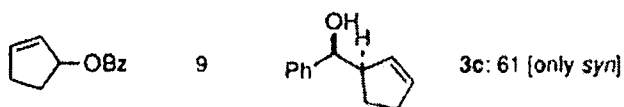


Among three metals Sn, In, Zn, only Zn-mediated reaction has been studied toward asymmetric variant. The reason is preliminary observation and the proposed mechanism by Tamaru et. al..

Y. Tamaru *J. Organomet. Chem.* **1999**, 576, 215.

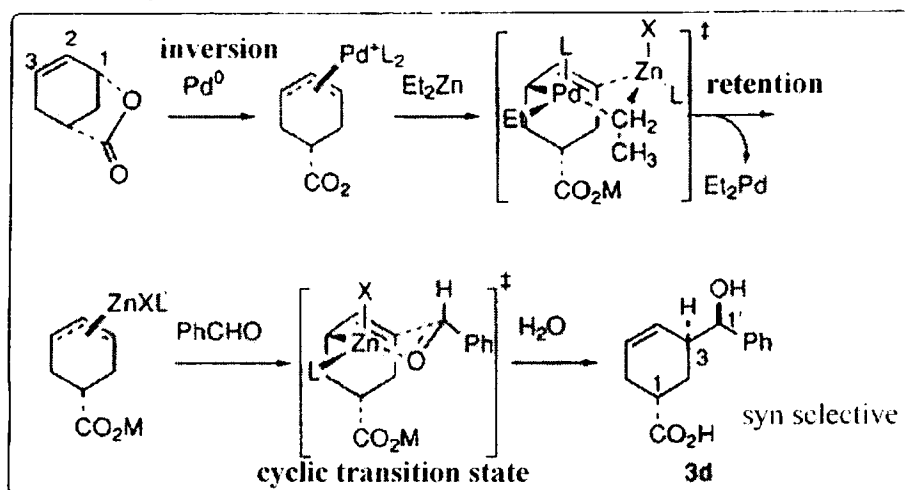


allyl benzoate	time (h)	product (% yield) [syn:anti]
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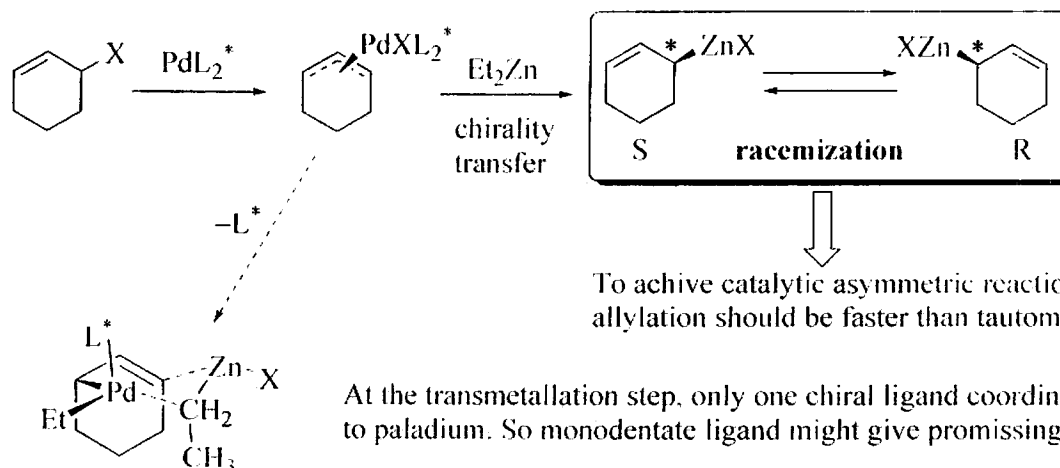


If the allyl benzoates are cyclic, the configuration is fixed to cis and resulting products are only syn isomer.

These results showed that allylation occurred from the other side of the leaving group. They explained it as follows: first step is oxidative addition to Pd(0) with **inversion**, then allyl moiety transfer from Pd(II) to Zn(II) with **retention** of configuration through six-membered transition state.



According to this mechanism, chiral ligands on palladium have potential of asymmetric induction.

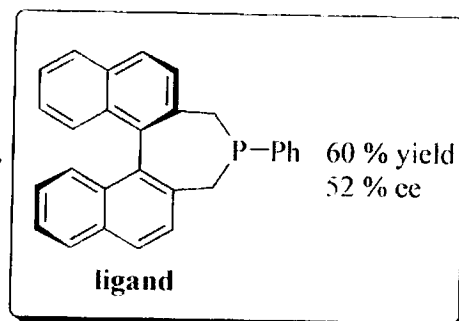
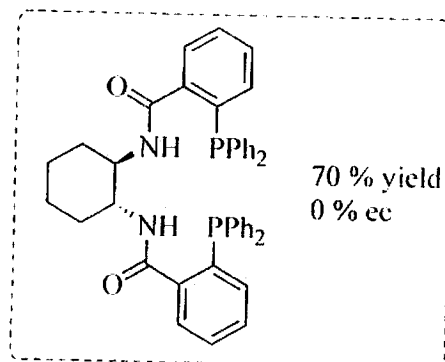
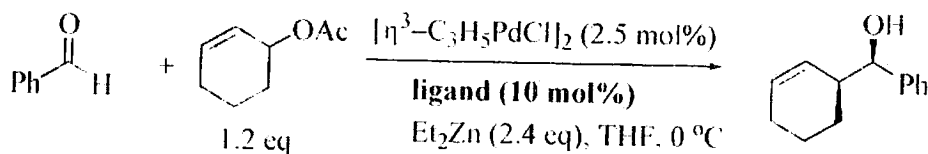


To achieve catalytic asymmetric reaction, allylation should be faster than tautomerization.

At the transmetalation step, only one chiral ligand coordinate to palladium. So monodentate ligand might give promising results.

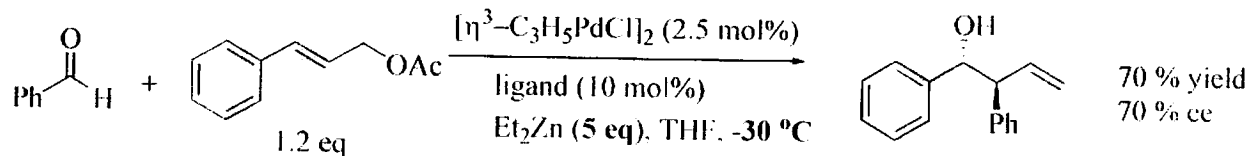
First example of catalytic asymmetric version was reported by Zanoni et. al.

G. Zanoni; S. Gladiali; A. Marchetti; P. Piccinini; I. Tredici; G. Vidari *Angew. Chem., Int. Ed.* **2004**, *43*, 846

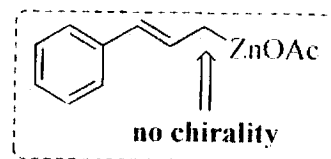


As expected, monodentate type ligand succeeded the asymmetric induction in catalytic manner.

Cinnamyl acetate also produced the chiral compound using this system.

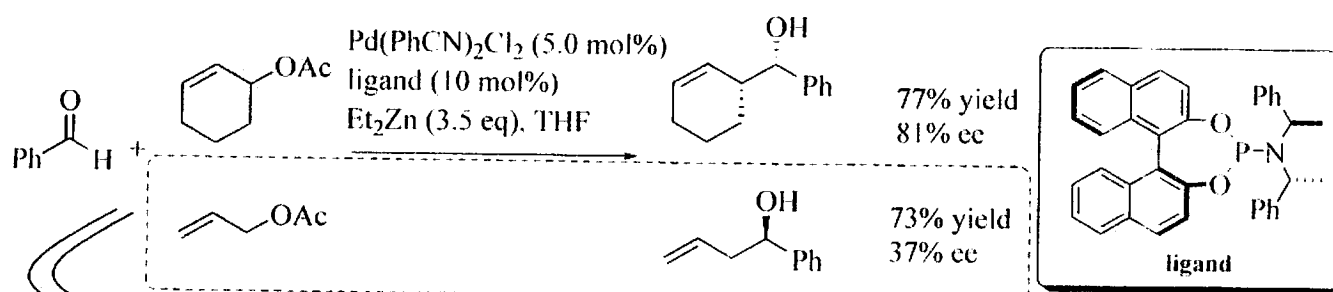


But considering the active allylating species mentioned above, this result was surprising!!
Generating allyl-zinc reagent has no chirality in this case.

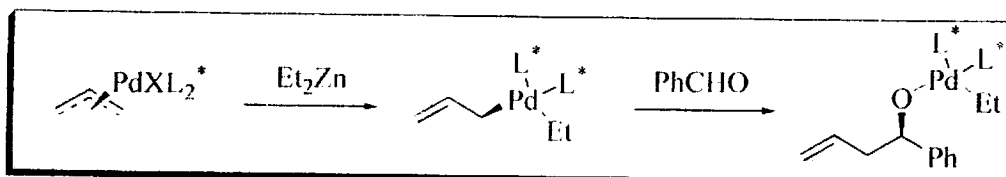


Recently Feringa et. al. suggested alternative mechanism based on their results.

G. P. Howell; A. J. Minnaard; B. L. Feringa *Org. Biomol. Chem.* **2006**, *4*, 1278.



This result also cannot be explained by the mechanism proposed by Tamaru.

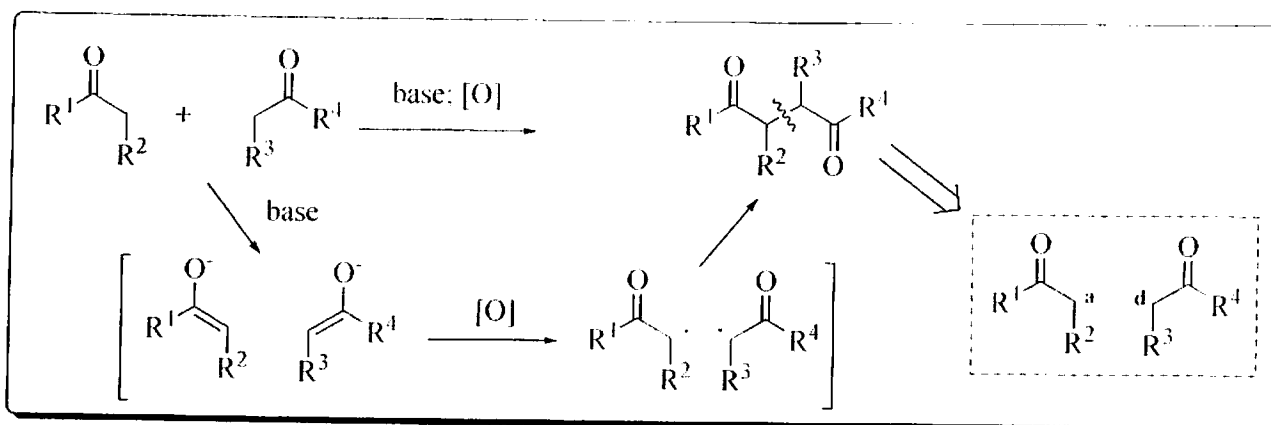


main points of Feringa's proposed mechanism

- >>> Chiral ligands should exist on the palladium.
(known stability of palladium/ phosphoramidite system)
- >>> η^1 -allylpalladium is the active species to allylate the aldehyde.
- >>> Et_2Zn promotes the formation of η^1 -allylpalladium by alkylating Pd.

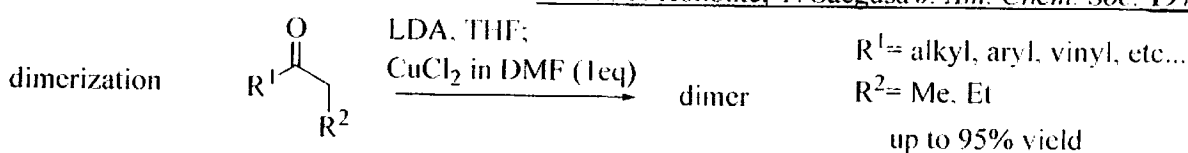
3. Oxidative Coupling of Enolates

1,4-dicarbonyl compounds which cannot be obtained through 'usual' reactivity are provided by this transformation.

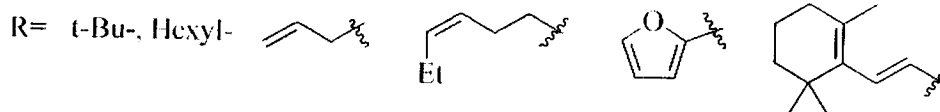
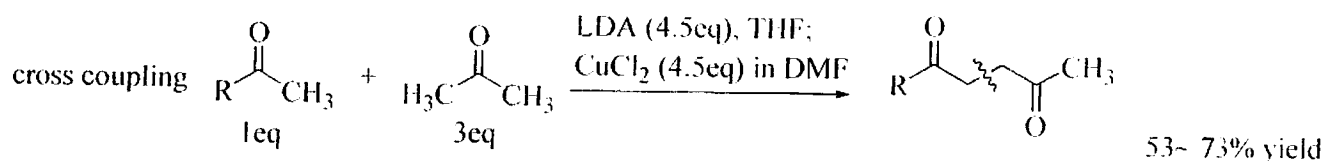


Oxidative coupling of ketone-enolates was studied intensively by Saegusa et. al. in the 1970s.

Y. Ito; T. Konoike; T. Saegusa *J. Am. Chem. Soc.* **1975**, *97*, 291



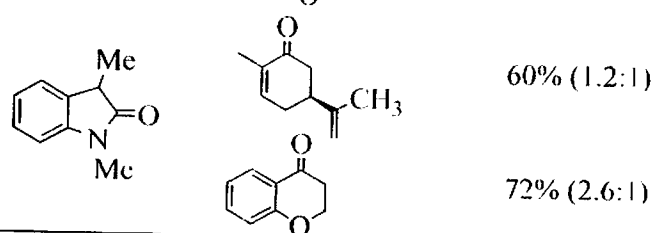
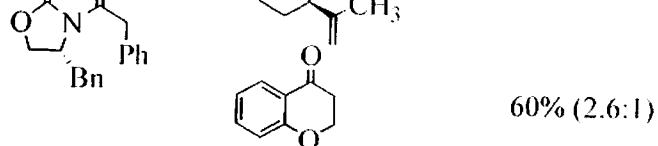
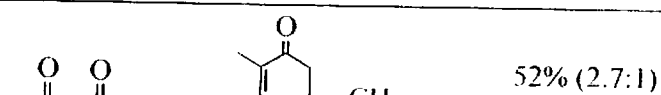
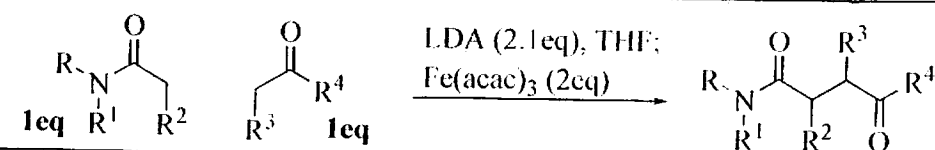
DMF was essential for this reaction. (solvation of ketone enolates, solubility of CuCl₂)
1eq of CuCl₂ gave the best result among other metals such as Ag, Fe, Zn etc...



Large excess of acetone over the other ketone was required.
Only methyl ketones were applicable.
Yields were not satisfactory.

Recent progress by Baran et. al.

P. S. Baran; M. P. DeMartino *Angew. Chem. Int. Ed.* **2006**, *45*, 7083



In contrast to Saegusa's case, excess amount of coupling partners was not required.

Homocoupling products were minor, remaining materials were largely starting materials.

Yields were still unsatisfactory and diastereoselectivity was also low.

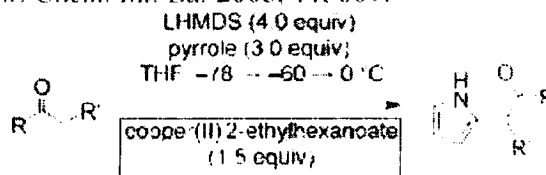
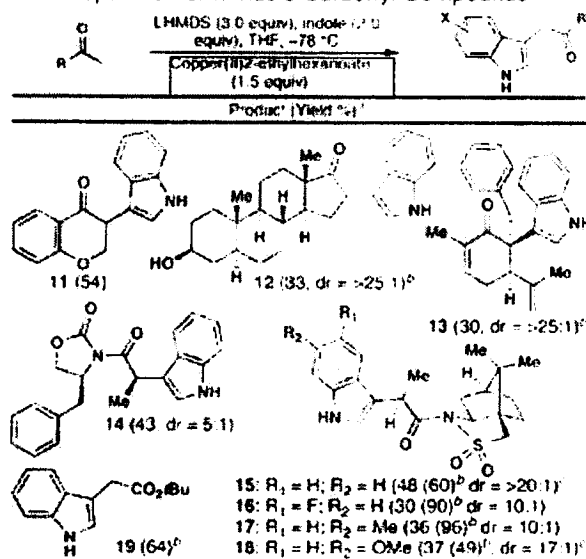
It seems narrow generality...

Baran et. al. has studied other coupling partners (indole and pyrrole).

P. S. Baran; J. M. Richter *J. Am. Chem. Soc.* **2004**, *126*, 7450.

P. S. Baran; J. M. Richter; D. W. Lin *Angew. Chem. Int. Ed.* **2005**, *44*, 609.

Table 2. Preparation of α -Indole Carbonyl Compounds



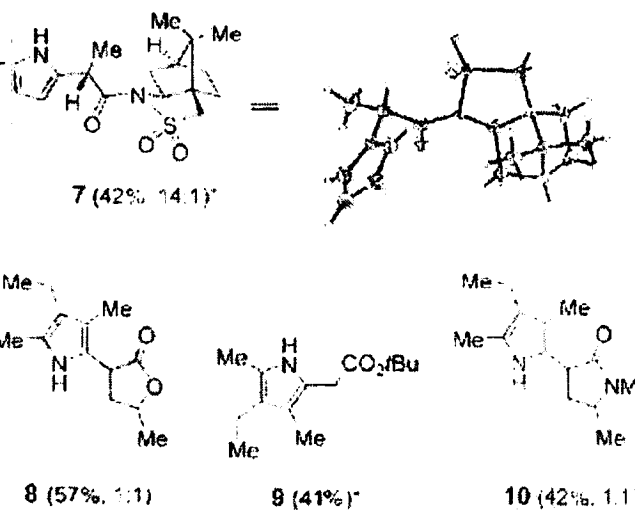
^a Isolated yield after chromatography ^b Yield based on recovered starting material (LDA used)

Although the yields were low, this system can be applied for construction of quaternary carbon centers.

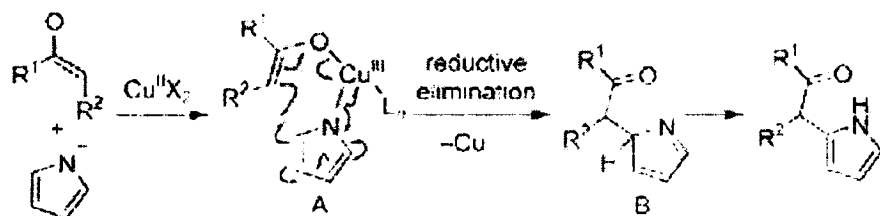
Reaction proceeded under substoichiometric quantities of oxidant.



This finding was surprising considering the mechanism mentioned above.



proposed mechanism



support for this mechanism

- >>>no observation of dimers of pyrroles and indoles
- >>>1eq of oxidant is necessary
- >>>N-protected substrates do not react