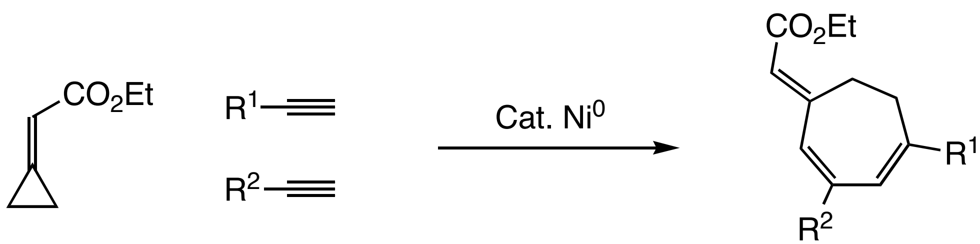
Nickel-Catalyzed Three-Component [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Selective Synthesis of Multisubstituted Cycloheptadienes



Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2446

Michel Grenon

April 1st, 2006

Presentation Outline

➩ Other Transition-Metal Catalyzed Cycloadditions for the Construction of Seven-Membered Rings

- [6+1] Cycloaddition of arenes with α-diazo carbonyl compounds
- [5+2] Cycloaddition of vinylcyclopropanes with alkynes
- [4+3] Cycloaddition of dienes with TMM derivatives

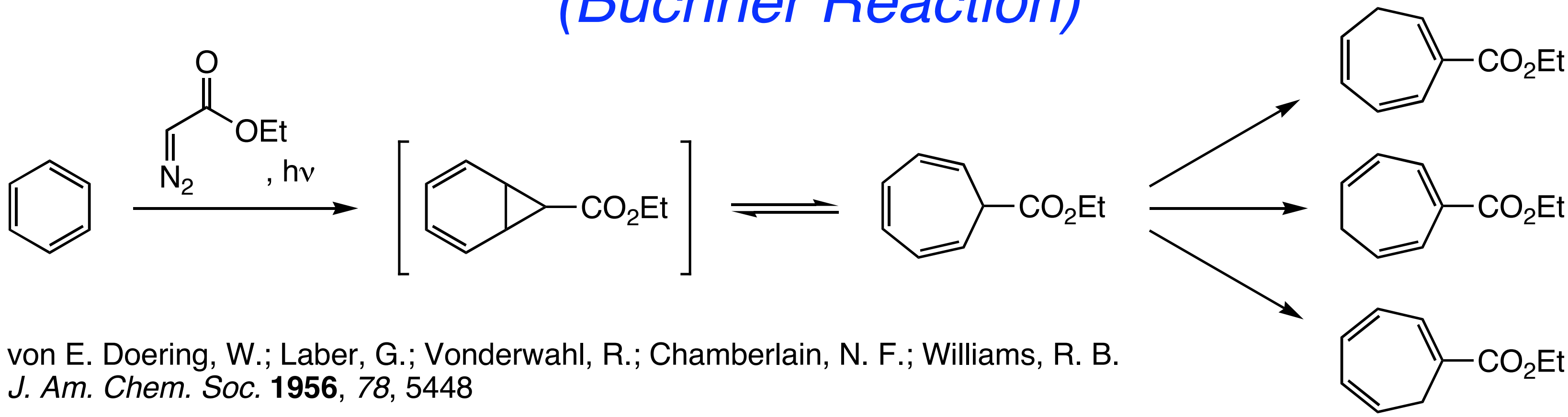
➩ Previous Examples of Transition-Metal Catalyzed(Mediated) [3+3+2] Cycloadditions for the Construction of Seven-Membered Rings

- Iridium-mediated allyl/alkyne [3+2+2] cycloaddition
- Cobalt-mediated allyl/alkyne [3+2+2] cycloaddition
- Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes

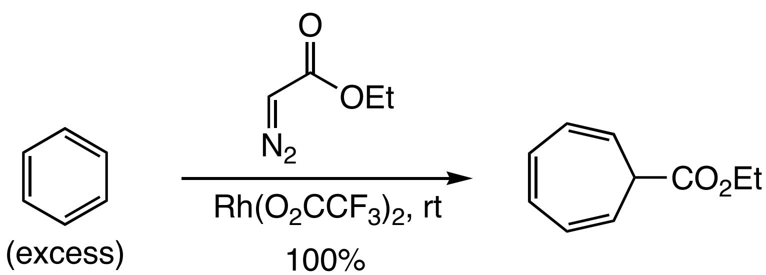
➩ Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

➩ Future Work

Transition-Metal Catalyzed [6+1] Cycloaddition (Buchner Reaction)

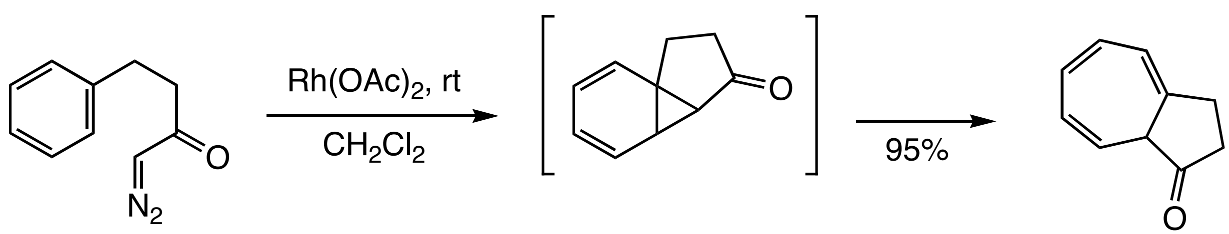


von E. Doering, W.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F.; Williams, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 5448



Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873

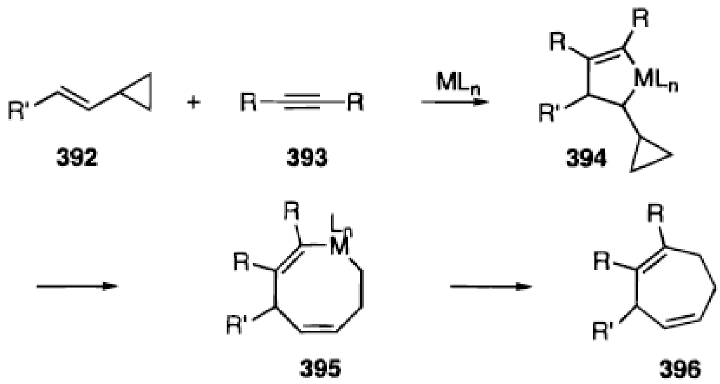
⇨ Substituted arenes give mixtures of isomeric products

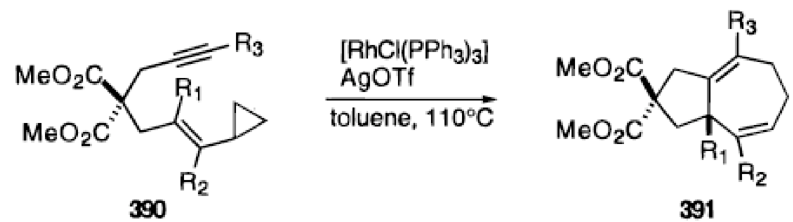


McKervey, M. A.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Chem. Commun.* **1984**, 129

Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091

Transition-Metal Catalyzed [5+2] Cycloaddition





entry	react. cond.	R_1	R_2	R_3	yield (%)
1	A, 20 min	H	H	Me	83
2	B, 2 d	H	H	Me	84
3	B, 2 d	H	Me	H	82
4	B, 16 h	H	Me	CO_2Me	81
5	B, 7 d	H	Me	TMS	71
6	C, 30 min	Me	H	Me	82

A: 0.5 mol % $[RhCl(PPh_3)_3]$, 0.5 mol % AgOTf;

B: 10 mol % $[RhCl(PPh_3)_3]$;

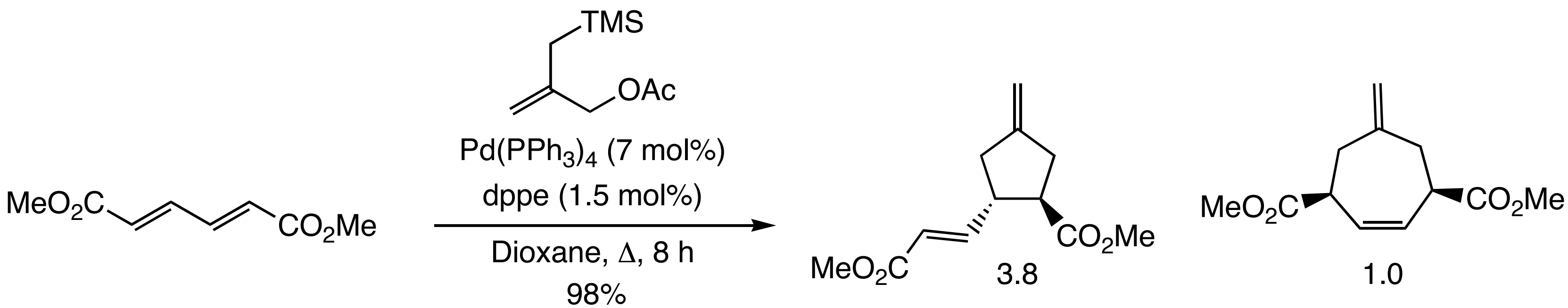
C: 10 mol % $[RhCl(PPh_3)_3]$, 10 mol % AgOTf.

- ⇨ Formation of a metallacycle, followed by a strain-driven cleavage of the cycloprane ring and a reductive elimination to the cycloheptadiene

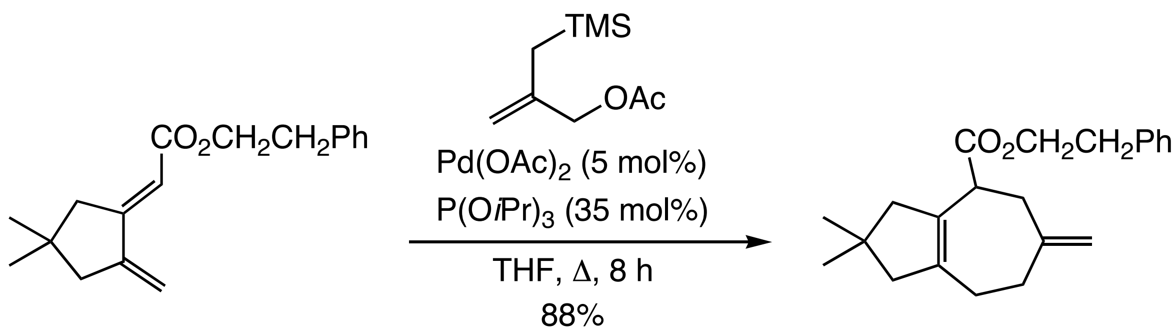
- ⇨ An increase in reaction rate is also observed when the reactions are performed in CF_3CH_2OH

Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720
Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49

Transition-Metal Catalyzed [4+3] Cycloaddition



Trost, B. M.; Nanninga, T. N.; Chan, D. M. T. *Organometallics* **1982**, *1*, 1543



Minor amounts of [3+2] cycloadduct observed

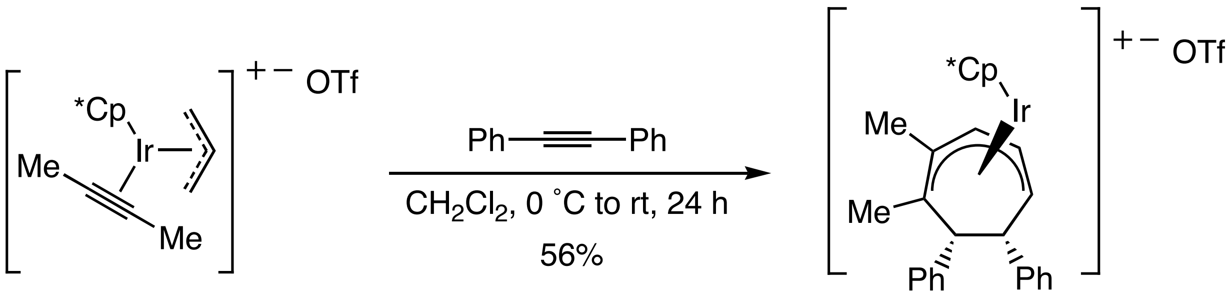
⇨ Freezing the diene in a cisoid conformation favors the formation of the seven-membered ring

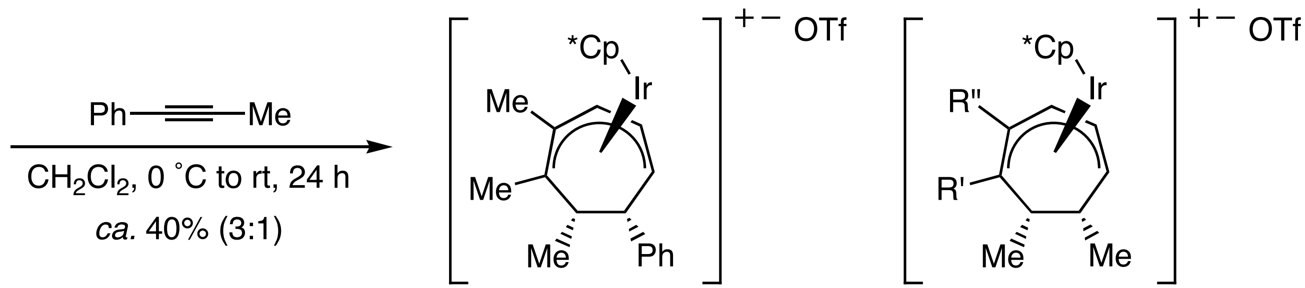
Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483

Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49

Previous Examples of [3+2+2] Cycloadditions

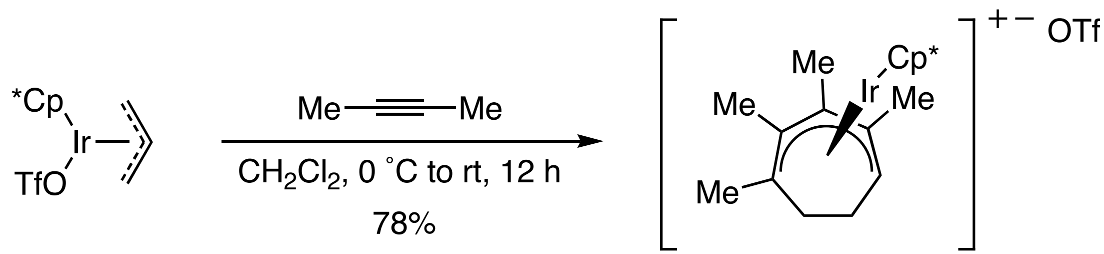
Iridium-mediated allyl/alkyne [3+2+2] cycloaddition





R', R" = Me, Ph

⇨ Similar results with phenylacetylene

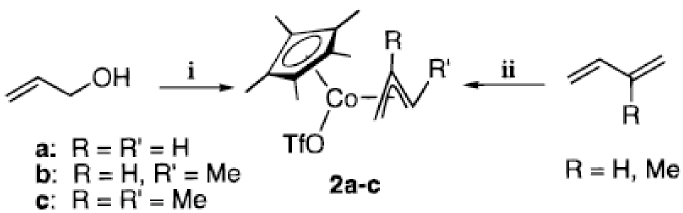


⇨ Stoichiometric reaction, and poor selectivities are obtained for unsymmetrical alkynes

Schwiebert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 8275

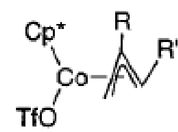
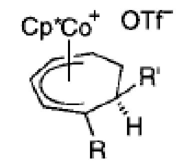
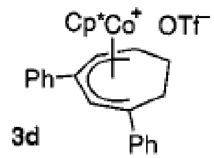
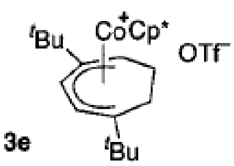
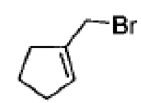
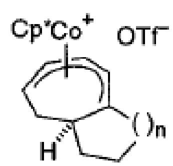
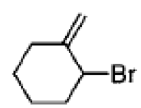
Previous Examples of [3+2+2] Cycloadditions

Cobalt-mediated allyl/alkyne [3+2+2] cycloaddition



Conditions: **i**. $(C_5Me_5)Co(C_2H_4)_2$ (**1**), TfOH, Et_2O, -78 °C→RT, 4h
ii. $(C_5Me_5)Co(C_2H_4)_2$ (**1**), hexane, 65 °C, 4-12h; then step **i**.

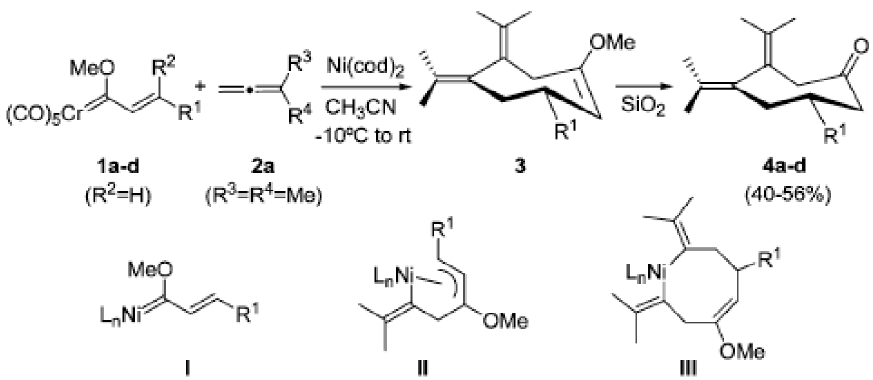
- Dramatic solvent effect (THF affords cyclopenta-dienyl complexes)
- Conditions: CH_2Cl_2, excess alkyne (3 to 10 equiv.), –78 ˚C to rt, 12 h
- Nucleophilic alkylation (Na-dimethylmalonate) of **3**, followed by an oxidative decomplexation using $[Cp_2Fe]^{+-}$OTf affords substituted cycloheptadienes

Entry	Allyl complex/ precursor	Alkyne	Product	Yield[b]
				
1	**2a**	H—≡—H	**3a** (R, R' = H)	52 (66)
2	**2b**	H—≡—H	**3b** (R = H, R' = Me)	79 (85)
3	**2c**	H—≡—H	**3c** (R, R' = Me)	80
4	**2a**	Ph—≡—H	 **3d**	59
5	**2a**	^{t}Bu—≡—H	 **3e**	88
6[c]		H—≡—H	 **3f** (n = 1)	47
7[c]		H—≡—H	**3g** (n = 2, BF_4 salt)	59

Etkin, N.; Dzwiniel, T. L.; Schweibert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 9702

Previous Examples of [3+2+2] Cycloadditions

Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes



- Reaction affords the [3+2] cycloadduct when performed in toluene
- Least substituted C=C bond of the allene inserts (head-to-head allene–allene coupling)

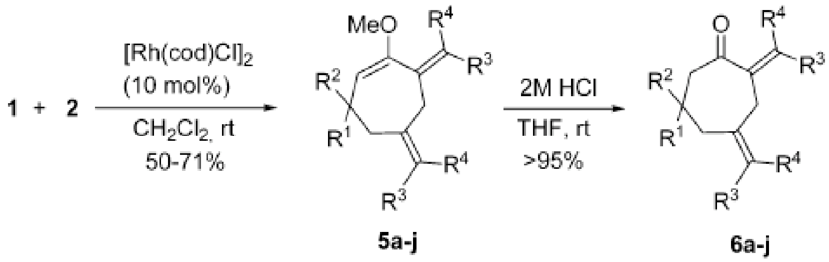
Done with $Ni(cod)_2$ (entries 1–4)

entry	R[1]	R[2]	R[3]	R[4]	**4** (%)[a,b]	**5** (%)[a]
1	*p*-$MeOC_6H_4$	H	Me	Me	**4a** (53)	**5a** (55)
2	^{n}Bu	H	Me	Me	**4b** (40)	**5b** (61)
3	Ph	H	Me	Me	**4c** (52)	
4	2-furyl	H	Me	Me	**4d** (56)	
5	^{i}Bu	H	Me	Me		**5c** (70)
6	^{t}Bu	H	Me	Me		**5d** (58)
7	Me	H	Me	Me		**5e** (60)
8	ferrocenyl	H	Me	Me		**5f** (63)
9	Me	Me	Me	Me		**5g** (71)
10	Me	H	$-(CH_2)_5-$			**5h** (64)
11	Me	Me	Ph	Ph		**5i** (55)
12	Me	H	Ph	H		**5j** (50)

Barluenga, J.; Vicente, R.; Barrio, P.; Lopez, L. A.; Tomas, M.; Borge, J. *J. Am. Chem. Soc.* **2004**, *126*, 14354

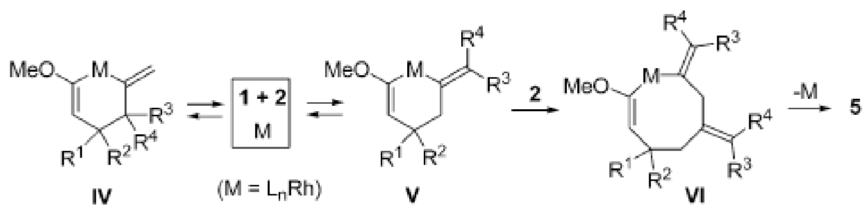
Previous Examples of [3+2+2] Cycloadditions

Nickel and Rhodium-catalyzed [3+2+2] cycloaddition of alkenyl Fischer carbene complexes and allenes



⇨ Least substituted C=C bond of the allene inserts (head-to-tail allene–allene coupling)

⇨ Reversible metalla-[4+2] cycloaddition gives **IV**, which evolves to the more stable **V**

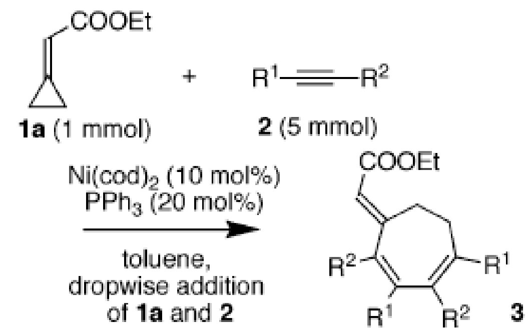


entry	R^1	R^2	R^3	R^4	**4** (%)[a,b]	**5** (%)[a]
1	*p*-MeOC_6H_4	H	Me	Me	**4a** (53)	**5a** (55)
2	^{n}Bu	H	Me	Me	**4b** (40)	**5b** (61)
3	Ph	H	Me	Me	**4c** (52)	
4	2-furyl	H	Me	Me	**4d** (56)	
5	^{i}Bu	H	Me	Me		**5c** (70)
6	^{t}Bu	H	Me	Me		**5d** (58)
7	Me	H	Me	Me		**5e** (60)
8	ferrocenyl	H	Me	Me		**5f** (63)
9	Me	Me	Me	Me		**5g** (71)
10	Me	H	−$(CH_2)_5$−			**5h** (64)
11	Me	Me	Ph	Ph		**5i** (55)
12	Me	H	Ph	H		**5j** (50)

Done with $[Rh(cod)Cl]_2$ (entries 5–12)

Barluenga, J.; Vicente, R.; Barrio, P.; Lopez, L. A.; Tomas, M.; Borge, J. *J. Am. Chem. Soc.* **2004**, *126*, 14354

Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes



entry	cmpd	R^1	R^2	yield of 3(%)[b]
1	**2a**	$(CH_3)_3Si$	H	70
2	**2a**	$(CH_3)_3Si$	H	25[c]
3	**2a**	$(CH_3)_3Si$	H	57[d]
4	**2a**	$(CH_3)_3Si$	H	59[e]
5	**2b**	$(CH_3)_3C$	H	89
6	**2c**	Ph	H	74
7	**2d**	4-MeOC_6H_4	H	72
8	**2e**	4-FC_6H_4	H	59[f]
9	**2f**	$HO(CH_3)_2C$	H	56
10	**2g**	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	31[c]
11	**2h**	$n\text{-}C_6H_{13}$	H	*g*

⇨ Good results obtained with sterically hindered terminal alkynes (entries 1–9)

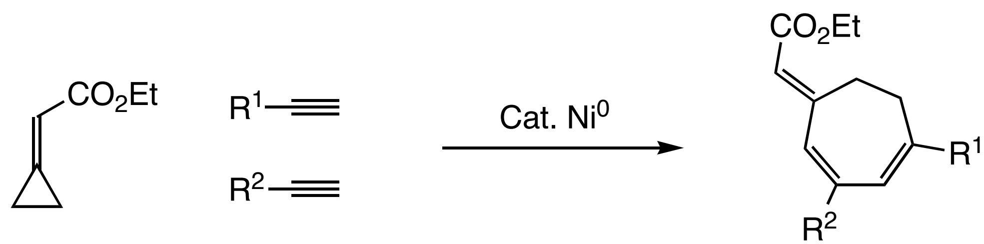
⇨ Other phosphines [$P(Bu)_3$, $P(Cy)_3$, $P(t\text{-}Bu)_3$, dppe] were less effective

⇨ Other catalysts [$RhCl(PPh_3)_3$, $CpCo(PPh_3)_2$, $CpCp(CO)_2$] were not effective

Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540

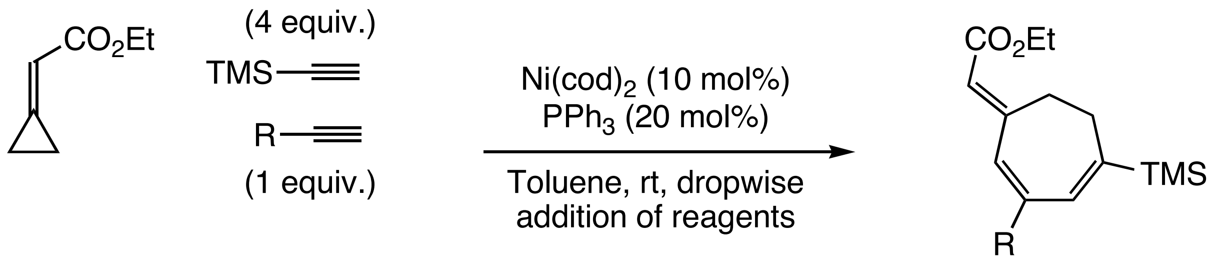
Nickel-Catalyzed Three-Component [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

Selective Synthesis of Multisubstituted Cycloheptadienes



Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2446

Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes

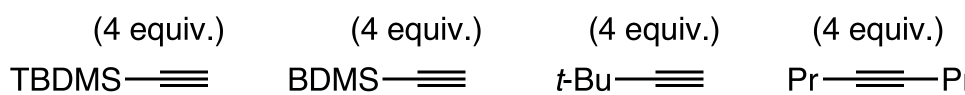


Entry	R	Yield (%)
1	$MeOCH_2$	69
2	$TBDMSOCH_2$	67
3	$PhCH_2$	66
4	*n*-C_6H_{13}	68
5	Ph	56
6	*p*-$MeOC_6H_4$	65
7	*p*-$CF_3C_6H_4$	74
8	$HO(CH_3)_2C$	69

⇨ DMF can also be used, but not THF, Et_2O or CH_2Cl_2

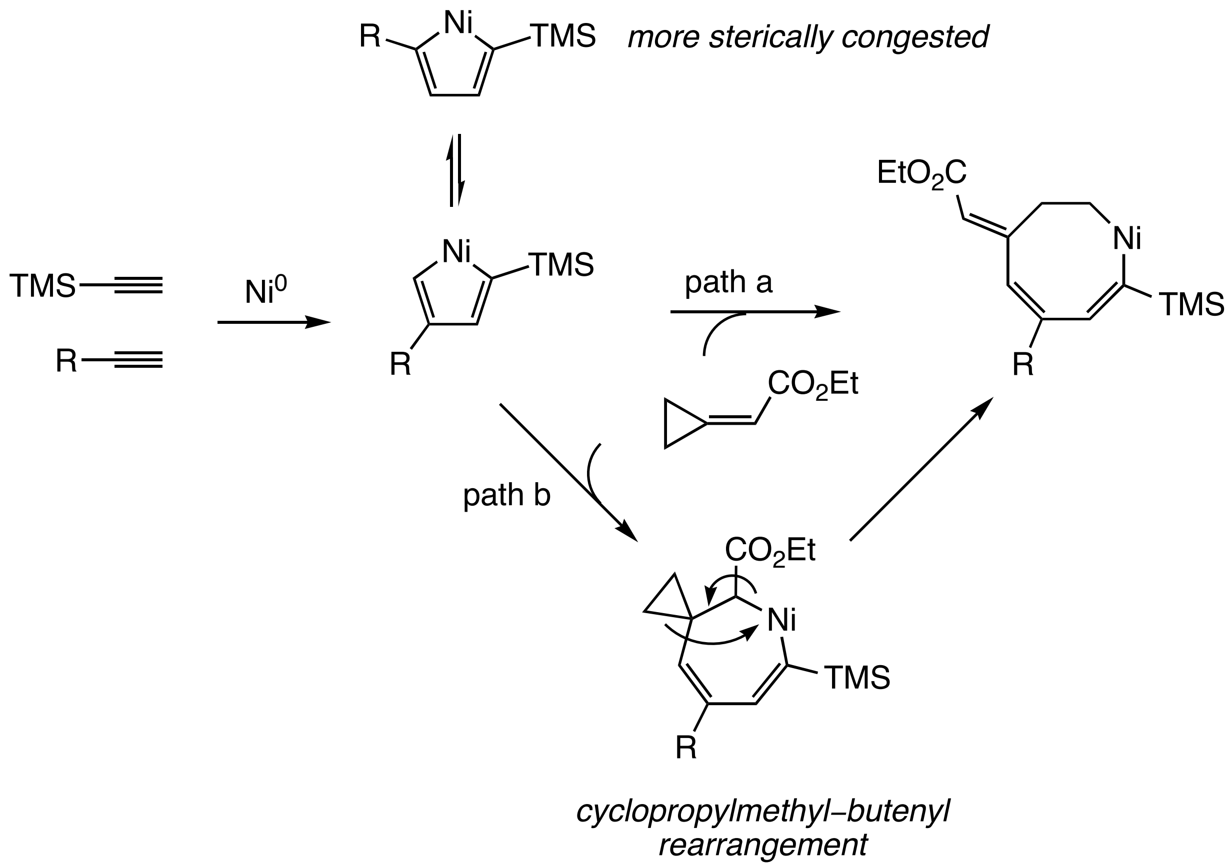
⇨ Terminal alkyne doesn't need to be bulky in order to get good regioselectivities (see different R groups)

⇨ Other alkynes;



Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2446

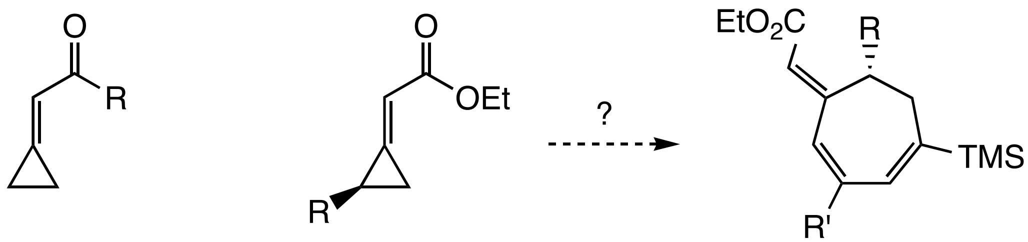
Nickel-Catalyzed Intermolecular [3+2+2] Cocyclization of Ethyl Cyclopropylideneacetate and Alkynes



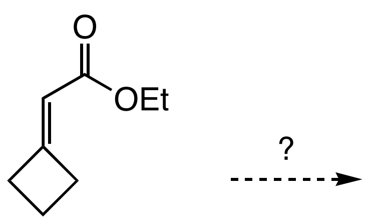
Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2446

Future Work

- Extend this reaction to other cyclopropylmethylene derivatives



- Extend this reaction to cyclobutylmethylene derivatives



(Feasible? Beilstein search resulted in no hits.)

- Attempt to apply this methodology to the synthesis of complex natural products