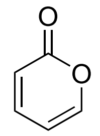
Problem Session (13) - Answer

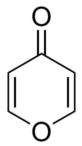
2024/10/26 Koichi Hagiwara

Topic: Synthesis of 2-pyrone

- For recent reviews, see: *Mar. Drugs* **2015**, *13*, 1581.
  Top. Curr. Chem. **2021**, *379*, 38.
  Eur. J. Org. Chem. **2021**, 6180.
  RSC Adv. **2024**, *14*, 28585.



2-pyrone
-9.1 kcal/mol

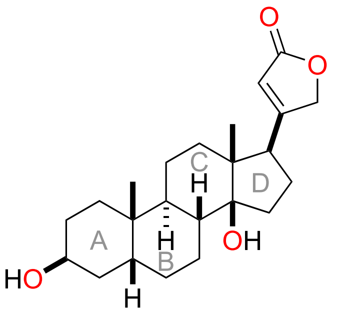


4-pyrone
0 kcal/mol

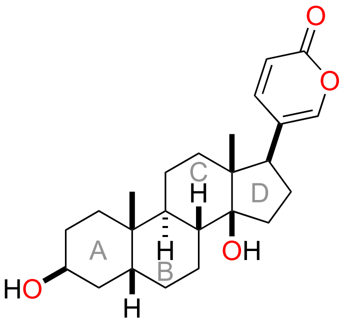
2-Pyrones show reactivity as conjugated dienes, lactones, and arenes (30-35% resonance energy of benzene)

G4 calculation
Phys. Chem. Chem. Phys. **2021**, *23*, 2046.

- Natural products and bioactivity

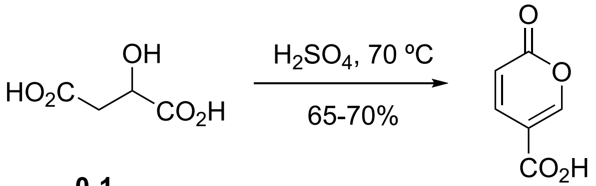


digitoxigenin
anti-cancer, IC_{50}: 2.5 µM



bufalin
anti-cancer, IC_{50}: 0.7 µM

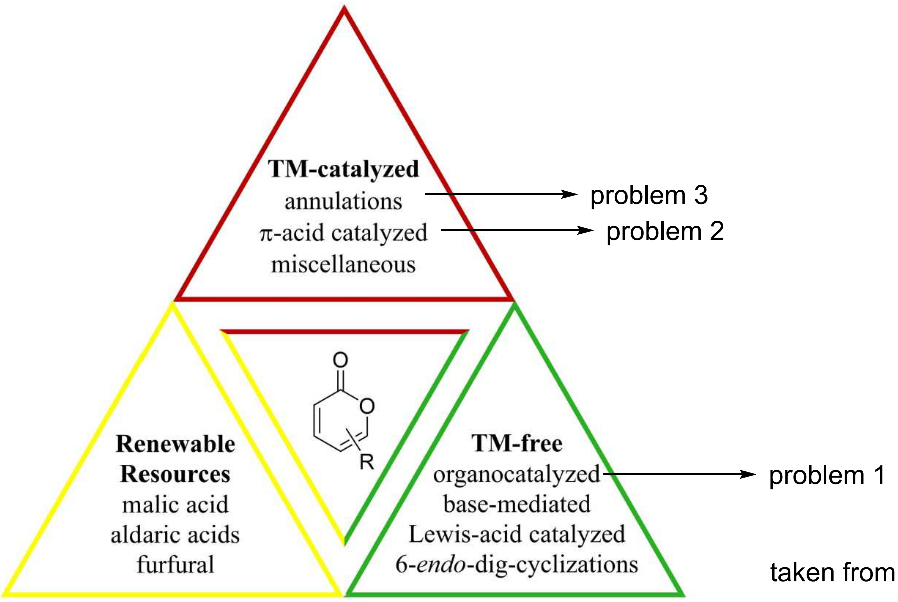
- One of the first syntheses of 2-pyrone
  Acidic conditions utilizing thermodynamic stability of 2-pyrone



0-1

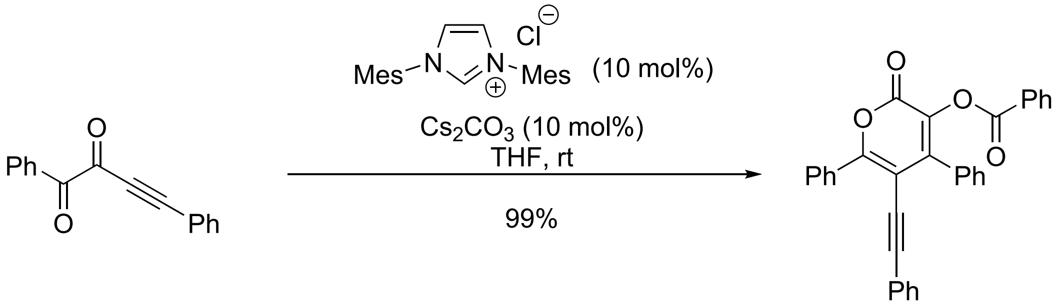
0-2

Liebigs Ann. **1891**, *264*, 261.
Org. Synth. **1951**, *31*, 23.



taken from *Eur. J. Org. Chem.* **2021**, 6180.

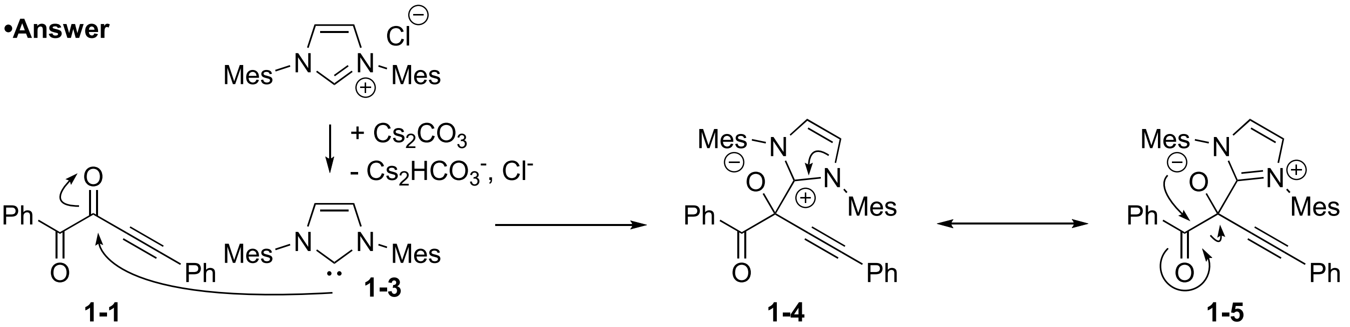
(1) Please explain the reasonable reaction mechanisms.



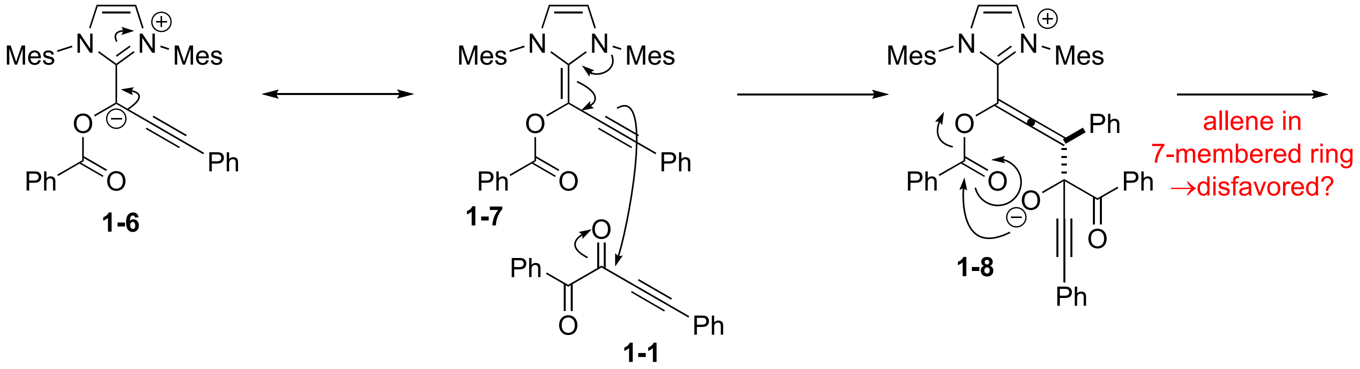
1-1 **1-2**

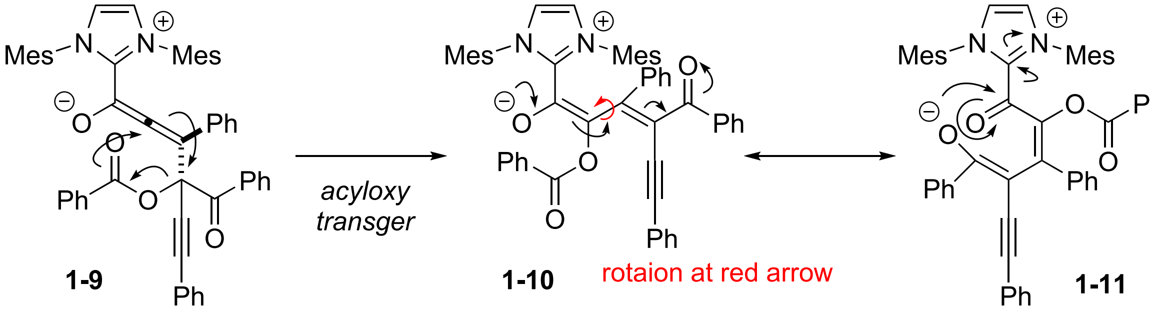
Kong, X.; Zhang, G.; Yang, S.; Liu, X.; Fang, X. *Adv. Synth. Catal.* **2017**, *359*, 2729.

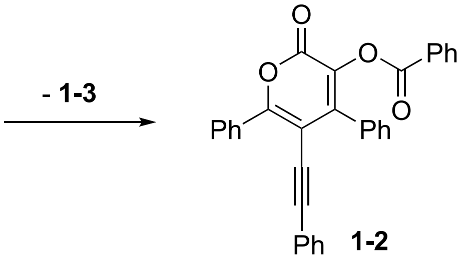
•**Answer**



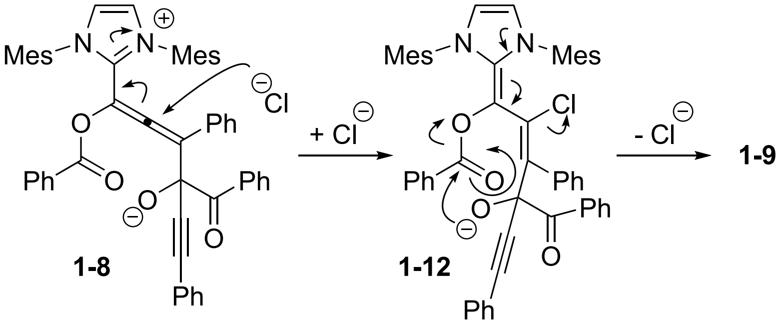
The 1,2-diketone would have higher electrophilicity due to the adjacent carbonyl group.
A bulky nucleophile would attack to alkynyl carbony group rather than phenyl carbonyl group.



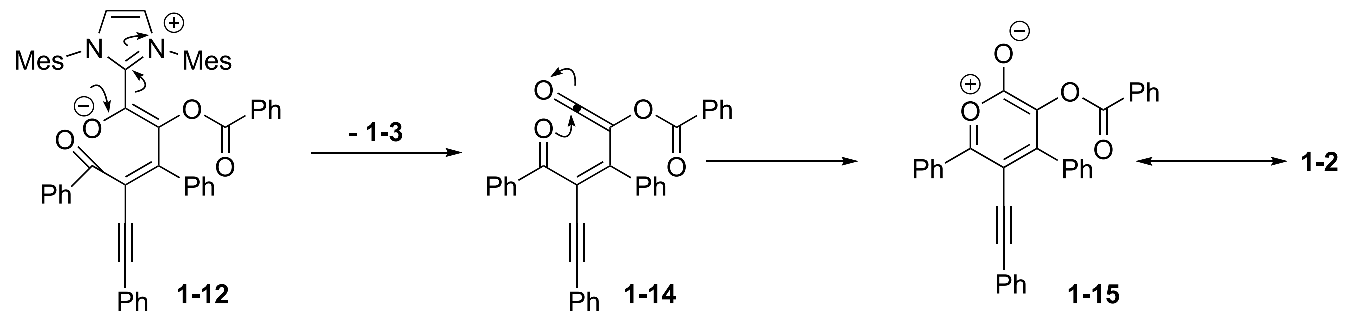




alternative path from **1-8** to **1-9**

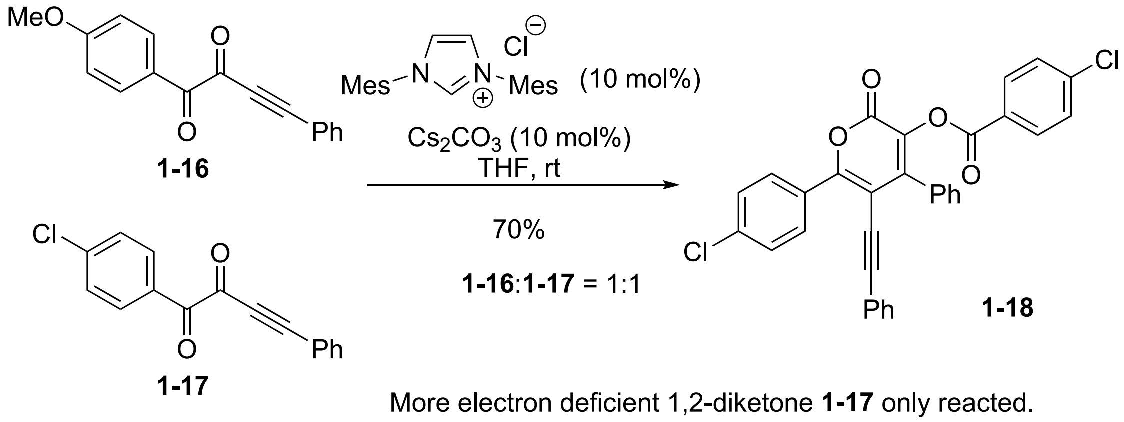


My proposed alternative path from **1-12**



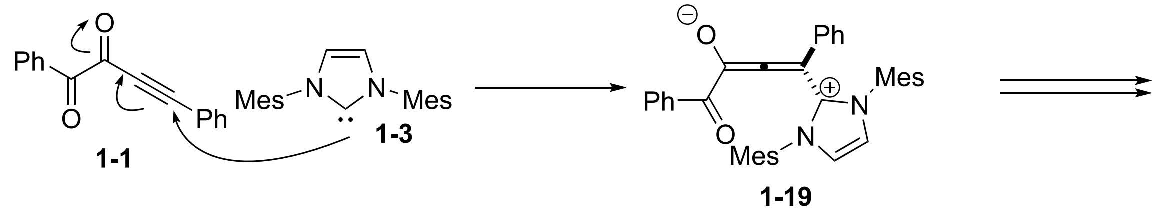
Discussion:

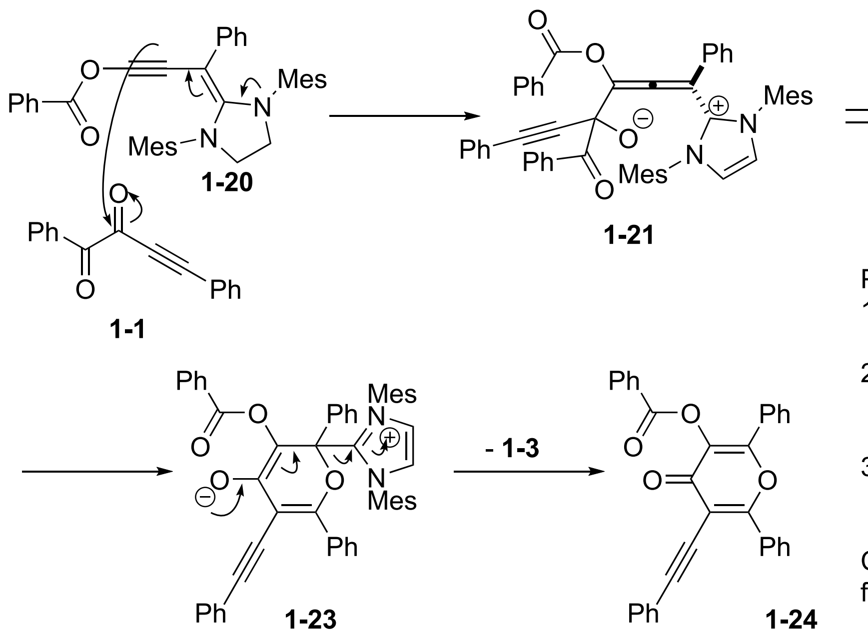
1. experimental result

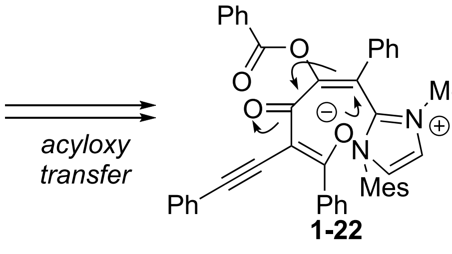


More electron deficient 1,2-diketone **1-17** only reacted.

2. Possibility of other reaction paths (My proposal)
The authors did not mention to side products. But there is possibility of 1,4-addition of NHC to alkynone.
In that case, 4-pyrone should be obtained.





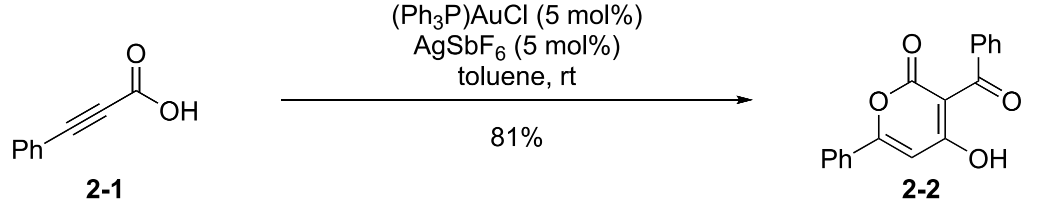


not detected

Possible eplanations
1. 1,4-addition of **1-3** to **1-1** is slow.
   (steric hindrance)
2. Addition of enolate **1-22** is slow.
   (steric hindrance and deactivated by OCOPh group)
3. 4-Pyrone is unstable compared to 2-pyrone.

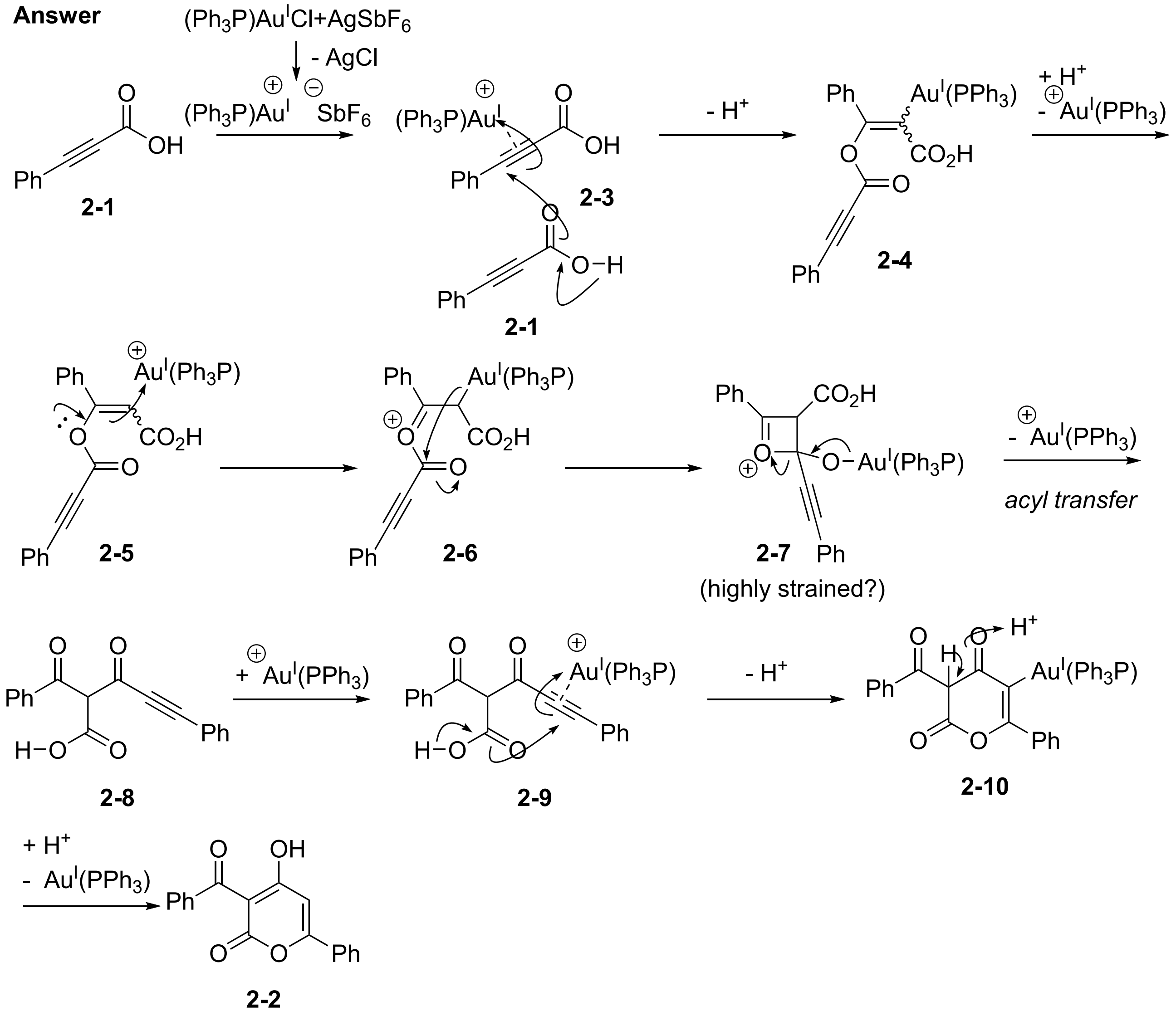
Considering the slow reverse reaction from **1-20** to **1-19**, I suggest explanation 1.

(2) Please explain the reasonable reaction mechanisms.

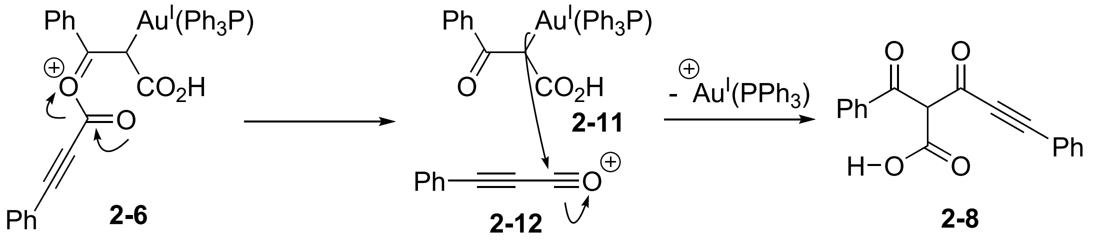


Luo, T.; Dai, M; Zheng, S.-L.; Schreiber, S. L. *Org. Lett.* **2011**, *13*, 2834.

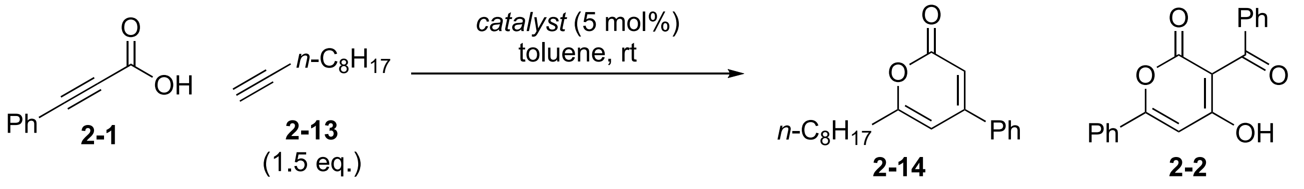
Answer



My proposed alternative path from **2-6** to **2-8**



experimental result



2-1 + **2-13** (1.5 eq.) → **2-14** + **2-2**

catalyst	**2-14**	**2-2**
$(Ph_3P)AuCl/AgSbF_6$	<5%	84%
$(Ph_3P)AuCl/AgOTf$	43%	<5%
	derived from **2-1** and **2-12**	derived from **2-1**

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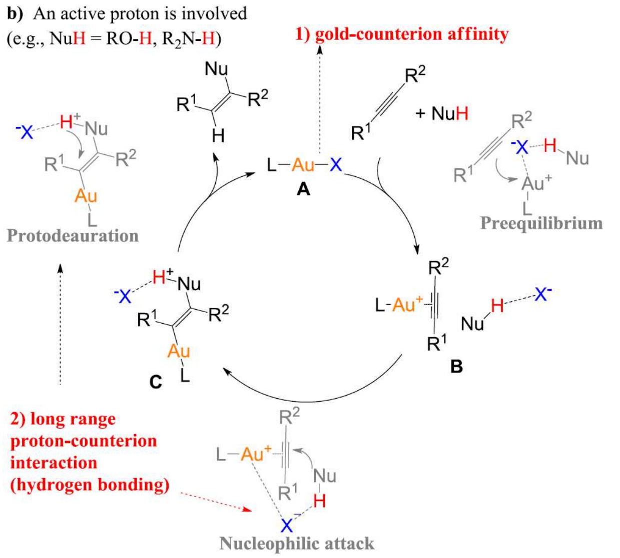
plausible interpretation Lu, Z.; Li, T.; Mudshinge, S. R.; Xu, B.; Hammomd, G. B. *Chem. Rev.* **2021**, *121*, 8452.

The important factor of counter anion for Au-catalyzed reaction;
1. Affinity toward Au
2. Hydrogen bond basicity when nucleophile have an active proton



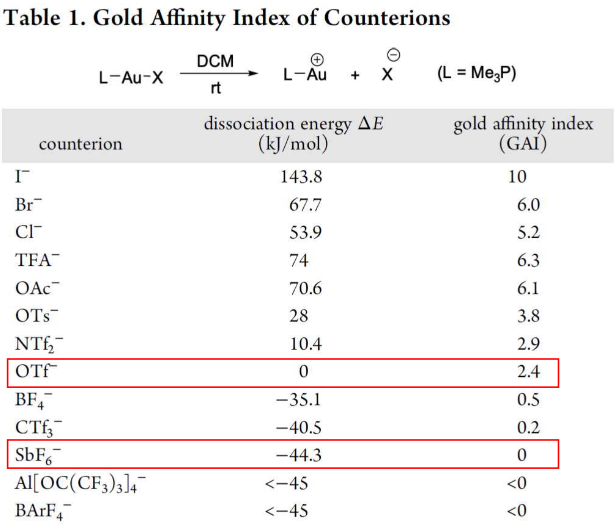


Table 1. Gold Affinity Index of Counterions

$$L{-}Au{-}X \xrightarrow[rt]{DCM} L{-}\overset{\oplus}{Au} + \overset{\ominus}{X} \quad (L = Me_3P)$$

counterion	dissociation energy ΔE (kJ/mol)	gold affinity index (GAI)
I^-	143.8	10
Br^-	67.7	6.0
Cl^-	53.9	5.2
TFA^-	74	6.3
OAc^-	70.6	6.1
OTs^-	28	3.8
NTf_2^-	10.4	2.9
OTf^-	0	2.4
BF_4^-	−35.1	0.5
CTf_3^-	−40.5	0.2
SbF_6^-	−44.3	0
$Al[OC(CF_3)_3]_4^-$	<−45	<0
$BArF_4^-$	<−45	<0

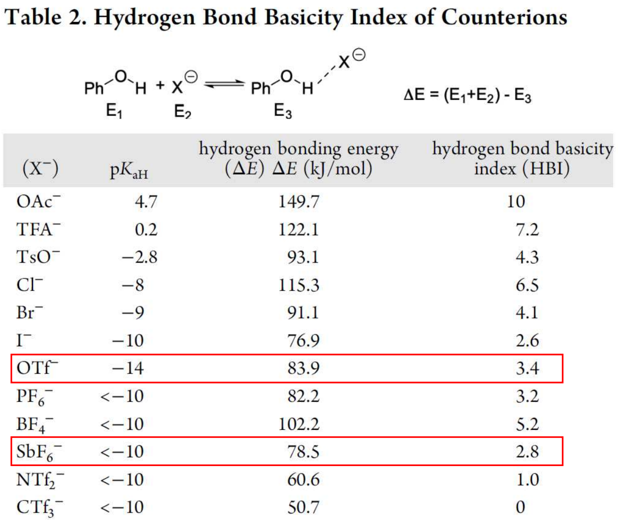


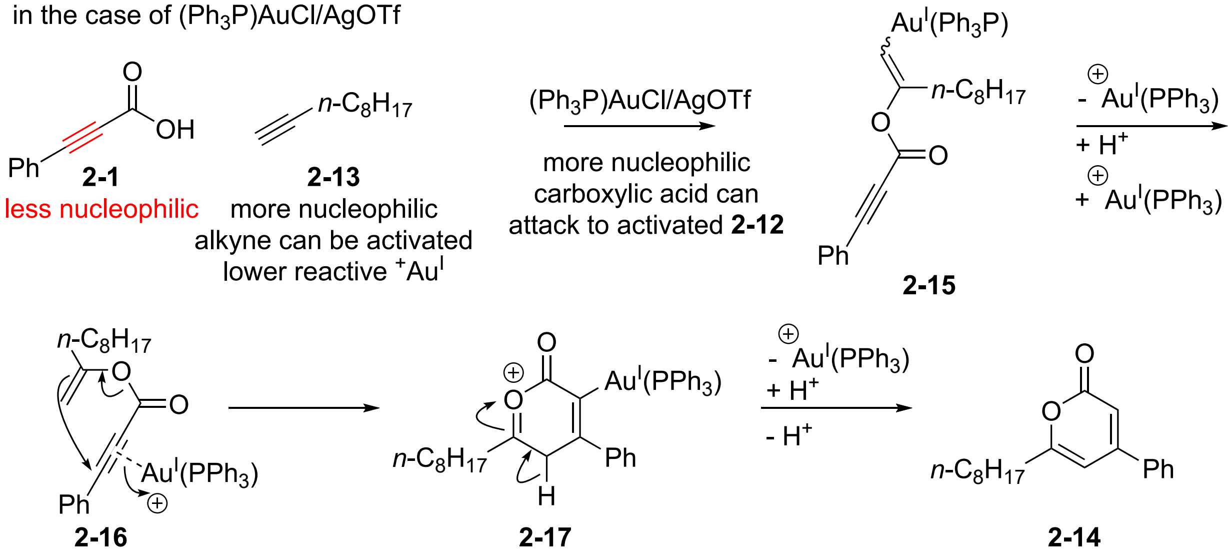
Table 2. Hydrogen Bond Basicity Index of Counterions

$$\underset{E_1}{PhO{-}H} + \underset{E_2}{X^{\ominus}} \rightleftharpoons \underset{E_3}{PhO{-}H\cdots X^{\ominus}} \qquad \Delta E = (E_1+E_2) - E_3$$

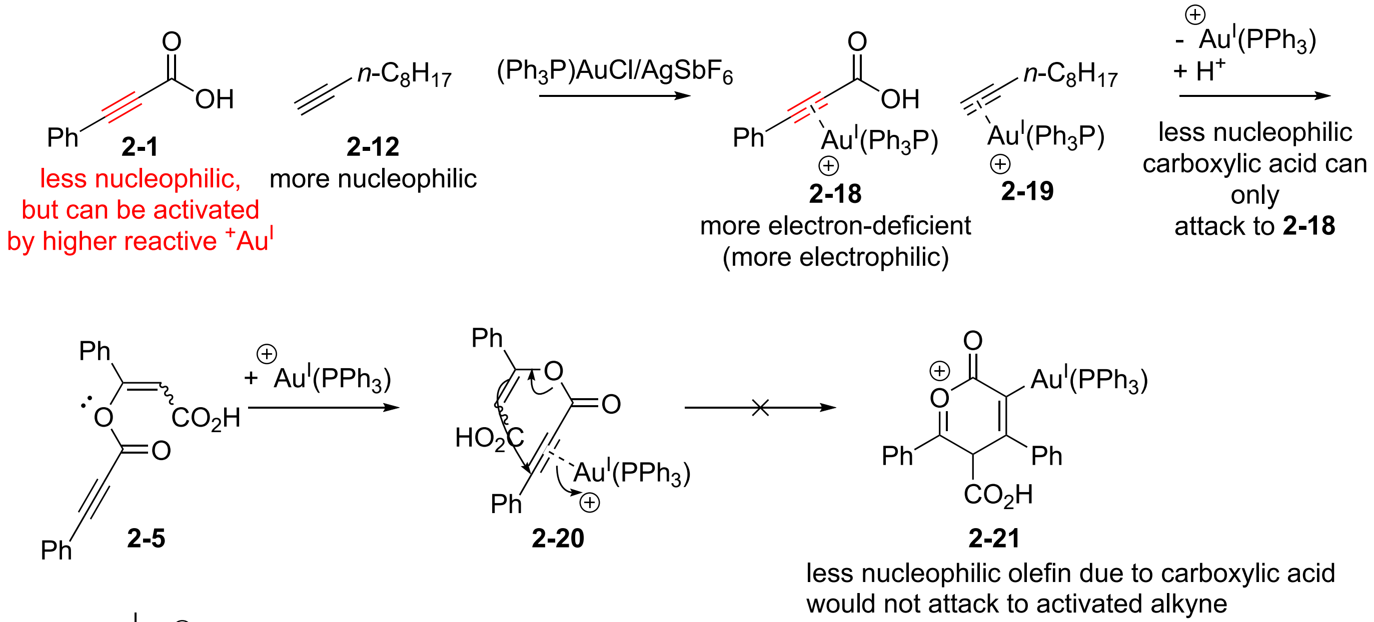
(X^-)	pK_{aH}	hydrogen bonding energy (ΔE) ΔE (kJ/mol)	hydrogen bond basicity index (HBI)
OAc^-	4.7	149.7	10
TFA^-	0.2	122.1	7.2
TsO^-	−2.8	93.1	4.3
Cl^-	−8	115.3	6.5
Br^-	−9	91.1	4.1
I^-	−10	76.9	2.6
OTf^-	−14	83.9	3.4
PF_6^-	<−10	82.2	3.2
BF_4^-	<−10	102.2	5.2
SbF_6^-	<−10	78.5	2.8
NTf_2^-	<−10	60.6	1.0
CTf_3^-	<−10	50.7	0

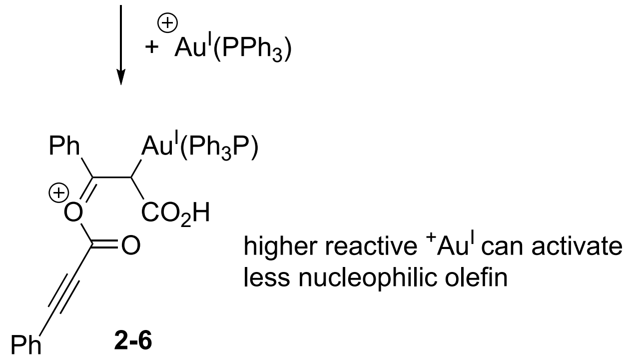
	Au affinity	hydrogen bonding basicity
^-OTf	higher (lower activity)	higher (more nucleophilic)
$^-SbF_6$	lower (higher activity)	lower (less nucleophilic)

My proposal
in the case of $(Ph_3P)AuCl/AgOTf$



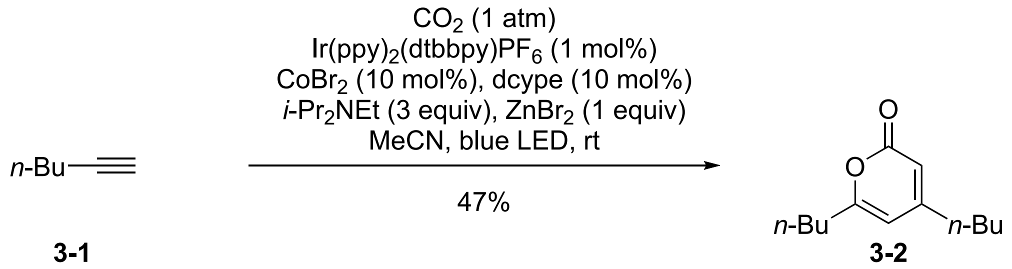
in the case of $(Ph_3P)AuCl/AgSbF_6$





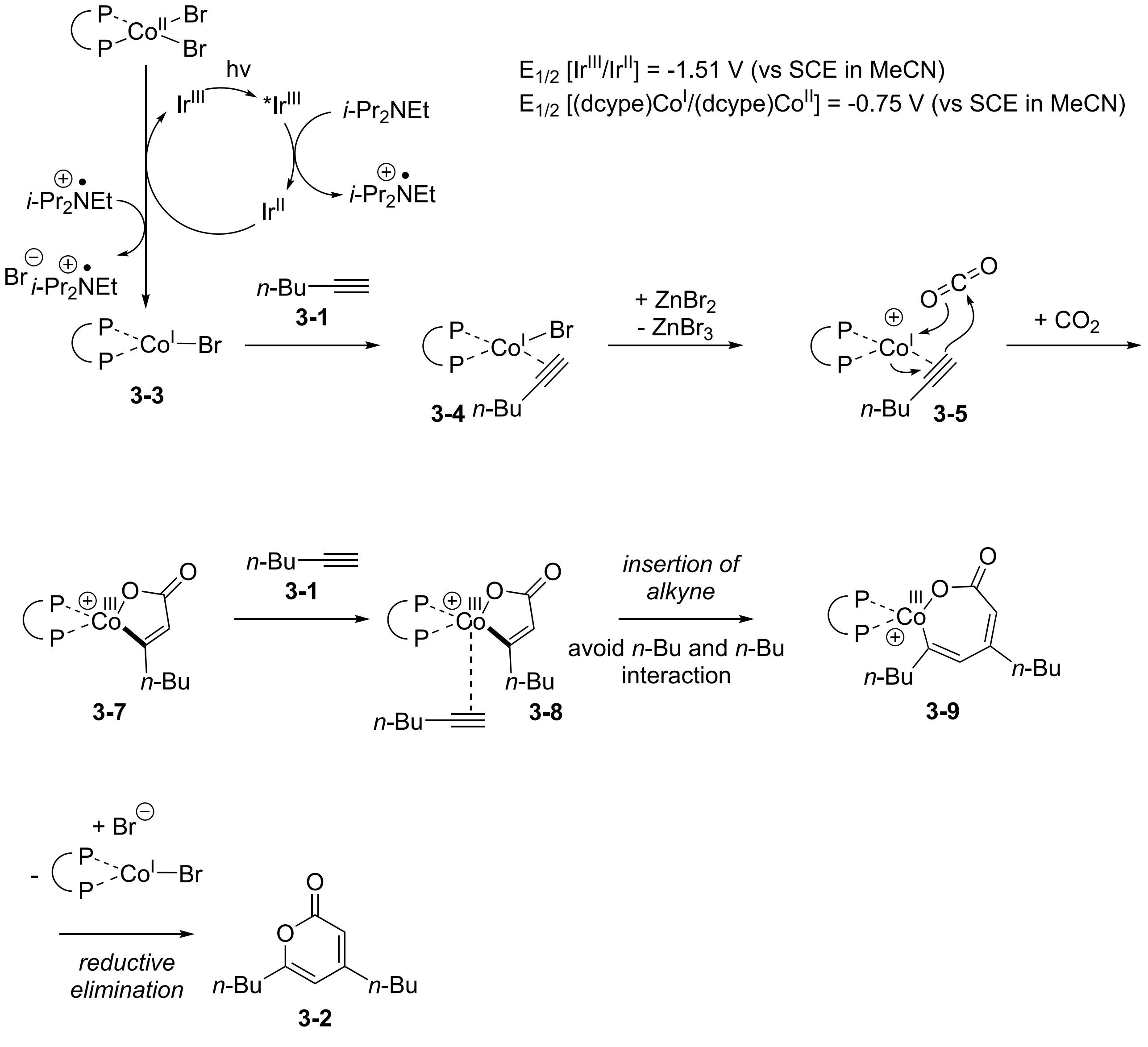
	Au affinity	hydrogen bonding basicity
^-OTf	higher (lower activity)	higher (more nucleophilic)
$^-SbF_6$	lower (higher activity)	lower (less nucleophilic)

(3) Please explain the reasonable reaction mechanisms.



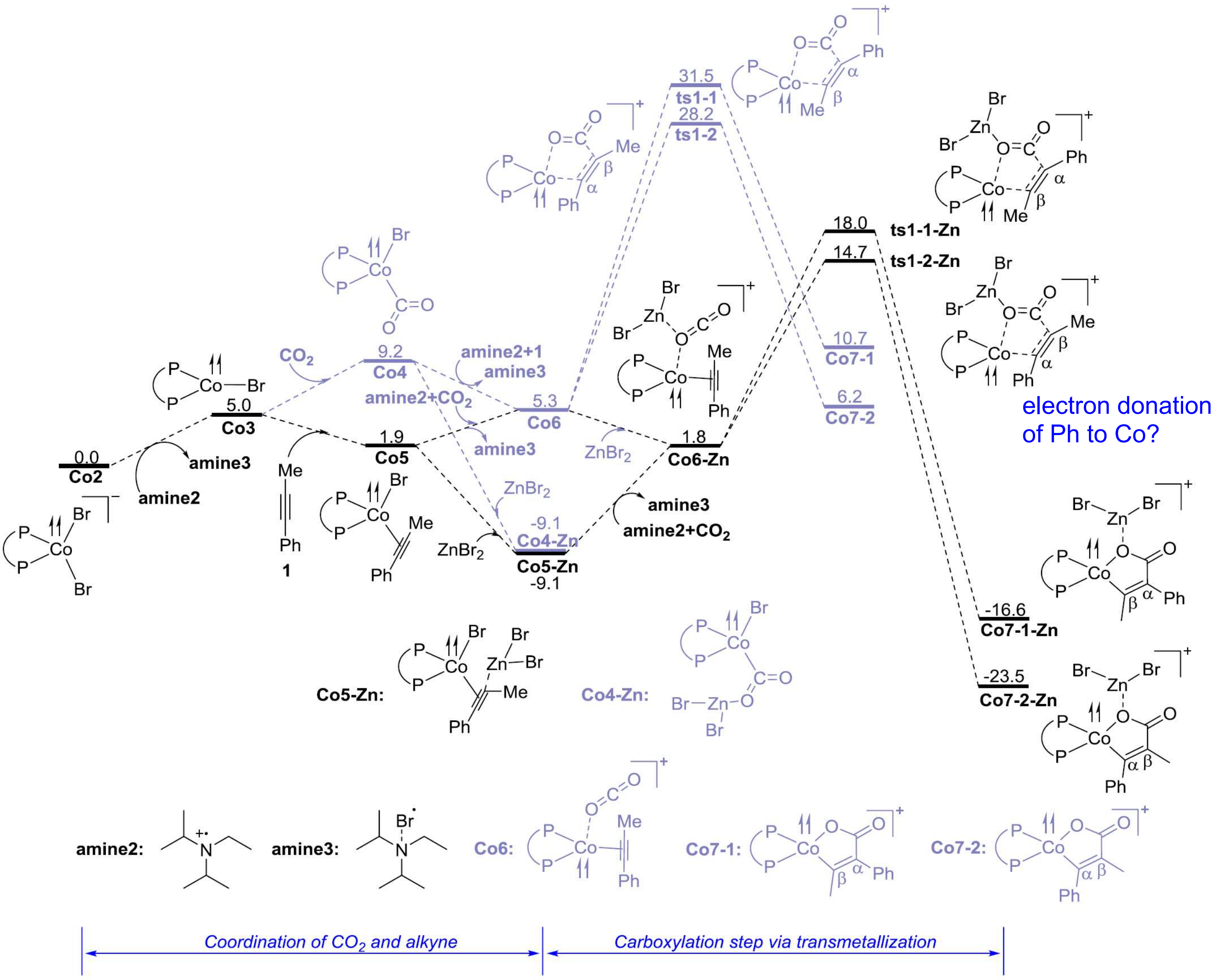
Hou, J.; Ee, A.; Feng, W.; Xu, J.-H.; Zhao, Y.; Wu, J. *J. Am. Chem. Soc.* **2018**, *140*, 5257.

Answer



$E_{1/2}$ [Ir^{III}/Ir^{II}] = -1.51 V (vs SCE in MeCN)
$E_{1/2}$ [$(dcype)Co^{I}/(dcype)Co^{II}$] = -0.75 V (vs SCE in MeCN)

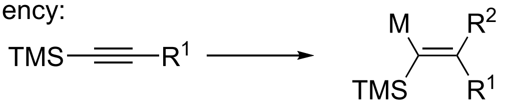
computational study (Xu, Y.; Shao, Y.; Ahlquist, M. S. G.; Yu, H.; Fu, Y. *J. Org. Chem.* **2021**, *86*, 1540.)



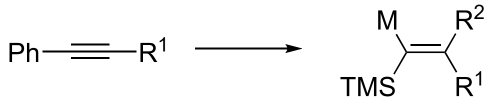
electron donation of Ph to Co?

$ZnBr_2$ was necessary to decrease the activation energy (see ts1-1 and ts1-2 vs. ts1-1-Zn and ts1-2-Zn).
Cationic Co^I species were proposed for the reaction instead of Co^I–Br (see Co6-Zn).

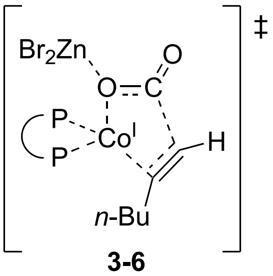
•Regioselectivity of alkyne insertion
Both the steric and electronic effect of alkyne substituents (and ligands) should be important (see *Eur. J. Org. Chem.* **2010**, 391.).
Tendency:



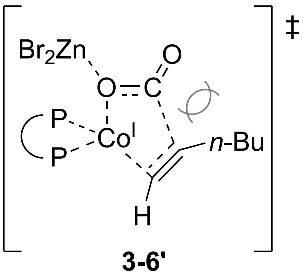
C-C bond formation distal to bulky substituent
(considered as steric effect)



C-C bond formation distal to Ph group
(considered as electronic effect
electron donation to metal?)



3-6



3-6'

disfavored by steric hindrance