Enantioselective copper-catalyzed decarboxylative propargylic alkylation of propargyl β-ketoesters with a chiral ketimine P,N,N-Ligand

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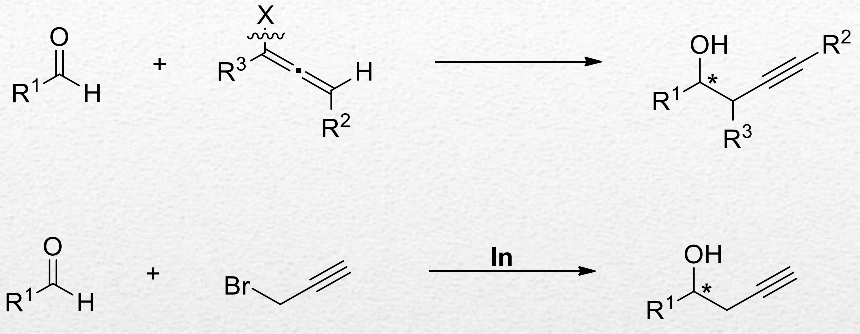
STéRéO Seminar group 17.02.2014

State of the art

- Start of asymmetric propargylation of carbonyl compound



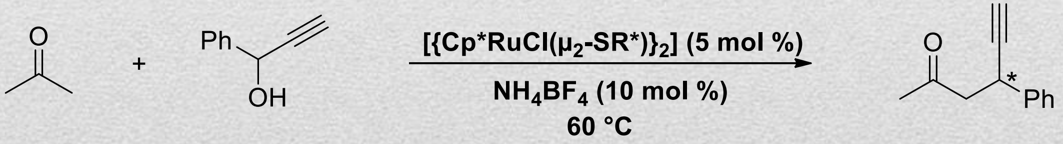
X = chiral boronic ester[1,2]
= $SnCl_3$, $InCl_2$, In (OMS)I, ZnOMS, $SiCl_3$[3]

R_1 = H, alkyl, phenyl
R_2, R_3 = H, alkyl

67-90% yield
34-99% ee

R_1 = alkyl, phenyl[4]

- First example of catalytic asymmetric propargylic substitution reaction[5]



41-95% yield
10-35% ee

[1] Haruta, R.; Ishiguro, M.; Ikeda, N; Yamamoto, H. *JACS*. **1982**, 104, 7667.
[2] Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *JACS*, *Chem. Commun*, **1993**, 1468.
[3] Marshall, J. A.; Grant, C. M. *J. Org. Chem*. **1999**, 64, 696.
[4] Nishibayashi, Y.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. *Organometallics*, **2003**, 22, 873.
[5] Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, 44, 507.1

State of the art

- This work

* Decarboxylation and propargylic alkylation reaction in situ

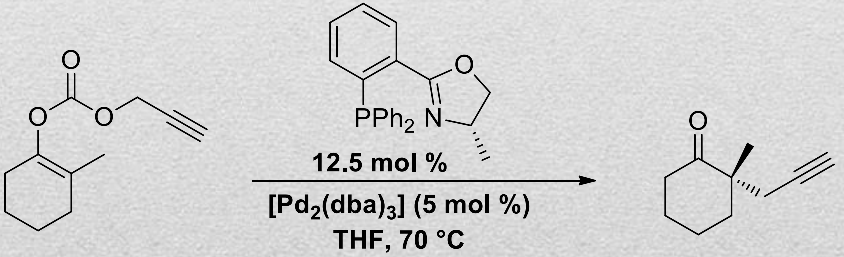
* Facile access to a large of β–ethynyl ketones in highly enantioenriched form

State of the art

- This work

* Decarboxylation and propargylic alkylation reaction in situ
* Facile access to a large of β–ethynyl ketones in highly enantioenriched form

- Catalytic asymmetric propargylic alkylation of enol carbonate with decarboxylation[6]


12.5 mol %

$[Pd_2(dba)_3]$ (5 mol %)

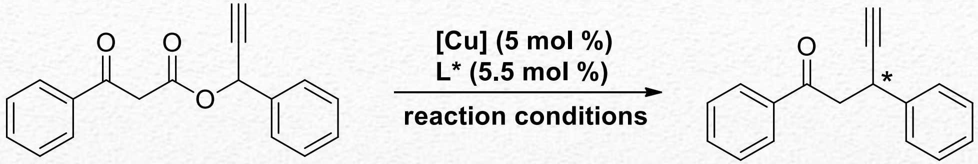
THF, 70 °C

R = tBu, CH_2tBu, CH_2Ph, CH_2-naphtyl,..

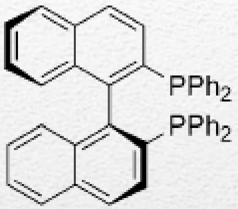
54-94% yield
12-44% ee

[6] D. C. Behenna, J. T. Mohr, N. H. Sherden, S. C. Marinescu, A.M. Harned, K. Tani, M. Steo, S. Ma, Z. Novak, M. R. Krout, R. M. McFadden, J. L. Roizen, J. A. Enquist, Jr., D. V. White, S. R. Levine, K. V. Petrova, A. Iwashita, S. C. Virgil, B. M. Sholtz, *Chem. Eur. J.* **2011**, *17*, 14199-14223,

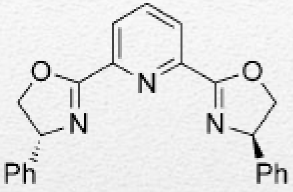
Condition optimization



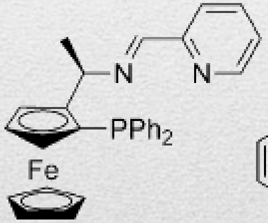
Entry	[Cu]	L*	Solvent	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	$Cu(OAc)_2 \cdot H_2O$	**L1**	MeOH	*i*Pr_2NEt	25	38	< 10
2	$Cu(OAc)_2 \cdot H_2O$	**L2**	MeOH	*i*Pr_2NEt	25	92	12
3	$Cu(OAc)_2 \cdot H_2O$	**L3**	MeOH	*i*Pr_2NEt	25	85	55
4	$Cu(OAc)_2 \cdot H_2O$	**L4**	MeOH	*i*Pr_2NEt	25	90	65



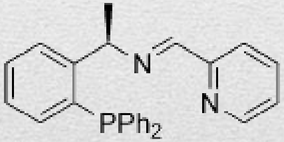
(*S*)-binap (**L1**)



Ph-pybox (**L2**)

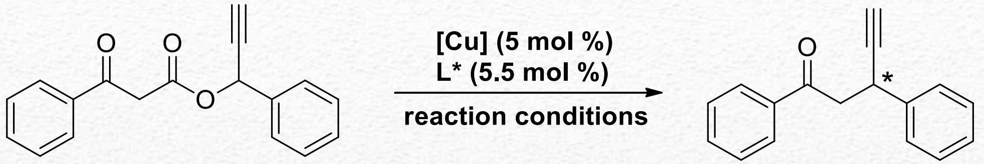


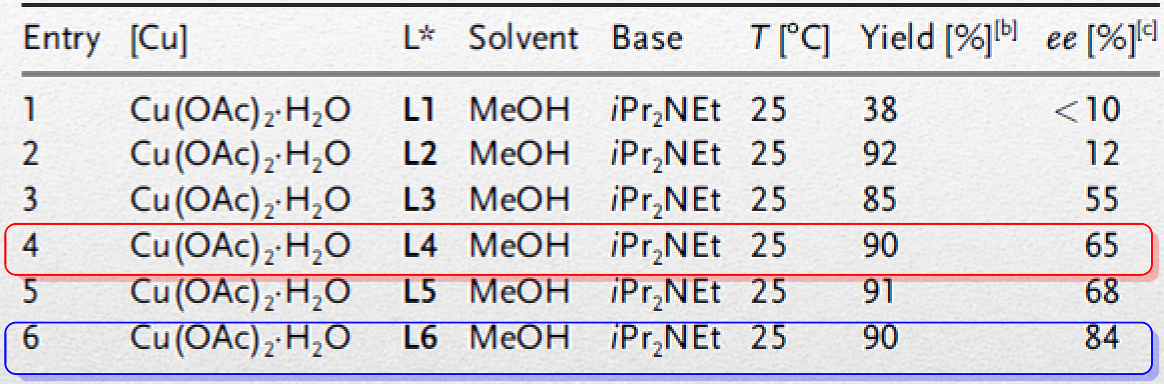
(R_c,S_p)-**L3**



(*R*)-**L4**

Condition optimization





Entry	[Cu]	L*	Solvent	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
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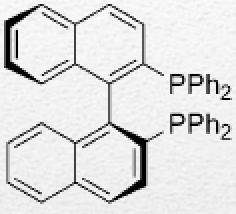
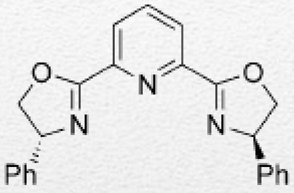
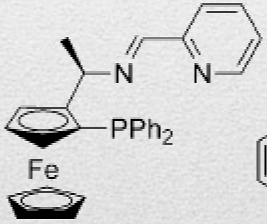
3	$Cu(OAc)_2{\cdot}H_2O$	**L3**	MeOH	*i*Pr_2NEt	25	85	55
4	$Cu(OAc)_2{\cdot}H_2O$	**L4**	MeOH	*i*Pr_2NEt	25	90	65
5	$Cu(OAc)_2{\cdot}H_2O$	**L5**	MeOH	*i*Pr_2NEt	25	91	68
6	$Cu(OAc)_2{\cdot}H_2O$	**L6**	MeOH	*i*Pr_2NEt	25	90	84



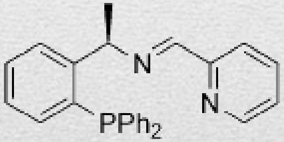
(*S*)-binap (**L1**)



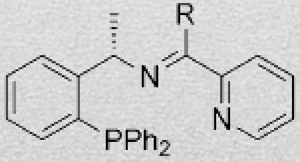
Ph-pybox (**L2**)



(R_c,S_p)-**L3**

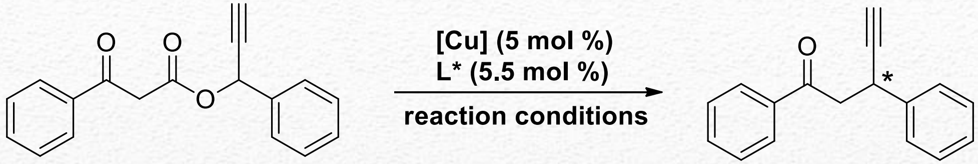


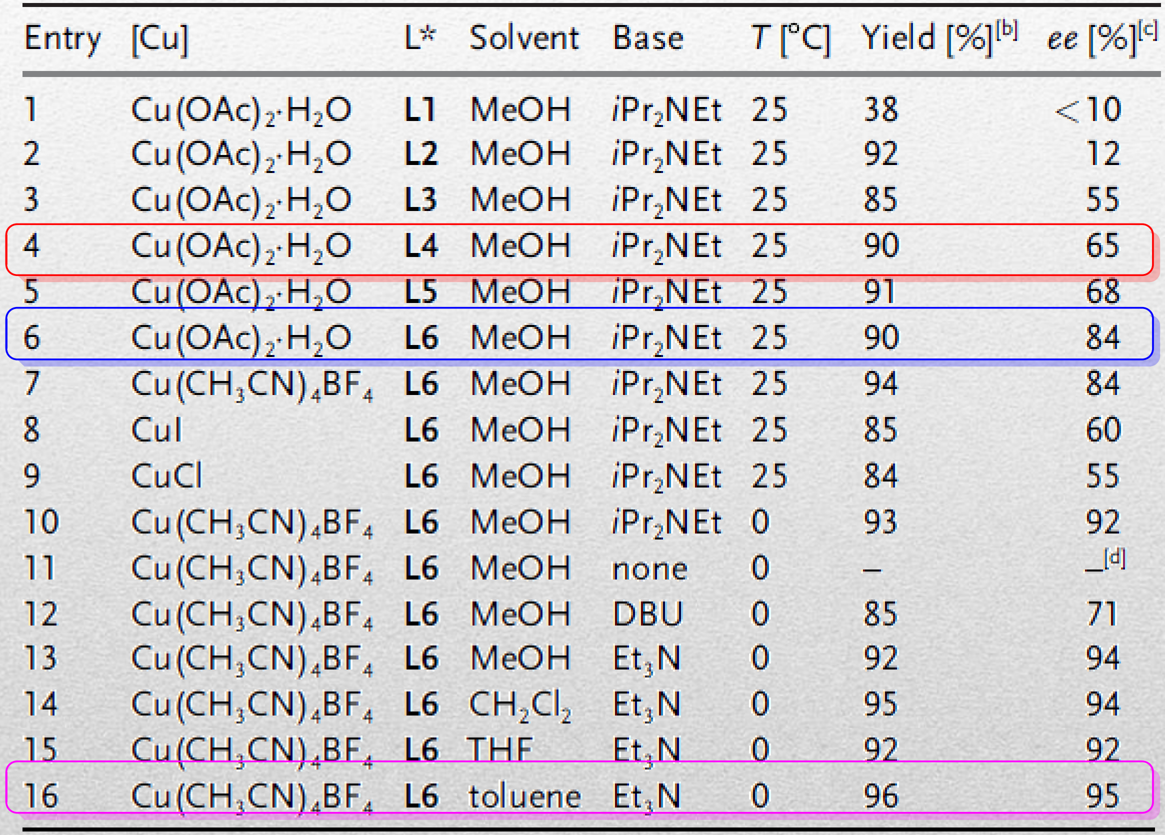
(*R*)-**L4**



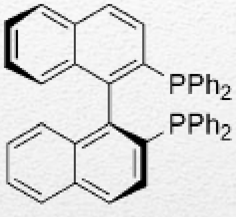
(*S*)-**L5**: R = Me
(*S*)-**L6**: R = Ph

Condition optimization

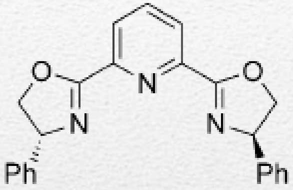




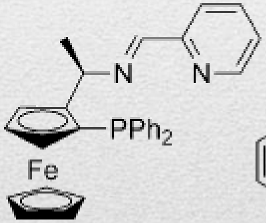
Entry	[Cu]	L*	Solvent	Base	T [°C]	Yield [%][b]	*ee* [%][c]
1	$Cu(OAc)_2{\cdot}H_2O$	**L1**	MeOH	*i*Pr_2NEt	25	38	<10
2	$Cu(OAc)_2{\cdot}H_2O$	**L2**	MeOH	*i*Pr_2NEt	25	92	12
3	$Cu(OAc)_2{\cdot}H_2O$	**L3**	MeOH	*i*Pr_2NEt	25	85	55
4	$Cu(OAc)_2{\cdot}H_2O$	**L4**	MeOH	*i*Pr_2NEt	25	90	65
5	$Cu(OAc)_2{\cdot}H_2O$	**L5**	MeOH	*i*Pr_2NEt	25	91	68
6	$Cu(OAc)_2{\cdot}H_2O$	**L6**	MeOH	*i*Pr_2NEt	25	90	84
7	$Cu(CH_3CN)_4BF_4$	**L6**	MeOH	*i*Pr_2NEt	25	94	84
8	CuI	**L6**	MeOH	*i*Pr_2NEt	25	85	60
9	CuCl	**L6**	MeOH	*i*Pr_2NEt	25	84	55
10	$Cu(CH_3CN)_4BF_4$	**L6**	MeOH	*i*Pr_2NEt	0	93	92
11	$Cu(CH_3CN)_4BF_4$	**L6**	MeOH	none	0	–	–[d]
12	$Cu(CH_3CN)_4BF_4$	**L6**	MeOH	DBU	0	85	71
13	$Cu(CH_3CN)_4BF_4$	**L6**	MeOH	Et_3N	0	92	94
14	$Cu(CH_3CN)_4BF_4$	**L6**	CH_2Cl_2	Et_3N	0	95	94
15	$Cu(CH_3CN)_4BF_4$	**L6**	THF	Et_3N	0	92	92
16	$Cu(CH_3CN)_4BF_4$	**L6**	toluene	Et_3N	0	96	95



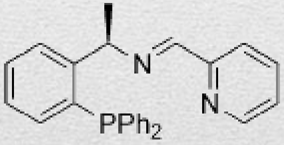
(*S*)-binap (**L1**)



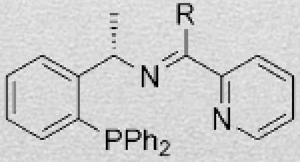
Ph-pybox (**L2**)



(*R*c,*S*p)-**L3**

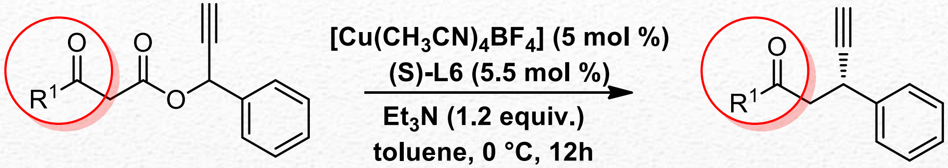


(*R*)-**L4**



(*S*)-**L5**: R = Me
(*S*)-**L6**: R = Ph

Scope of ketone moieties of propargylic β-ketoesters

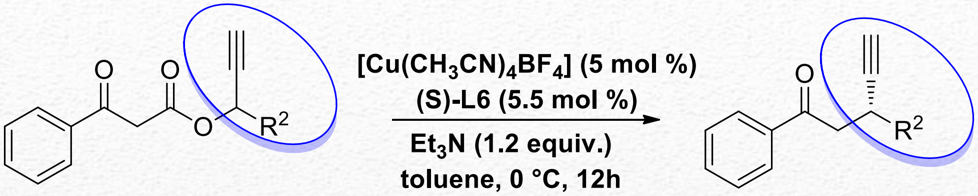


1

2

Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	**1 aa**: $R^1 = Ph$	**2 aa**	96	95
2	**1 ba**: $R^1 = 2\text{-}ClC_6H_4$	**2 ba**	65	93
3	**1 ca**: $R^1 = 3\text{-}ClC_6H_4$	**2 ca**	92	95
4	**1 da**: $R^1 = 4\text{-}ClC_6H_4$	**2 da**	96	94
5	**1 ea**: $R^1 = 4\text{-}FC_6H_4$	**2 ea**	96	95
6	**1 fa**: $R^1 = 4\text{-}BrC_6H_4$	**2 fa**	95	95
7	**1 ga**: $R^1 = 4\text{-}MeC_6H_4$	**2 ga**	93	95
8	**1 ha**: $R^1 = 4\text{-}MeOC_6H_4$	**2 ha**	95	93
9	**1 ia**: $R^1 = 4\text{-}NO_2C_6H_4$	**2 ia**	96	94
10	**1 ja**: $R^1 =$ 2-naphthyl	**2 ja**	95	96
11	**1 ka**: $R^1 =$ 6-MeO-2-naphthyl	**2 ka**	96	98
12	**1 la**: $R^1 =$ thienyl	**2 la**	91	95
13[d]	**1 ma**: $R^1 = Me$	**2 ma**	88	85
14[d]	**1 na**: $R^1 = n\text{Pr}$	**2 na**	85	86
15[d]	**1 oa**: $R^1 = Bn$	**2 oa**	90	83

Scope of propargylic moieties

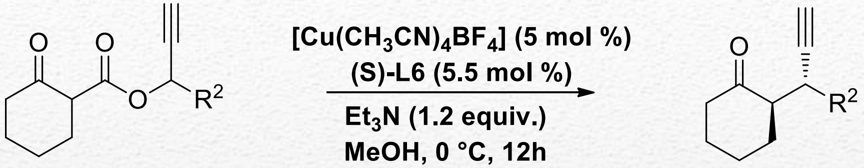


1 **2**

Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	**1aa**: $R^2 = Ph$	**2aa**	96	95
2	**1ab**: $R^2 = 2\text{-}ClC_6H_4$	**2ab**	92	93
3	**1ac**: $R^2 = 3\text{-}ClC_6H_4$	**2ac**	95	96
4	**1ad**: $R^2 = 4\text{-}ClC_6H_4$	**2ad**	96	95
5	**1ae**: $R^2 = 4\text{-}FC_6H_4$	**2ae**	96	94
6	**1af**: $R^2 = 4\text{-}BrC_6H_4$	**2af**	93	95
7	**1ag**: $R^2 = 4\text{-}MeC_6H_4$	**2ag**	91	89
8	**1ah**: $R^2 = 4\text{-}MeOC_6H_4$	**2ah**	94	85
9	**1ai**: $R^2 = 4\text{-}CF_3C_6H_4$	**2ai**	96	95
10	**1aj**: $R^2 = 2\text{-naphthyl}$	**2aj**	94	97
11	**1ak**: $R^2 = \text{thienyl}$	**2ak**	92	88
12	**1al**: $R^2 = Me$	**2al**	–	–[d]

Limites of the scope

- Substitution on the α position



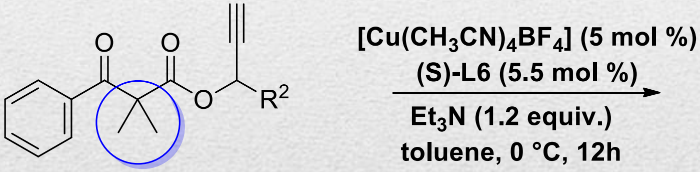
$[Cu(CH_3CN)_4BF_4]$ (5 mol %)
(S)-L6 (5.5 mol %)
Et_3N (1.2 equiv.)
MeOH, 0 °C, 12h

1

2

88% Yield
anti/syn = 7/1, 86% ee for anti

- Substitution on the α,α position

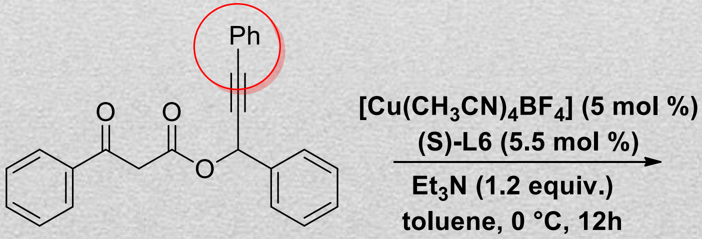


$[Cu(CH_3CN)_4BF_4]$ (5 mol %)
(S)-L6 (5.5 mol %)
Et_3N (1.2 equiv.)
toluene, 0 °C, 12h

1

no reaction

- Reaction with a non-terminal alkyne

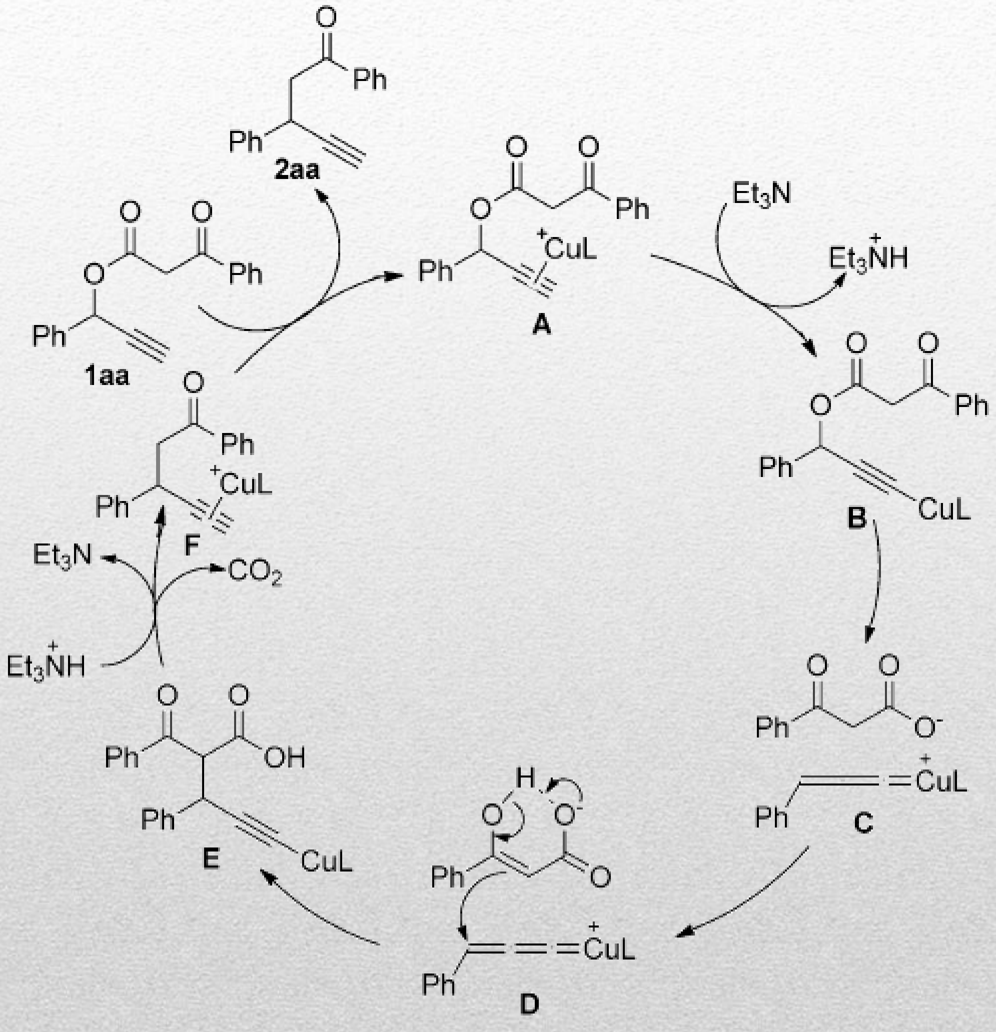


$[Cu(CH_3CN)_4BF_4]$ (5 mol %)
(S)-L6 (5.5 mol %)
Et_3N (1.2 equiv.)
toluene, 0 °C, 12h

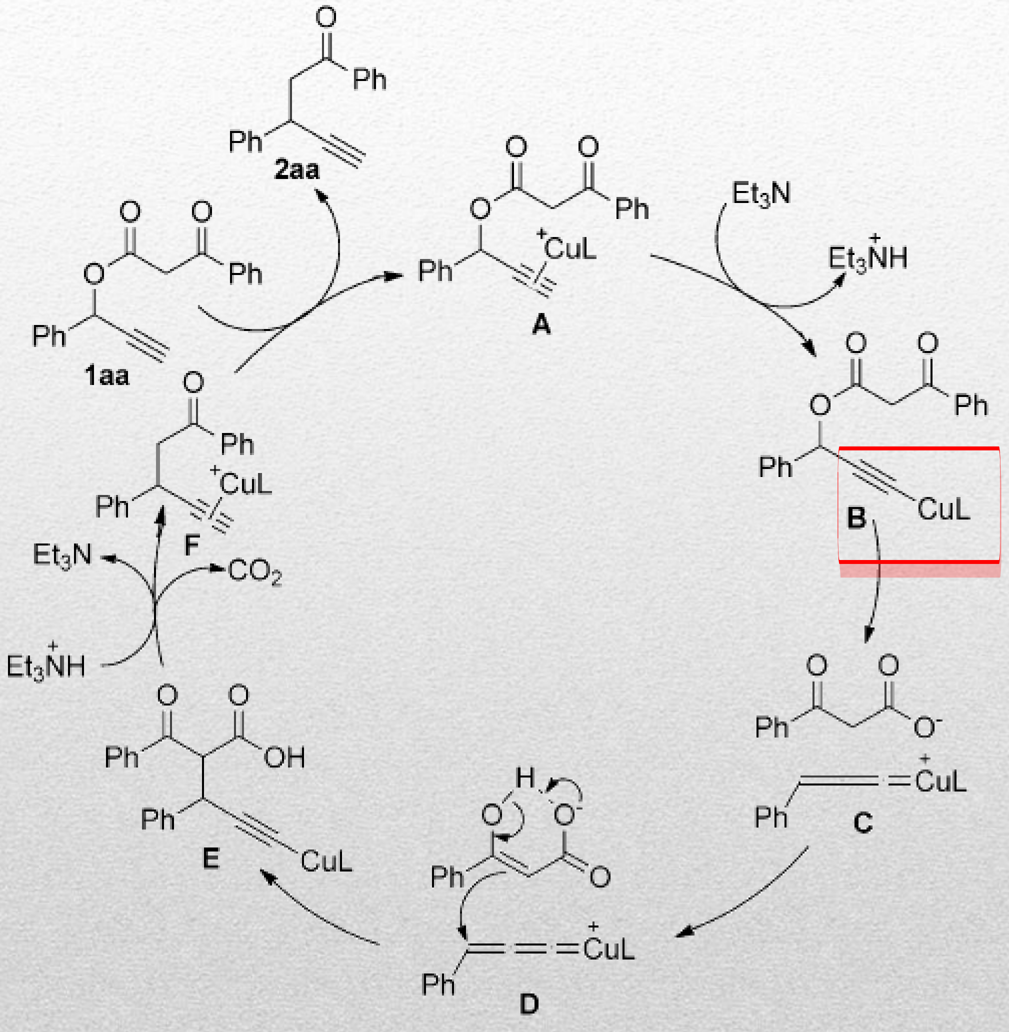
1

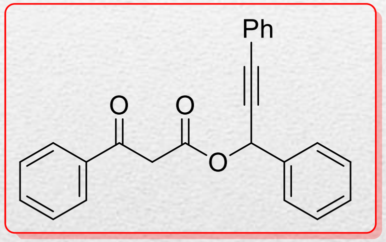
no reaction

Supposed mecanism



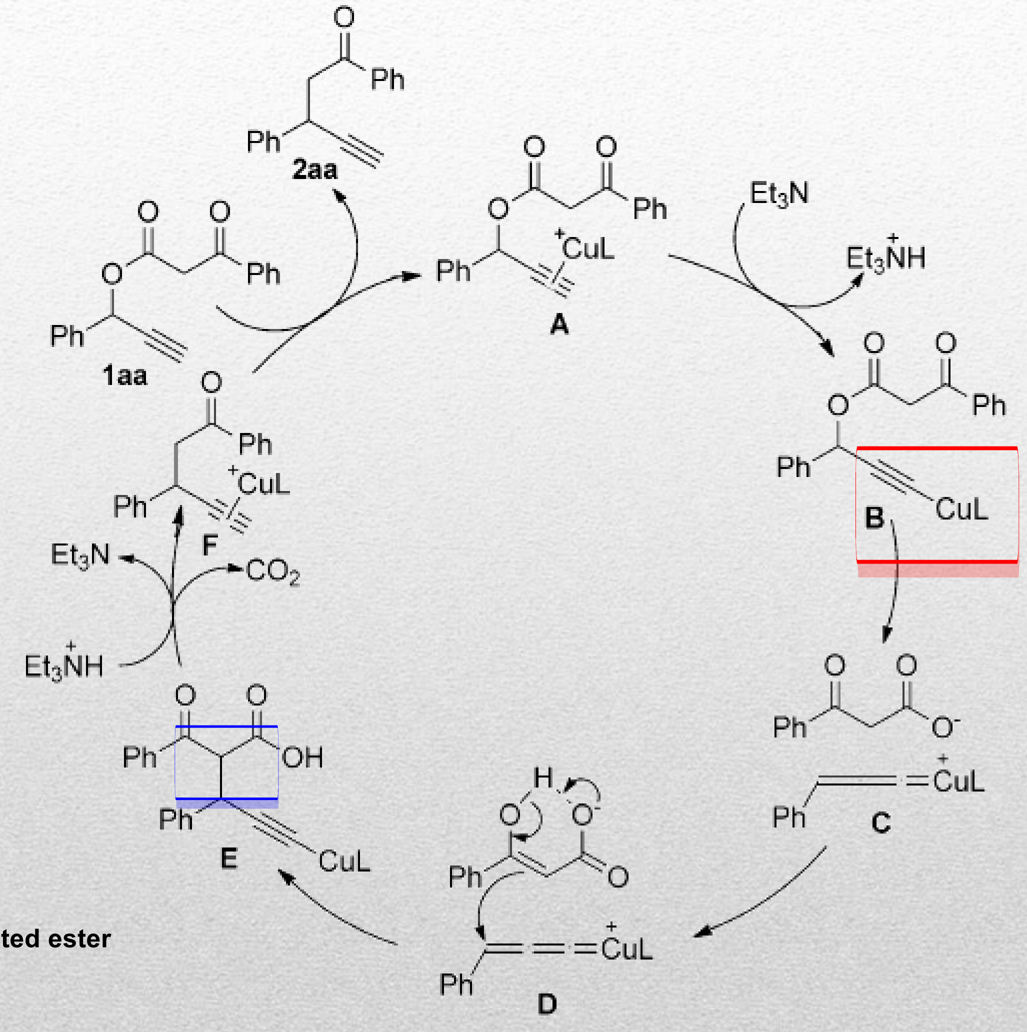
Supposed mecanism

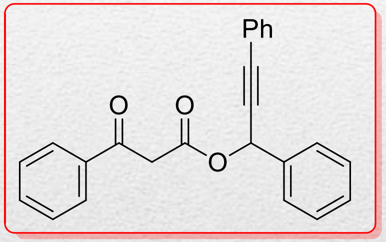




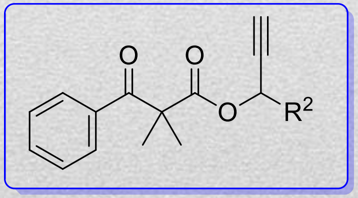
did not work with non terminal alkyne

Supposed mecanism





did not work with non terminal alkyne



did not work with α,α-disubstituted ester

Conclusion

- ☐ The first enantioselective copper-catalyzed decarboxylative propargylic alkylation developped.
- ☐ Formation of activated electrophile and nucleophile in situ in catalytic concentration.
- ☐ Large β-ethynyl ketones, excellent yield and ee.

Thank you for your attention.