Organocatalytic β-Functionalization of Saturated Carbonyl Compounds

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Checker: Chang-Bin Yu

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Chi, Y. R. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 13506.

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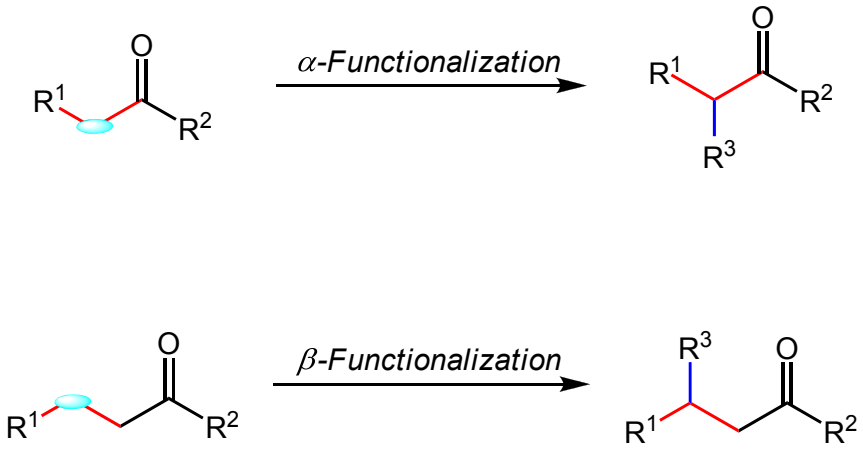
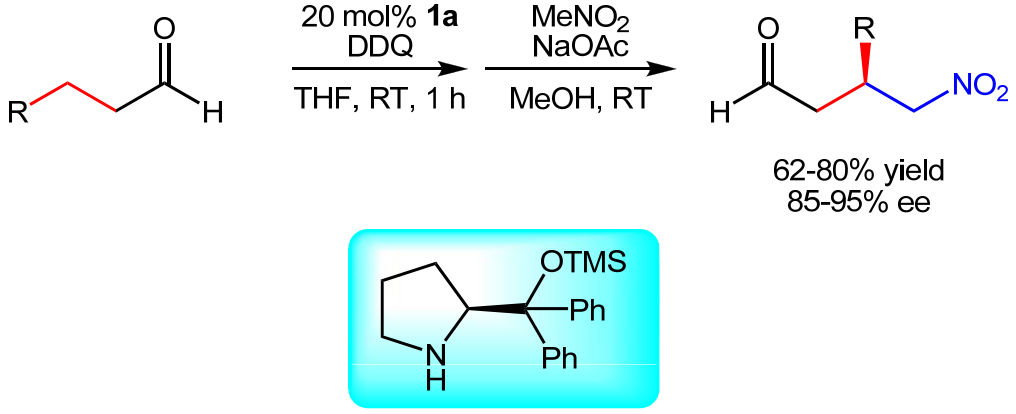
Introduction

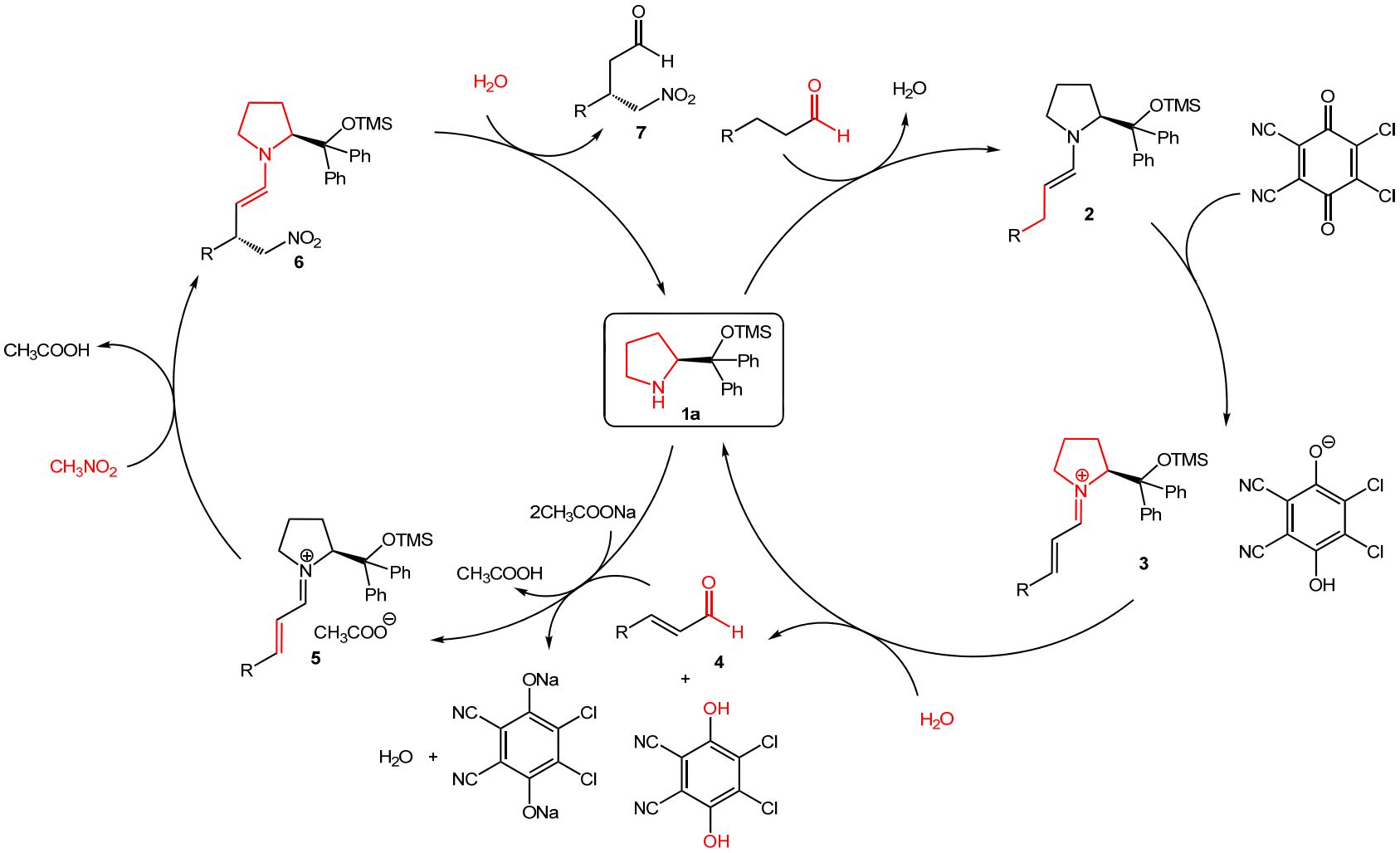


β-Carbon Atom as an Electrophilic Carbon

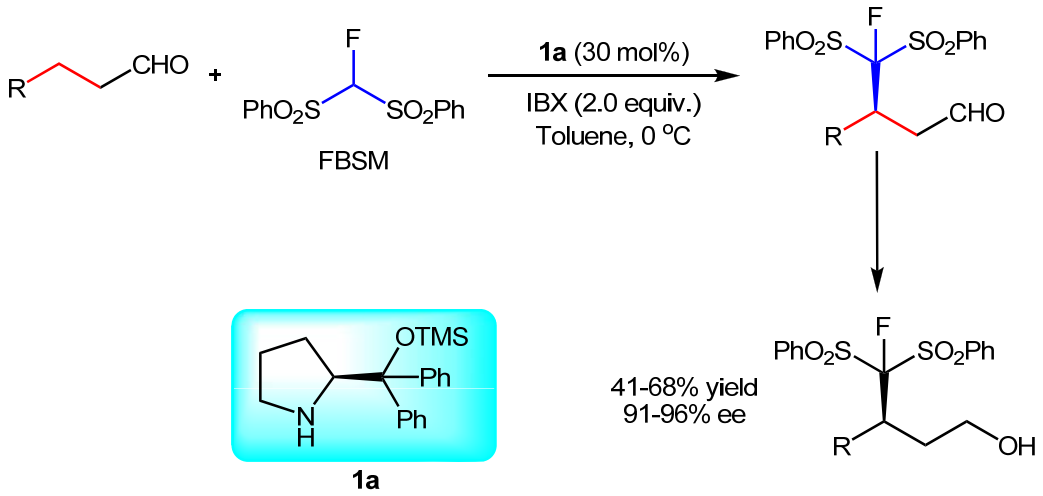


Hayashi, Y. *et al. Angew Chem. Int. Ed.* **2011**, *50*, 3920.

β-Carbon Atom as an Electrophilic Carbon

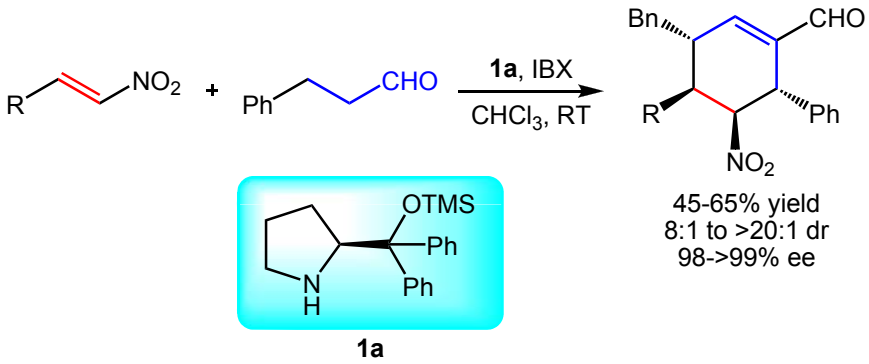


β-Carbon Atom as an Electrophilic Carbon



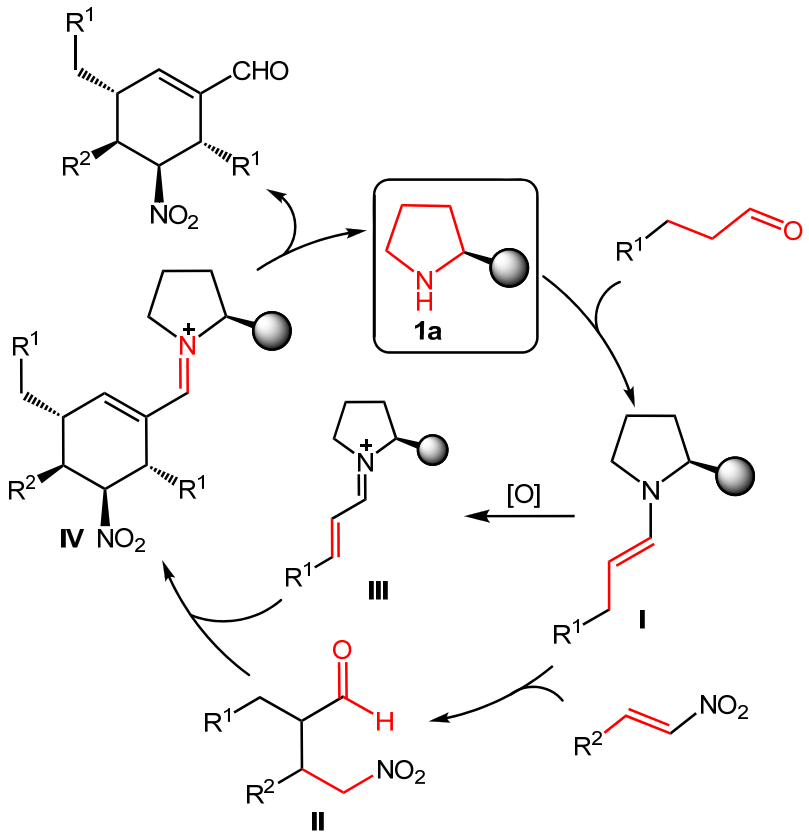
Wang, W. *et al. Nat. Commun.* **2011**, *2*, 211.

β-Carbon Atom as an Electrophilic Carbon

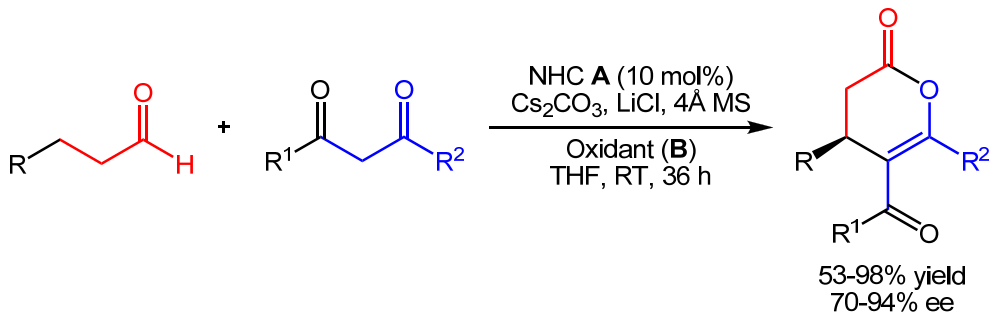


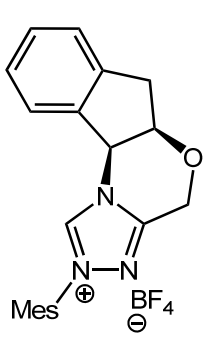
Enders, D. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 2977.

β-Carbon Atom as an Electrophilic Carbon

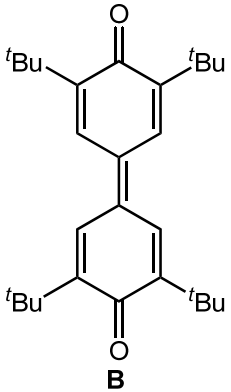


β-Carbon Atom as an Electrophilic Carbon





A

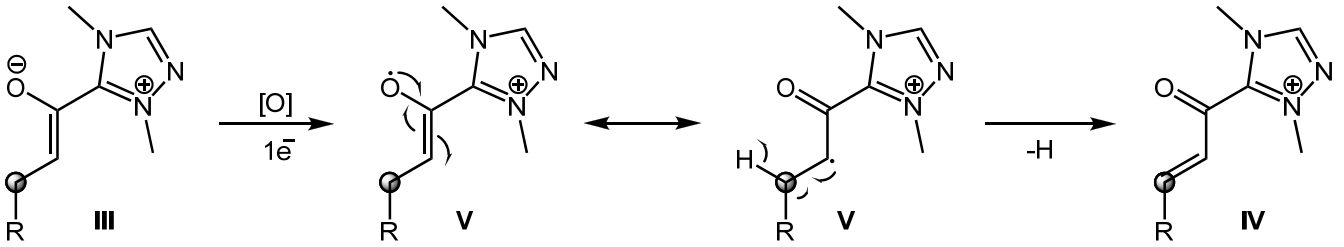


B

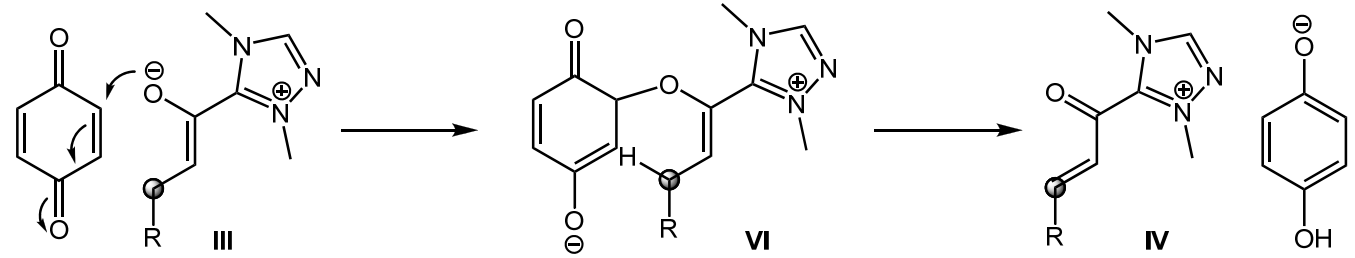
Chi, Y. R. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 8588.

β-Carbon Atom as an Electrophilic Carbon

a) single-electron-transfer (radical) mechanism:



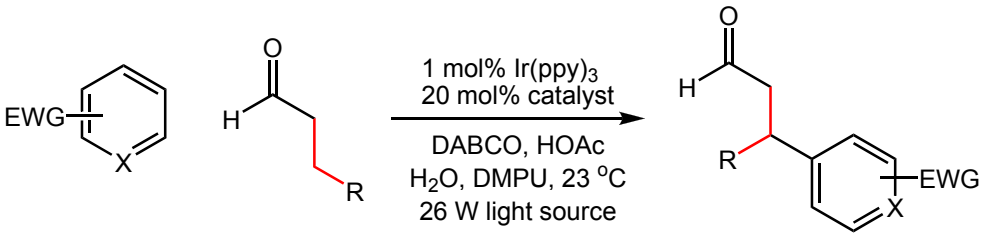
b) electron-pair-transfer mechanism:



simplified oxidant

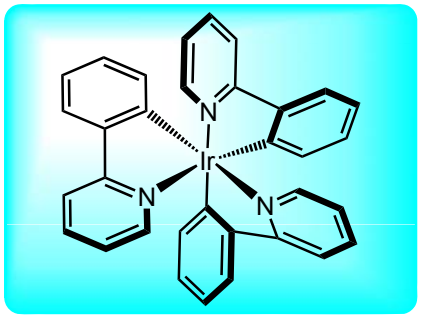
R = Ar, more acidic β-CH
Alkyl, less acidic β-CH

β-Carbon Atom as a Radical Carbon

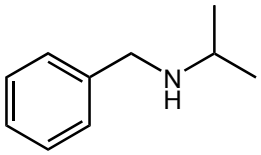


arene aldehyde β-aryl aldehyde

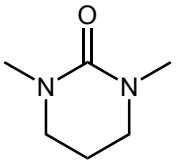
44-88% yield



Ir(ppy)$_3$ (1 mol%)



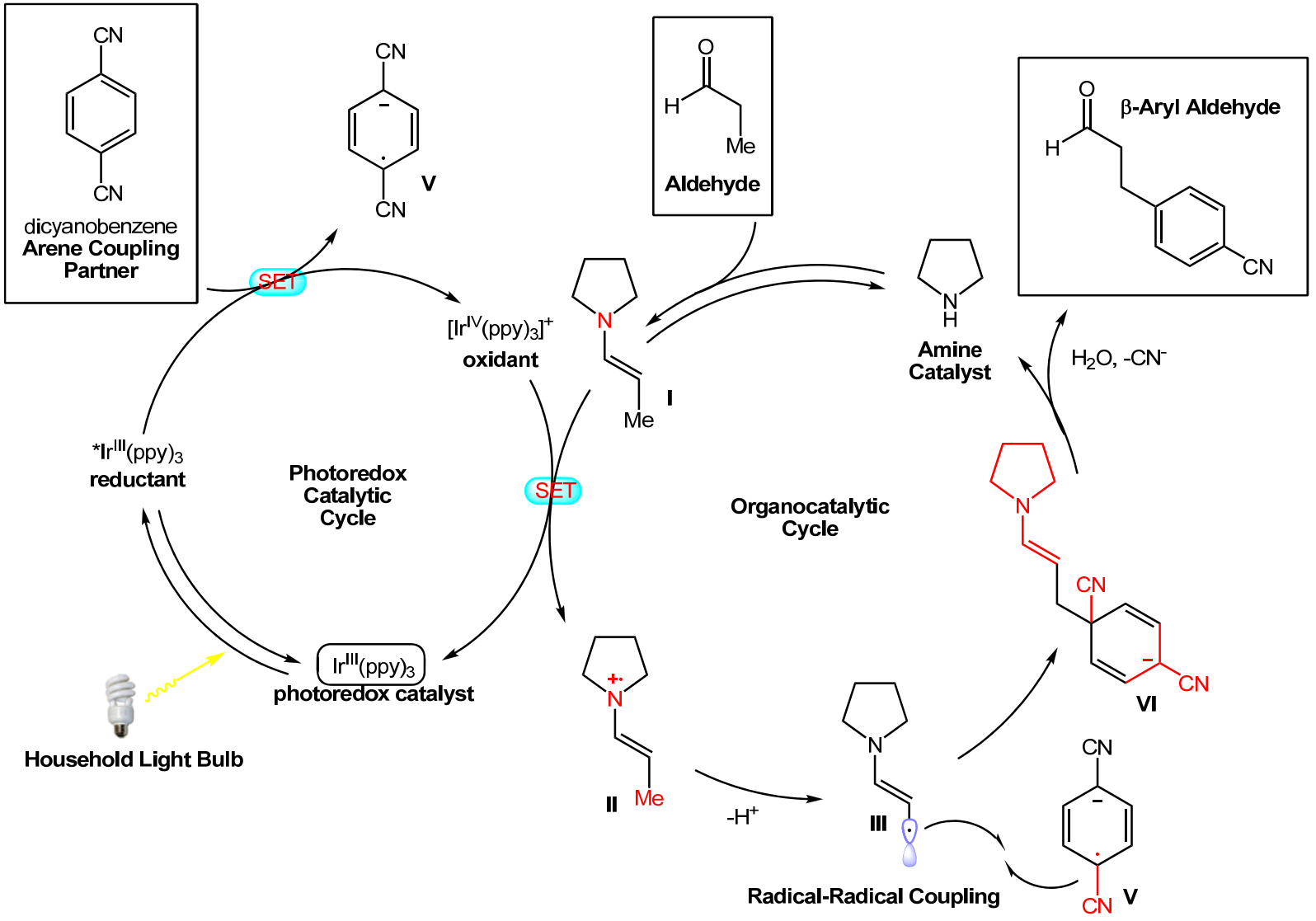
organocatalyst (20 mol%)



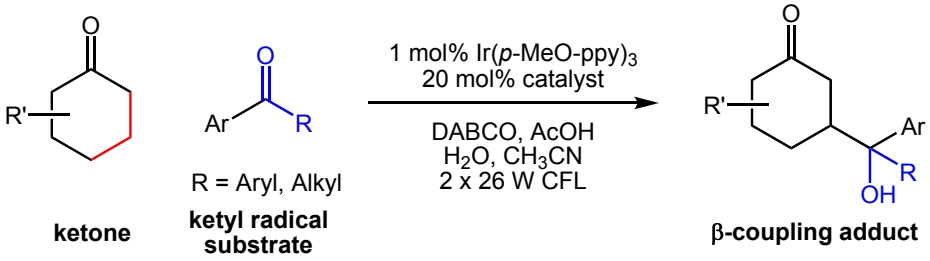
DMPU

MacMillan, D. W. C. *et al. Science* **2013**, *339*, 1593.

β-Carbon Atom as a Radical Carbon

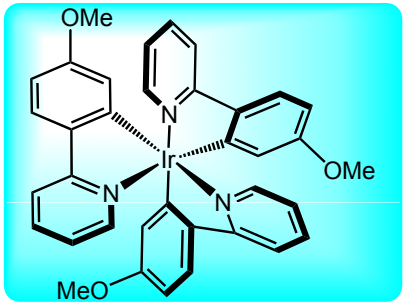


β-Carbon Atom as a Radical Carbon

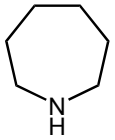


ketone **ketyl radical substrate** **β-coupling adduct**

43-81% yield



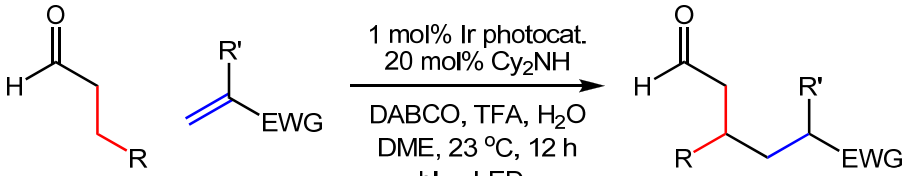
Ir(*p*-MeO-ppy)$_3$ (1 mol%)



catalyst

MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2013**, *135*, 18323.

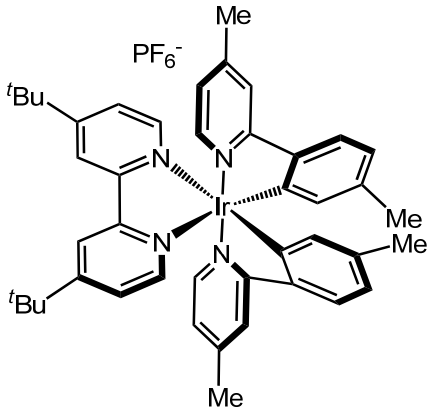
β-Carbon Atom as a Radical Carbon



R = Alkyl, EWG = Ester, Amide, Nitrile

β-alkyl product

50-83% yield

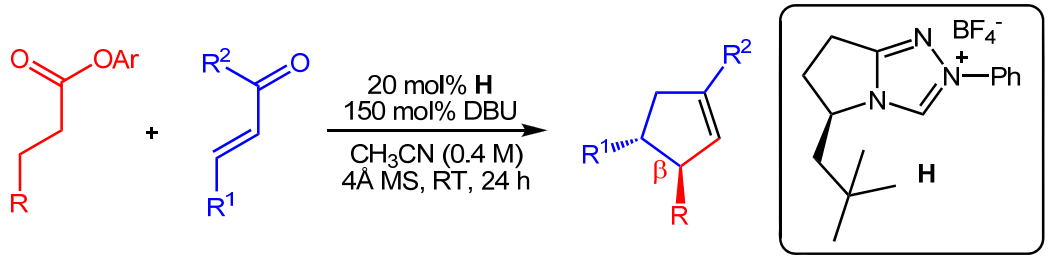


$Ir(dmppy)_2(dtbbpy)PF_6$

MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2014**, *136*, 6858.

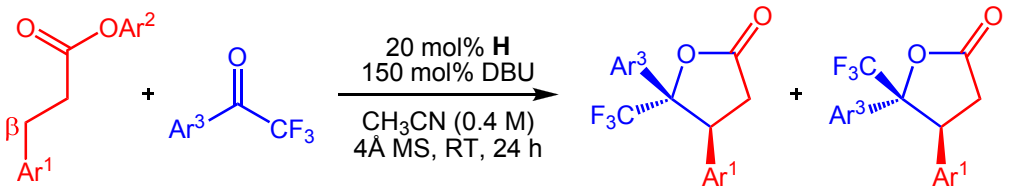
β-Carbon Atom as a Nucleophilic Carbon

1) *α*, β-Unsaturated ketone as electrophile:



up to 81% yield
up to 20:1 dr
up to 94% ee

2) Trifluoroketone as electrophile:

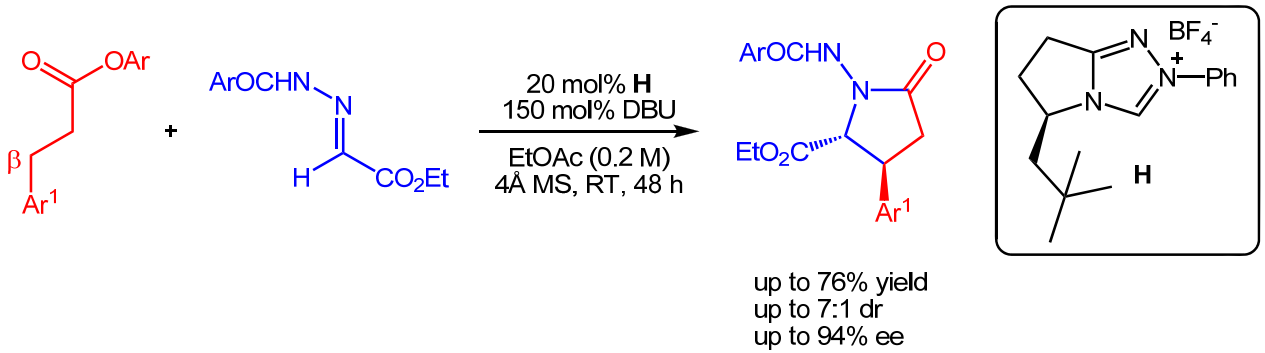


up to 80% yield
up to 4.5:1 dr
up to 90% ee

Chi, Y. R. *et al. Nat. Chem.* **2013**, *5*, 835.

β-Carbon Atom as a Nucleophilic Carbon

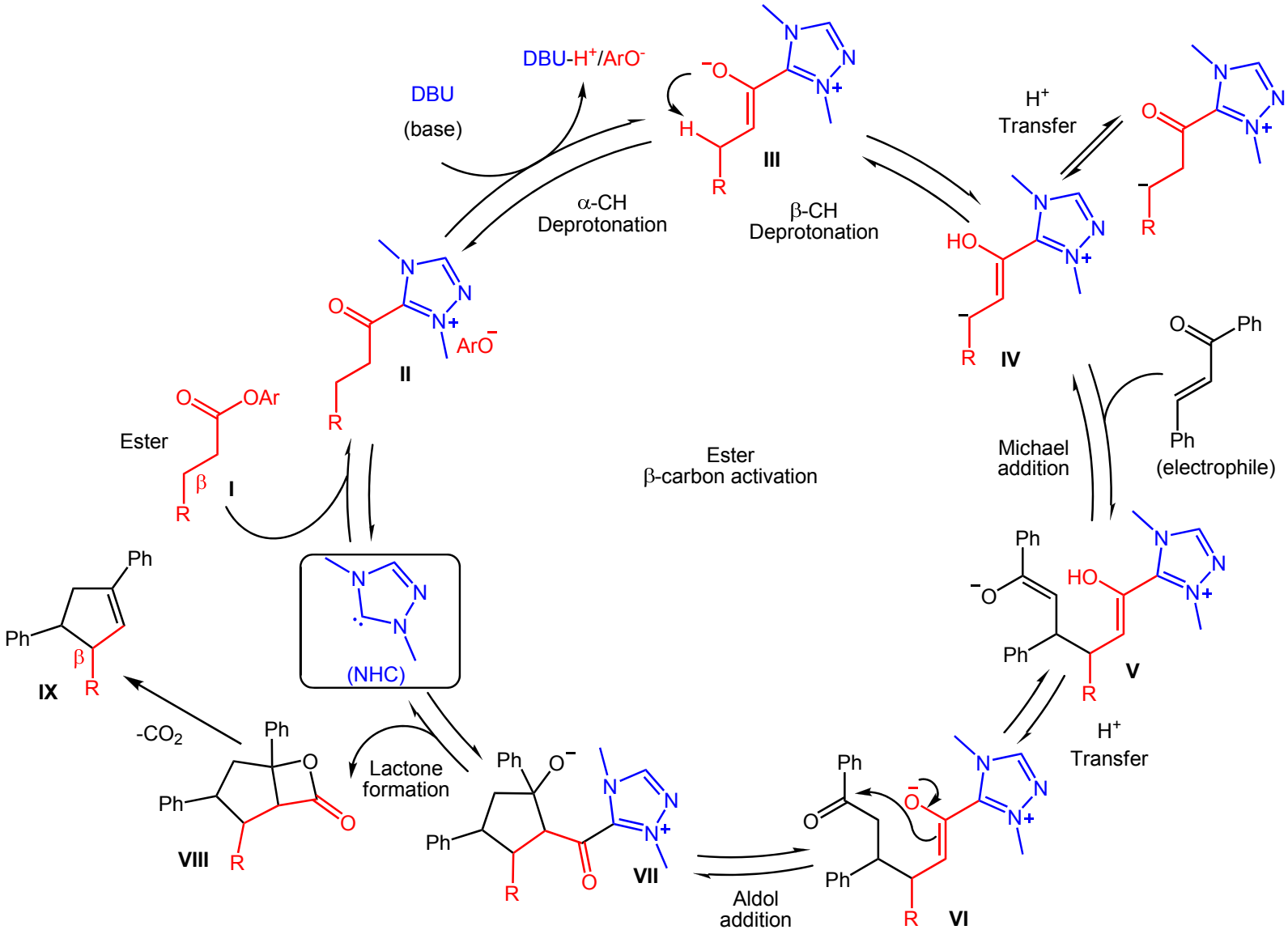
3) Hydrazone as electrophile:



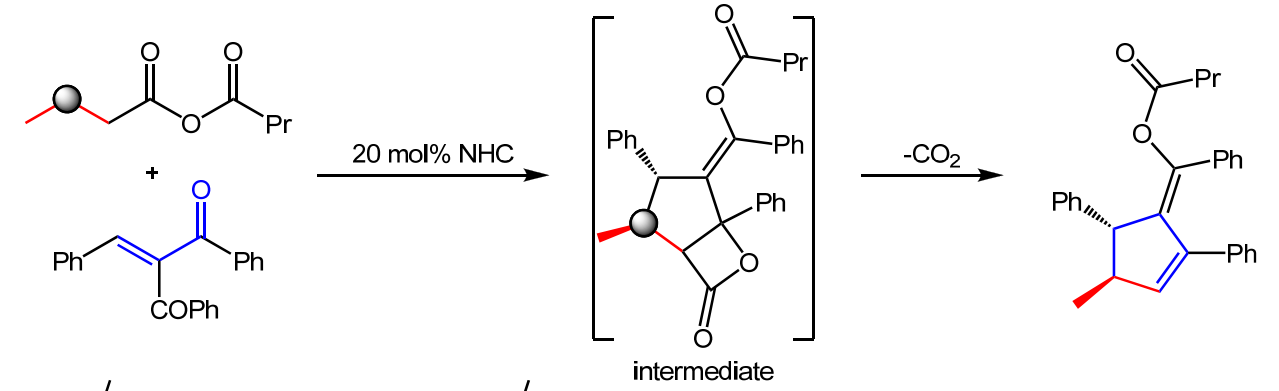
up to 76% yield
up to 7:1 dr
up to 94% ee

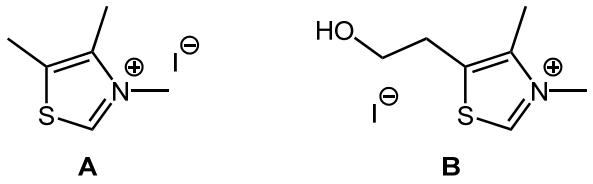
Chi, Y. R. *et al. Nat. Chem.* **2013**, *5*, 835.

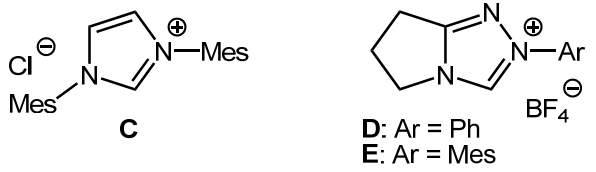
β-Carbon Atom as a Nucleophilic Carbon

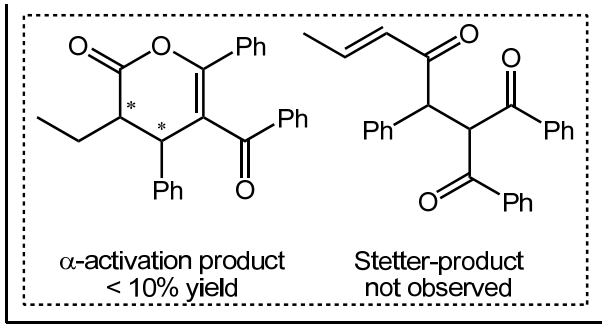


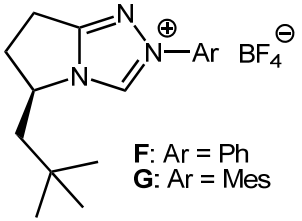
β-Carbon Atom as a Nucleophilic Carbon

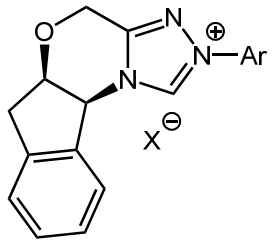












H: Ar = Ph, X = BF_4
I: Ar = Mes, X = BF_4
J: Ar = 2,4-diethylphenyl, X = Cl
K: Ar = 2,4,6-trichlorophenyl, X = Cl
L: Ar = Ph, X = Cl

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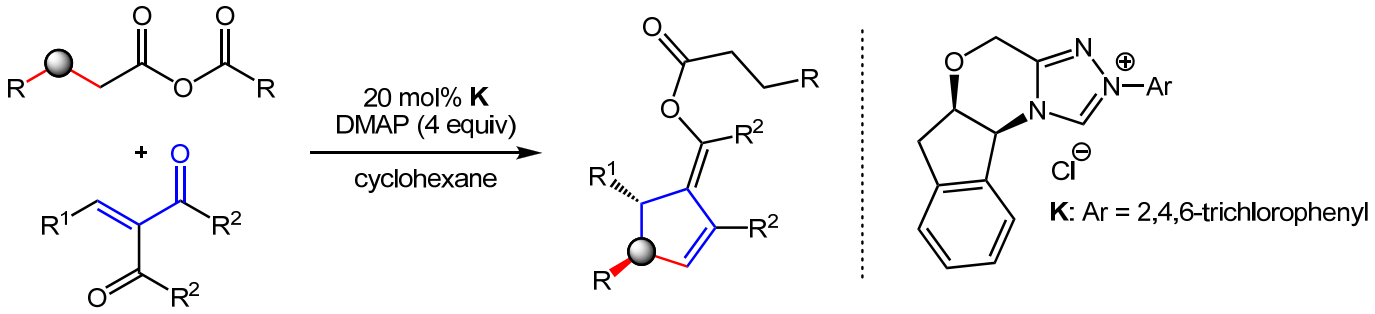
β-Carbon Atom as a Nucleophilic Carbon

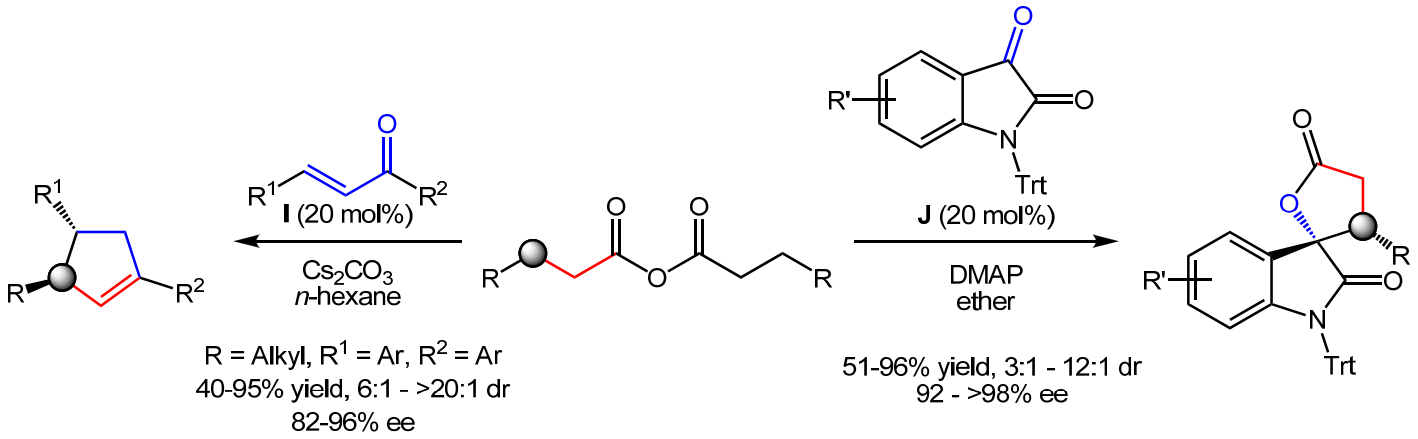
Entry	NHC	Base	Solvent	Yield (%)	Er (%)
1	**A**, **B** or **C**	Cs_2CO_3	ether	0 or <5	-
2	**D**	Cs_2CO_3	ether	< 10	-
3	**E**	Cs_2CO_3	ether	54	-
4	**F**	Cs_2CO_3	ether	< 10	94:6
5	**G**	Cs_2CO_3	ether	73	88:12
6	**H**	Cs_2CO_3	ether	< 10	87:13
7	**I**	Cs_2CO_3	ether	74	81:19
8	**J**	Cs_2CO_3	ether	60	81:19
9	**K**	Cs_2CO_3	ether	22	98:2
10	**L**	Cs_2CO_3	ether	0	-
11	**K**	DMAP	ether	28	96:4
12	**K**	DMAP	hexane	36	94:6
13	**K**	DMAP	cyclohexane	44	96:4
14	**K**	**DMAP**	**cyclohexane**	**61**	**95:5**

β-Carbon Atom as a Nucleophilic Carbon

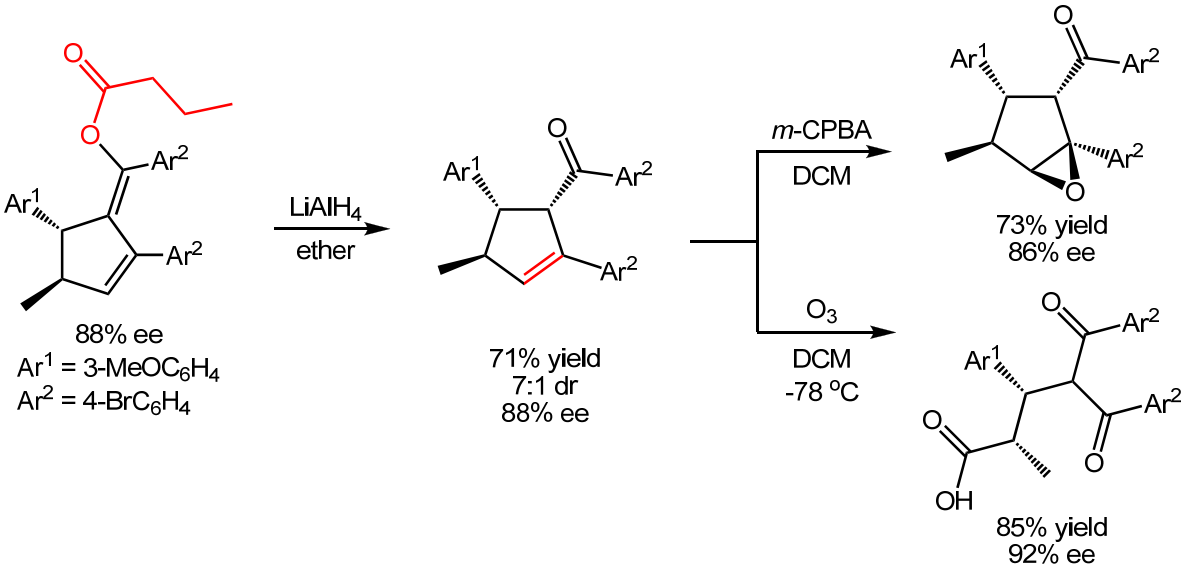


R = Alkyl, R^1 = Ar, R^2 = Ar, 47-75% yield, 88-98% ee
R = Me, R^1 = Me, R^2 = Ph, 0% yield
R = Me, R^1 = Ph, R^2 = Et, 0% yield
R = Ar, R^1 = Ar, R^2 = Ph, 60-72% yield, 62-74% ee

β-Carbon Atom as a Nucleophilic Carbon



β-Carbon Atom as a Nucleophilic Carbon



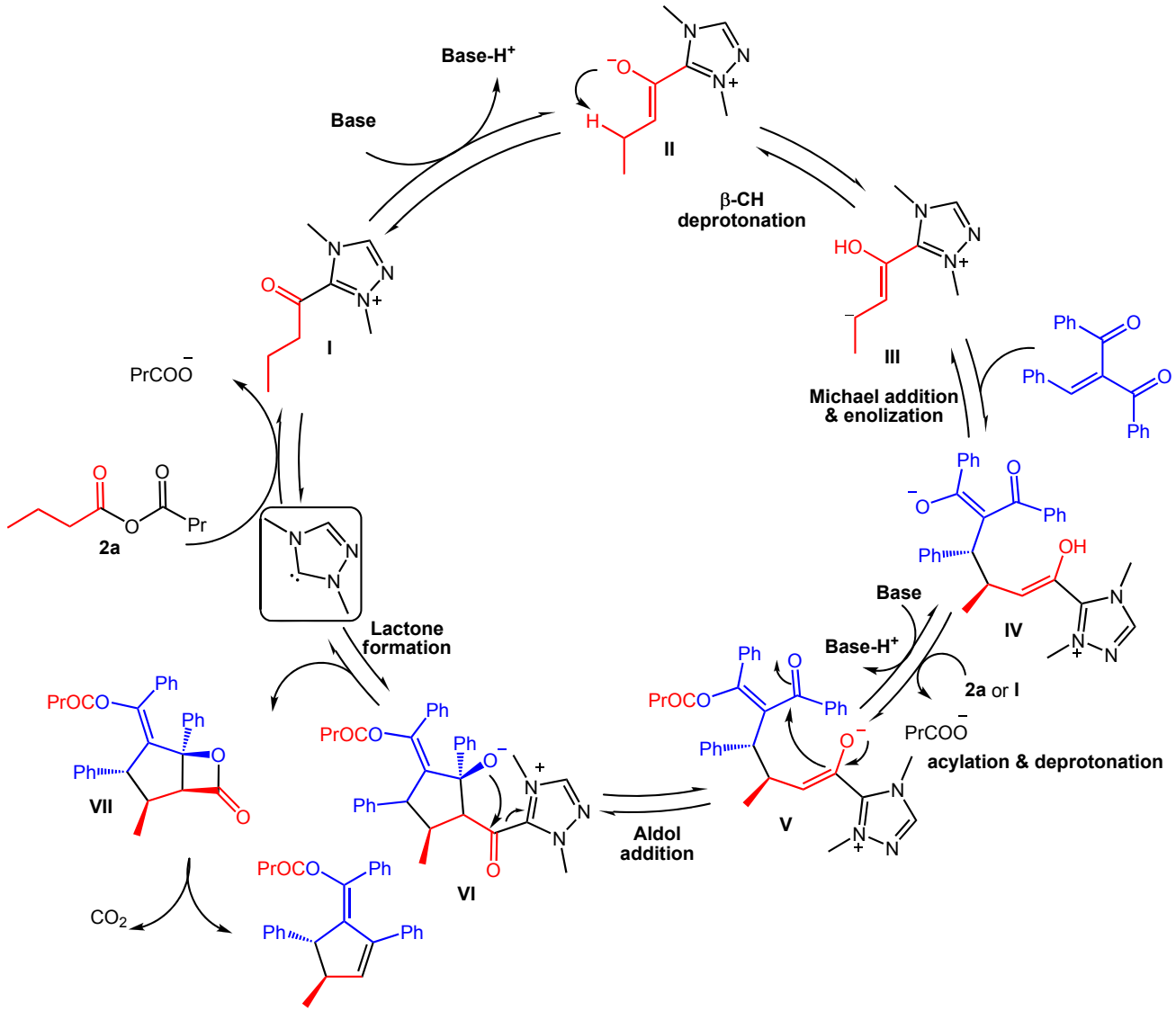
88% ee
Ar^1 = 3-$MeOC_6H_4$
Ar^2 = 4-BrC_6H_4

71% yield
7:1 dr
88% ee

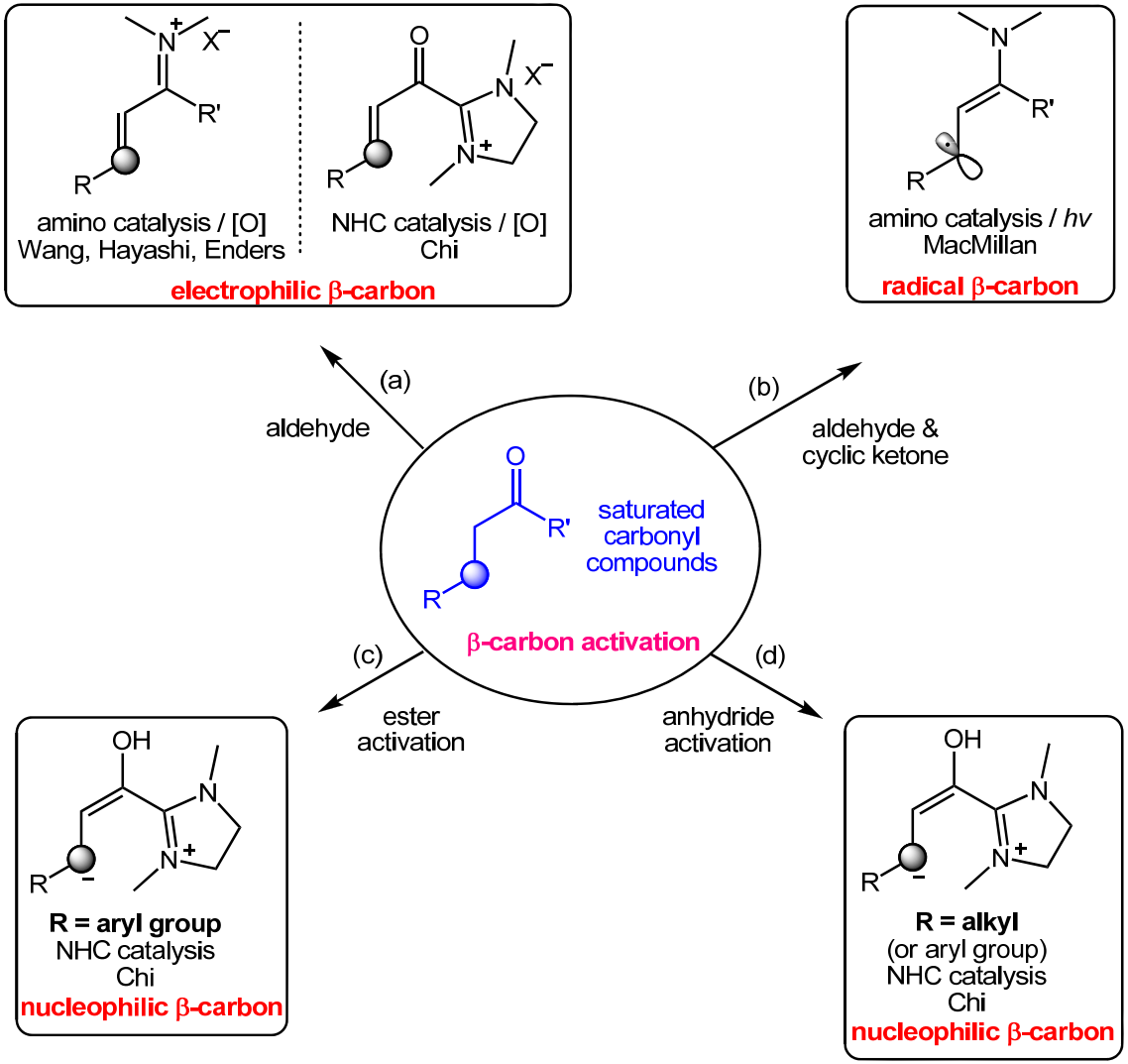
73% yield
86% ee

85% yield
92% ee

β-Carbon Atom as a Nucleophilic Carbon



Summary


amino catalysis / [O]
Wang, Hayashi, Enders
NHC catalysis / [O]
Chi
electrophilic β-carbon
amino catalysis / hv
MacMillan
radical β-carbon
(a)
aldehyde
(b)
aldehyde &
cyclic ketone
saturated
carbonyl
compounds
β-carbon activation
(c)
ester
activation
(d)
anhydride
activation
R = aryl group
NHC catalysis
Chi
nucleophilic β-carbon
R = alkyl
(or aryl group)
NHC catalysis
Chi
nucleophilic β-carbon

Carbonyl compounds are readily available and inexpensive raw materials. The direct functionalization of β carbon atoms of saturated carbonyl compounds can provide a shortcut for the rapid installation of useful functional units, and therefore received intense attention in recent years. Similar to the development of other types of inert chemical bond activations, success in the matter came from transition metal catalysis. In recent years, also organocatalysis was established in the area of inert chemical bond functionalizations. The β carbon atom of a saturated carbonyl compound can be possibly activated as a reactive electrophilic carbon, radical carbon, or nucleophilic carbon.

In 2011, the groups of Hayashi and Wang reported the amino-catalyzed oxidation of saturated aldehydes to the corresponding *α*,β-unsaturated iminium intermediates, in which the formal aldehyde β carbon behaved as an electrophilic reactive carbon. With an *N*-heterocylic carbene (NHC) as the organic catalyst under oxidative conditions the β carbon of a saturated aldehyde can also be activated as an electrophilic carbon, as disclosed in our earlier studies. MacMillan's group has pioneered the activation of the β carbon of saturated aldehydes and ketones as reactive radical carbon through amino catalysis in a single-electron transfer process.

In summary, we have developed the first NHC-catalyzed functionalization of carboxylic anhydrides. The β carbon behaved as a reactive nucleophilic carbon and underwent asymmetric reactions. With this approach, anhydrides with β alkyl substituents work effectively. We expect this study to encourage further explorations in the area of inert chemical bond activations by organocatalysis and to provide additional options for synthetic C-H bond activations.