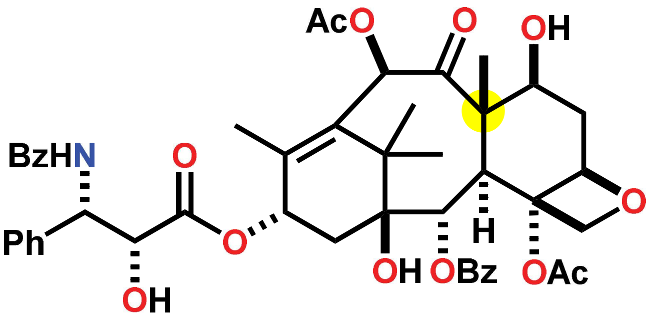
Radical Conjugate Addition

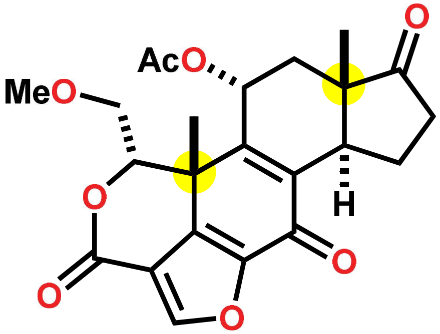
2017.7.8

M2 Daiki Kuwana

Chiral Quaternary Carbon

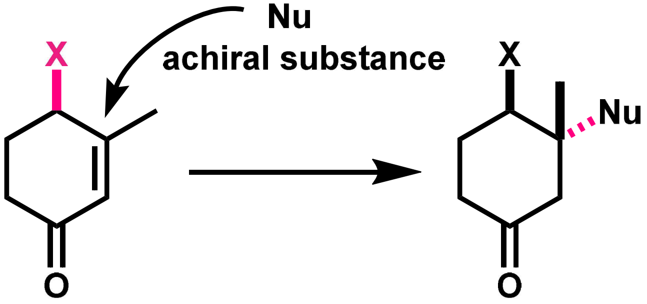


(-)-taxol



(+)-wortmannin

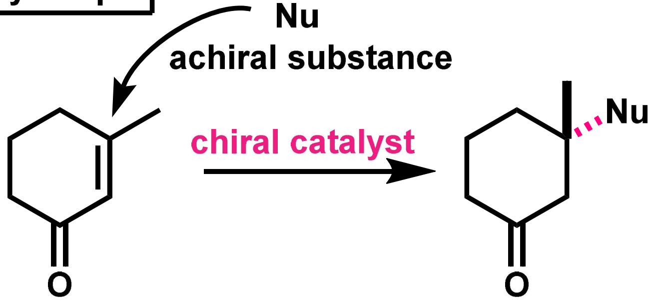
Ways to form chiral quaternary carbon



chiral substance

chiral adduct

today's topic

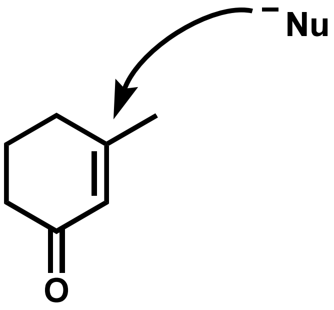


achiral substance

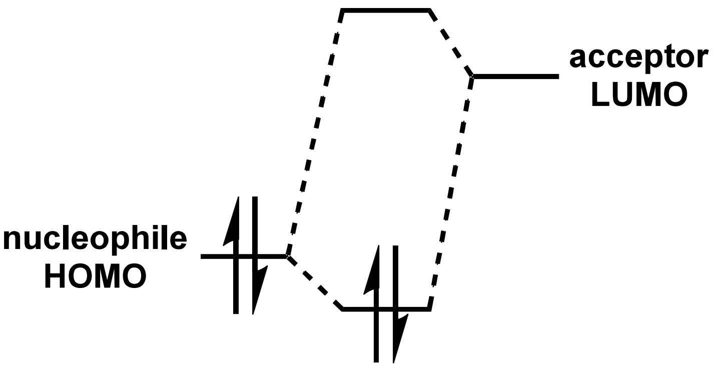
chiral adduct

Radical Conjugate Addition (RCA)

conjugated addition



high reactivity
cryogenic conditions etc.



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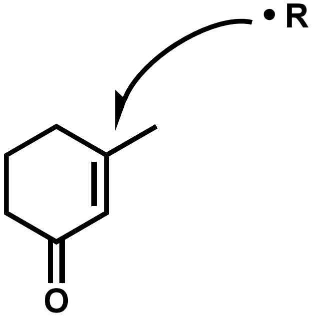
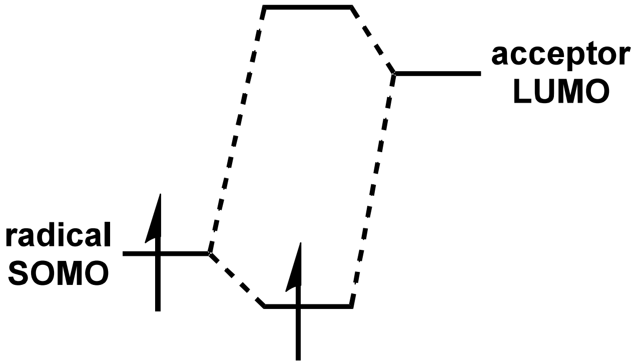
radical conjugated addition



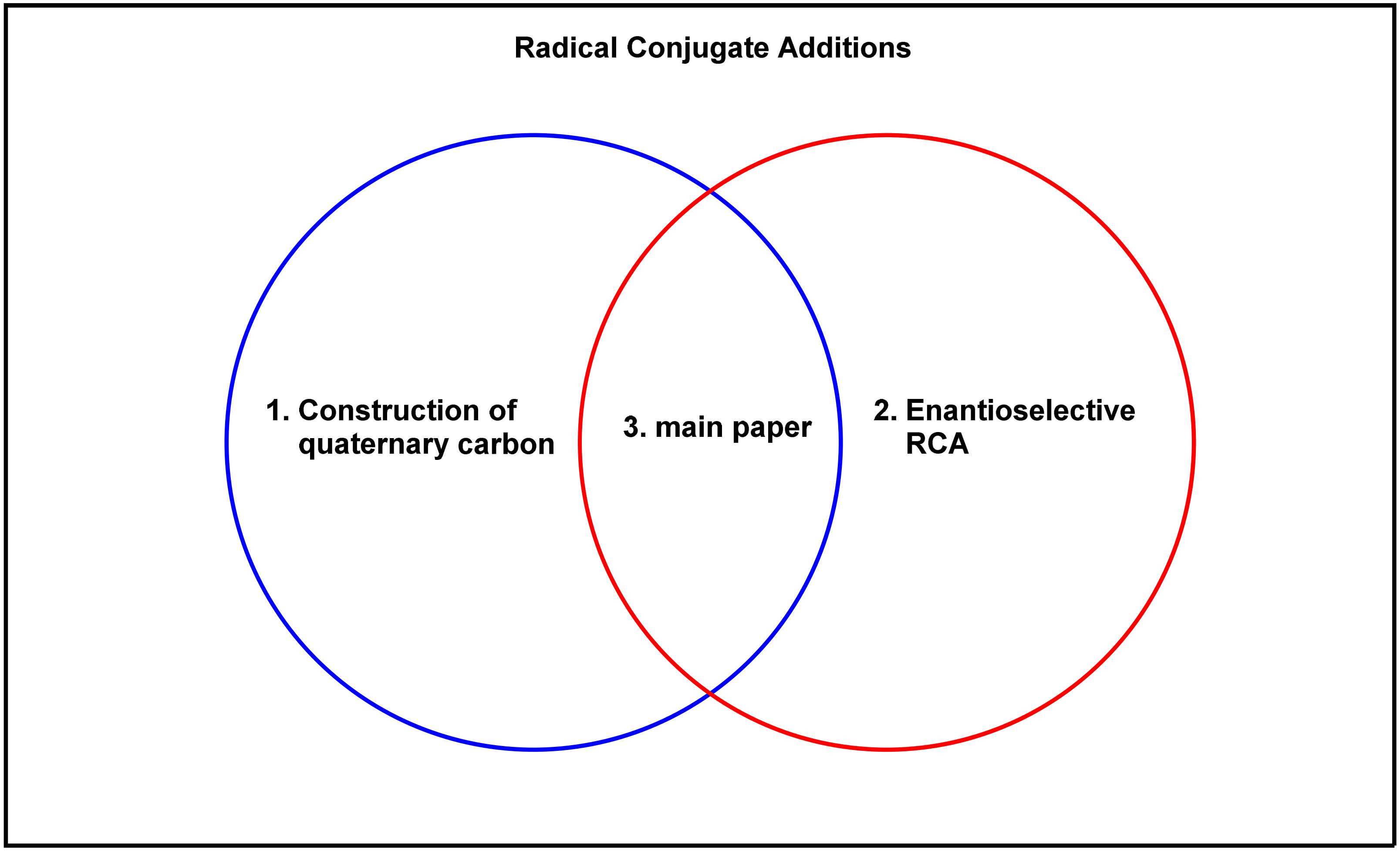
high reactivity
mild conditions



Usually, radicals are viewed as neutral.
But there are "nucleophilic" radicals and "electrophilic" radicals because of polar effect.

Reviews of RCA:
1) Zhang, W. *Tetrahedron* **2001**, *57*, 7237.
2) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377.

Contents



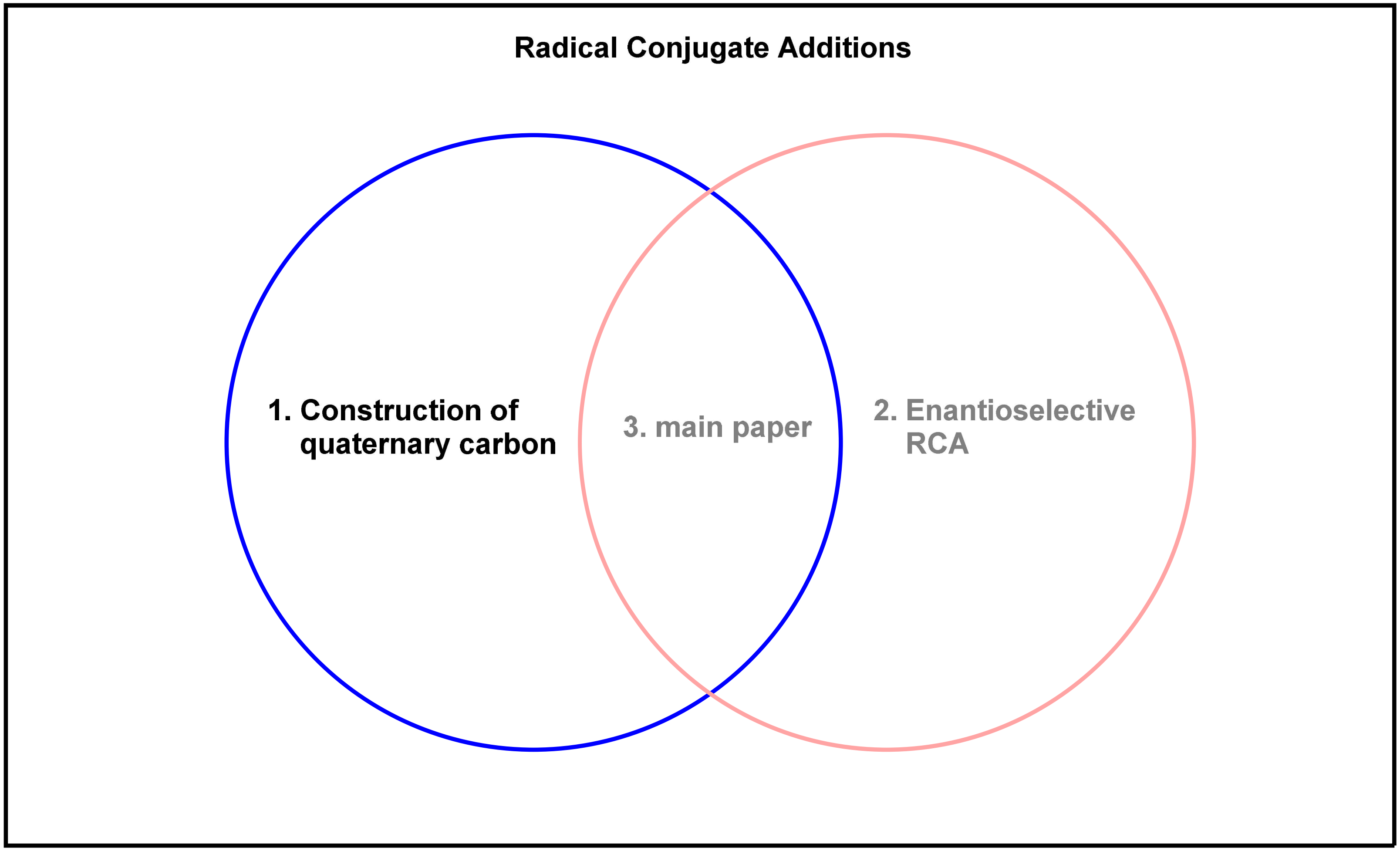
Radical Conjugate Additions

1. Construction of quaternary carbon

3. main paper

2. Enantioselective RCA

Contents



Radical Conjugate Additions

1. Construction of quaternary carbon

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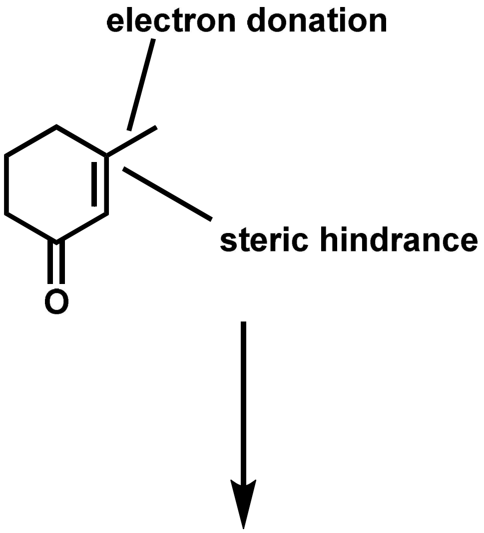
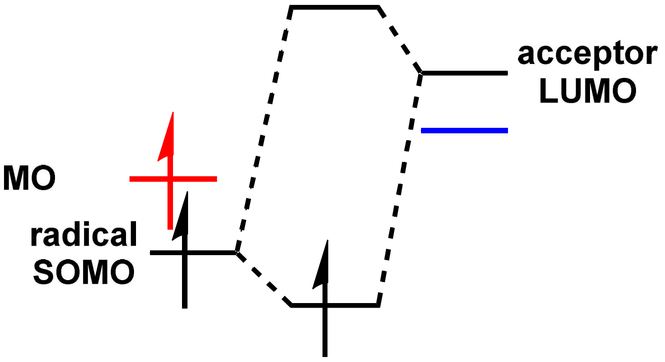
Challenge to Forming Quaternary Carbon



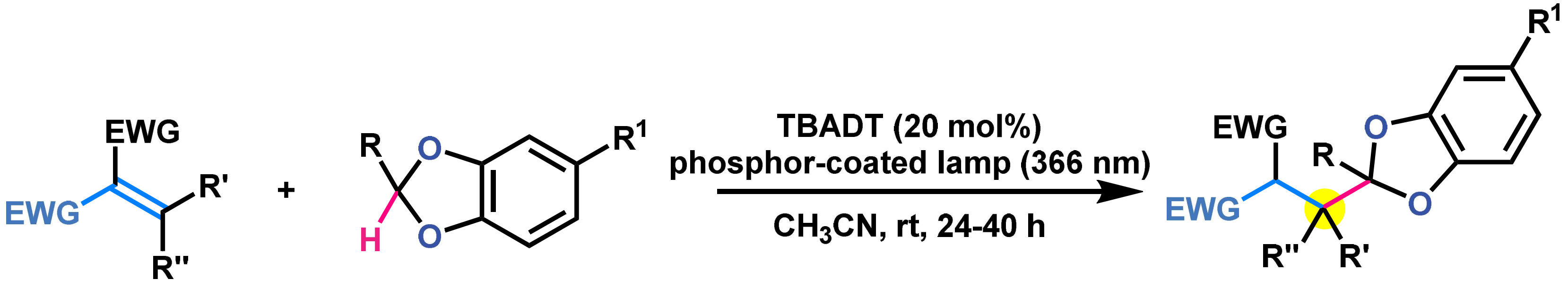
Ways to raise reactivity of radical addition

1. High energy level of radical SOMO

2. Low energy level of radical acceptor LUMO

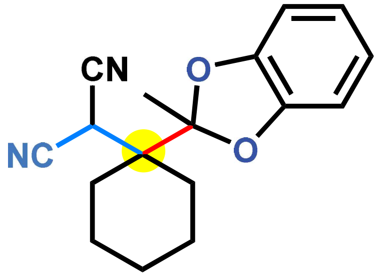


Construction of Quaternary Carbon (2)

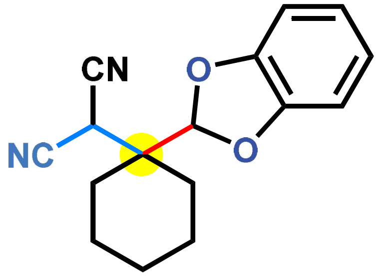


TBADT (20 mol%)
phosphor-coated lamp (366 nm)

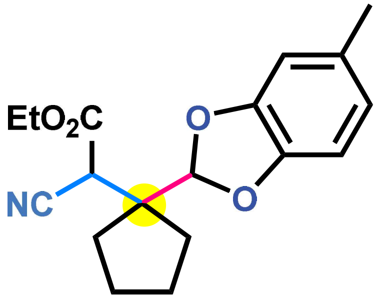
CH_3CN, rt, 24-40 h



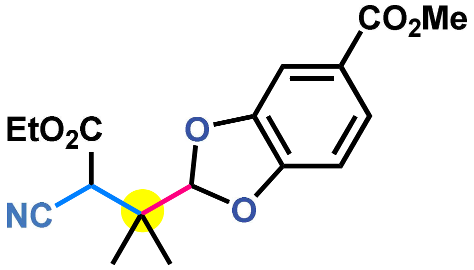
77%



66%

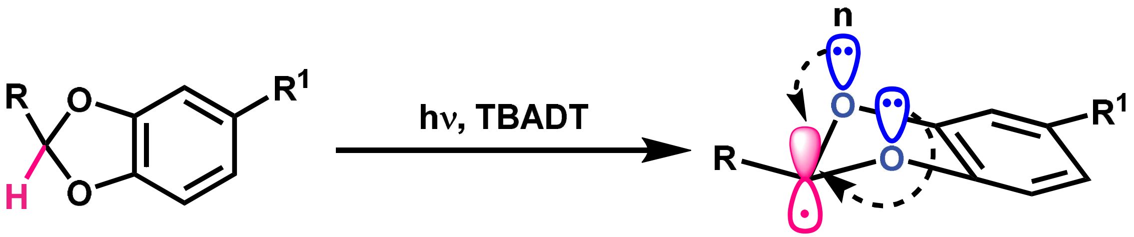


70%



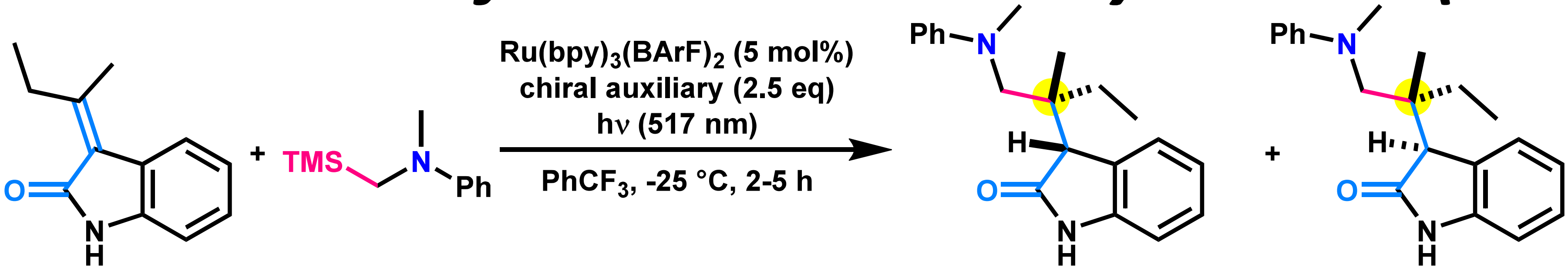
65%

TBADT = $(n\text{-}Bu_4N)_4\,W_{10}O_{32}$



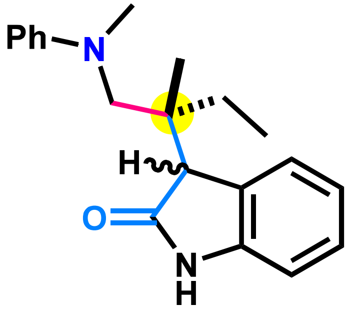
1) Ravelli, D.; Albini, A.; Fagnoni, M. *Chem. Eur. J.* **2011**, *17*, 572.

Construction of Chiral Quaternary Carbon (1-1)

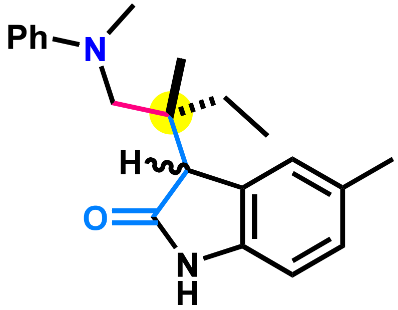


$Ru(bpy)_3(BArF)_2$ (5 mol%)
chiral auxiliary (2.5 eq)
hν (517 nm)
$PhCF_3$, -25 °C, 2-5 h

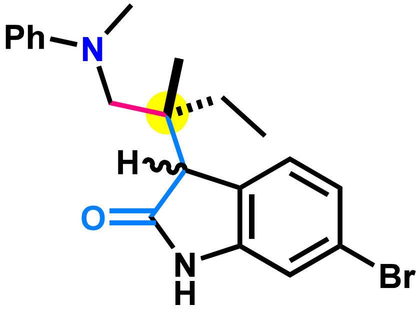
a-d **epi-a-d**



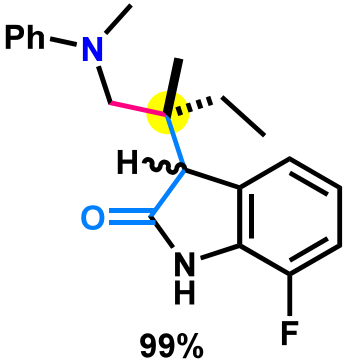
99%
a:*epi*-a = 1.3:1
a: 62% ee, *epi*-a: 66% ee



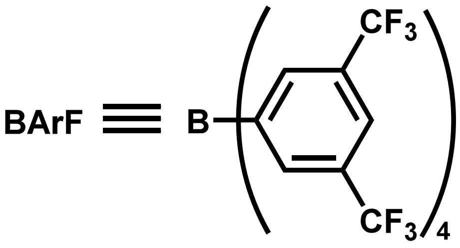
88%
b:*epi*-b = 1.4:1
b: 58% ee, *epi*-b: 59% ee

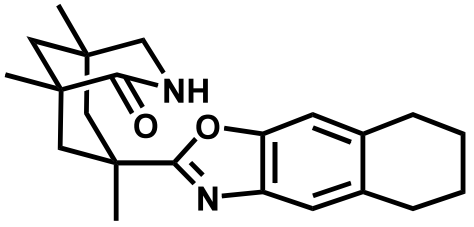


94%
b:*epi*-b = 1.5:1
b: 69% ee, *epi*-b: 68% ee



99%
d:*epi*-d = 1.5:1
b: 63% ee, *epi*-b: 64% ee

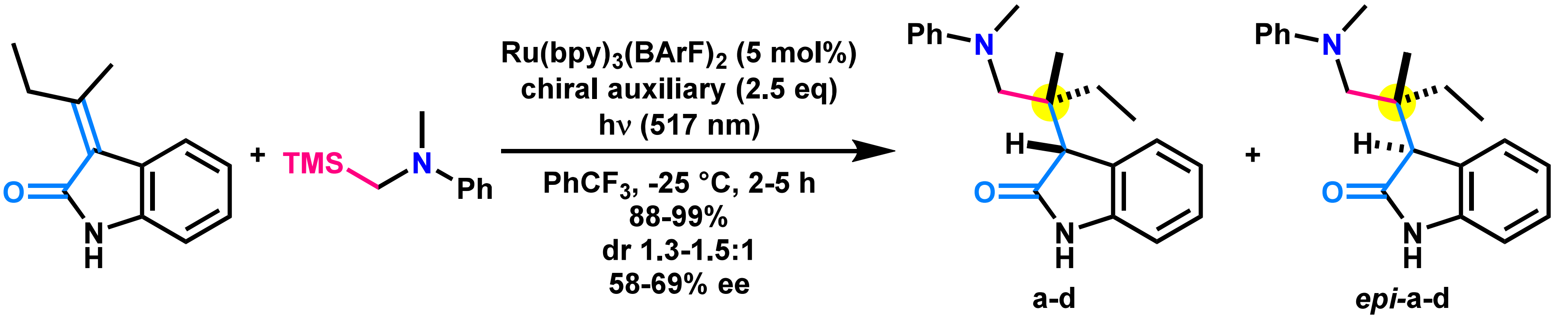


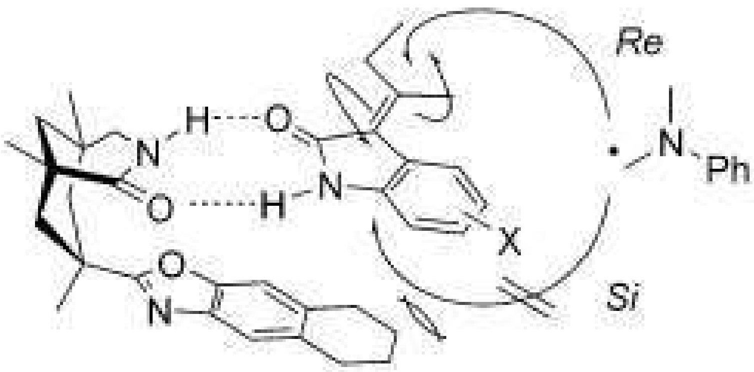


chiral auxiliary

1) Lenhart, D.; Bauer, A.; Pöthig, A.; Bach, T. *Chem. Eur. J.* **2016**, *22*, 6519.

Construction of Chiral Quaternary Carbon (1-2)





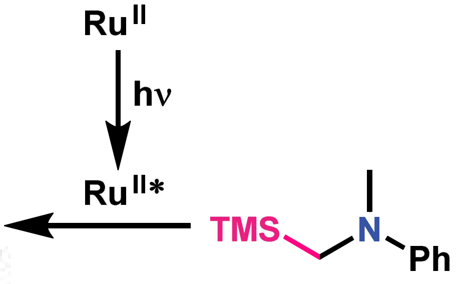


Figure 4. Model for enantioface differentiation in a 1:1 complex of template 1 and substrate (*Z*)-**7**.

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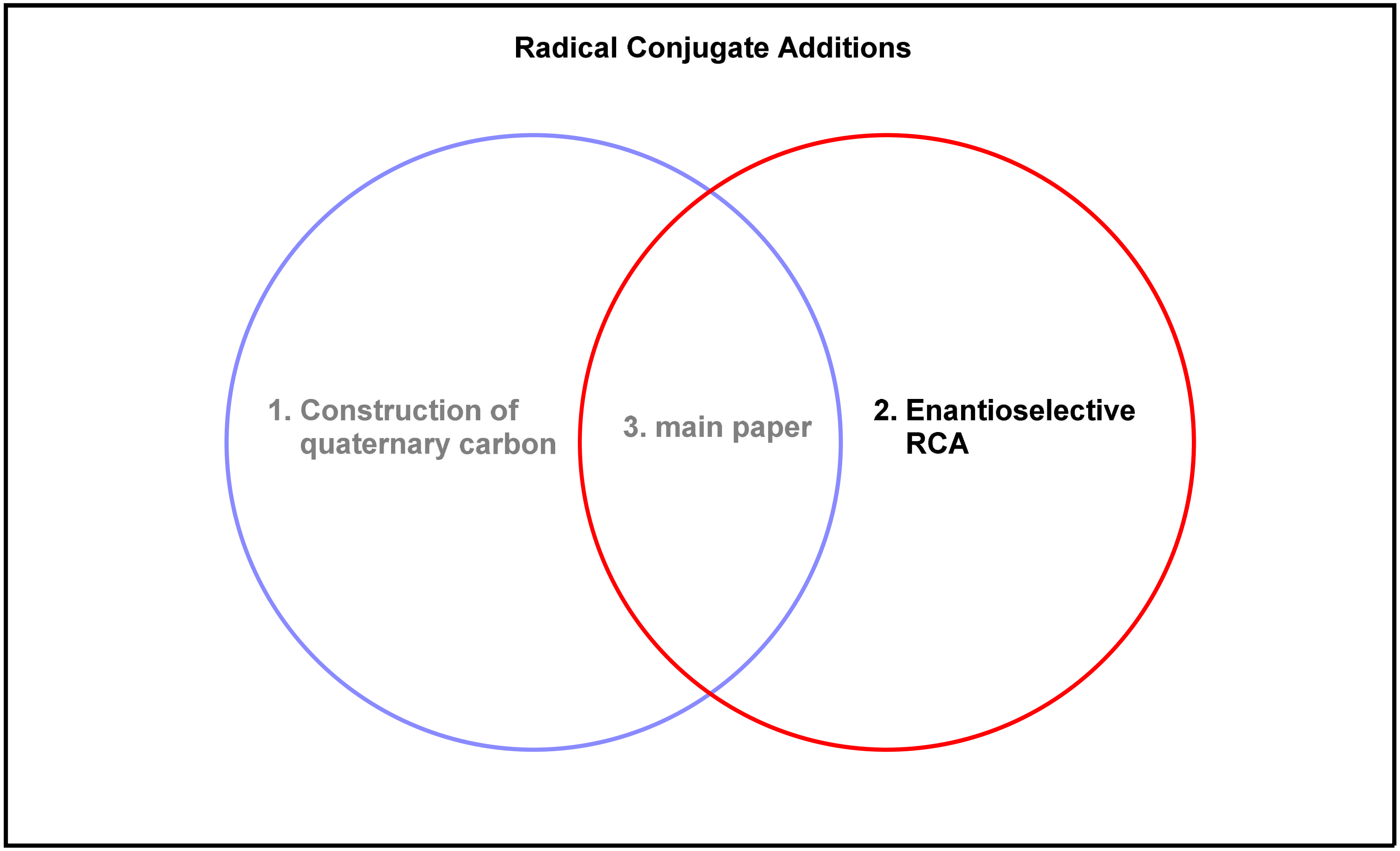
1) Lenhart, D.; Bauer, A.; Pöthig, A.; Bach, T. *Chem. Eur. J.* **2016**, *22*, 6519.

Contents



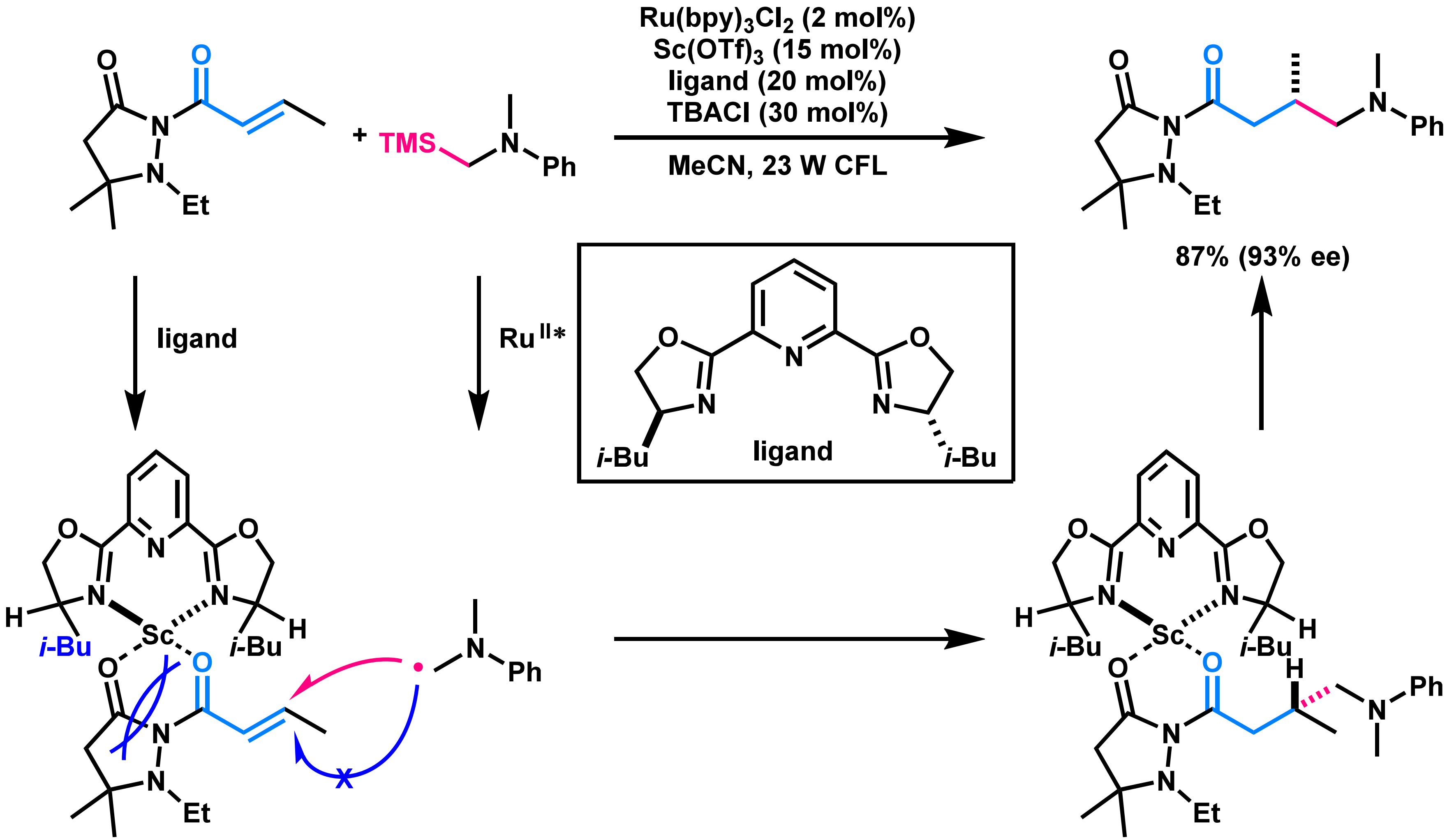
Radical Conjugate Additions

1. Construction of quaternary carbon

3. main paper

2. Enantioselective RCA

Metal-catalyzed Asymmetric RCA



$Ru(bpy)_3Cl_2$ (2 mol%)
$Sc(OTf)_3$ (15 mol%)
ligand (20 mol%)
TBACl (30 mol%)

MeCN, 23 W CFL

87% (93% ee)

---

1) Espelt, R. L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452.
2) 160521_LS_Benjamin_Ovadia

Prof. Paolo Melchiorre

1973	**Born in Camerino (Italy)**
1993-99	**B.S. University of Bologna (Italy)**
2002	**Research Period at Centre for Catalysis at University of Arhus (Denmark)** **(working with Prof. Karl Anker Jørgensen)**
2003	**P.D. at Bologna University** **(under direction of Prof. Achille Umani-Ronchi)**
2003-06	**Postdoctoral associate with Prof. Giuseppe Bartoli** **(Industrial Chemistry Faculty of the Bologna University)**
2007-09	**Assistant Professor at Bologna University**
2009-	**Professor at the Institute of Chemical Research of Catalonia (ICIQ)-Tarragona (Spain)**

Research Project

i) Controlling the stereochemical outcome of catalytic photochemical reactions driven by visible light

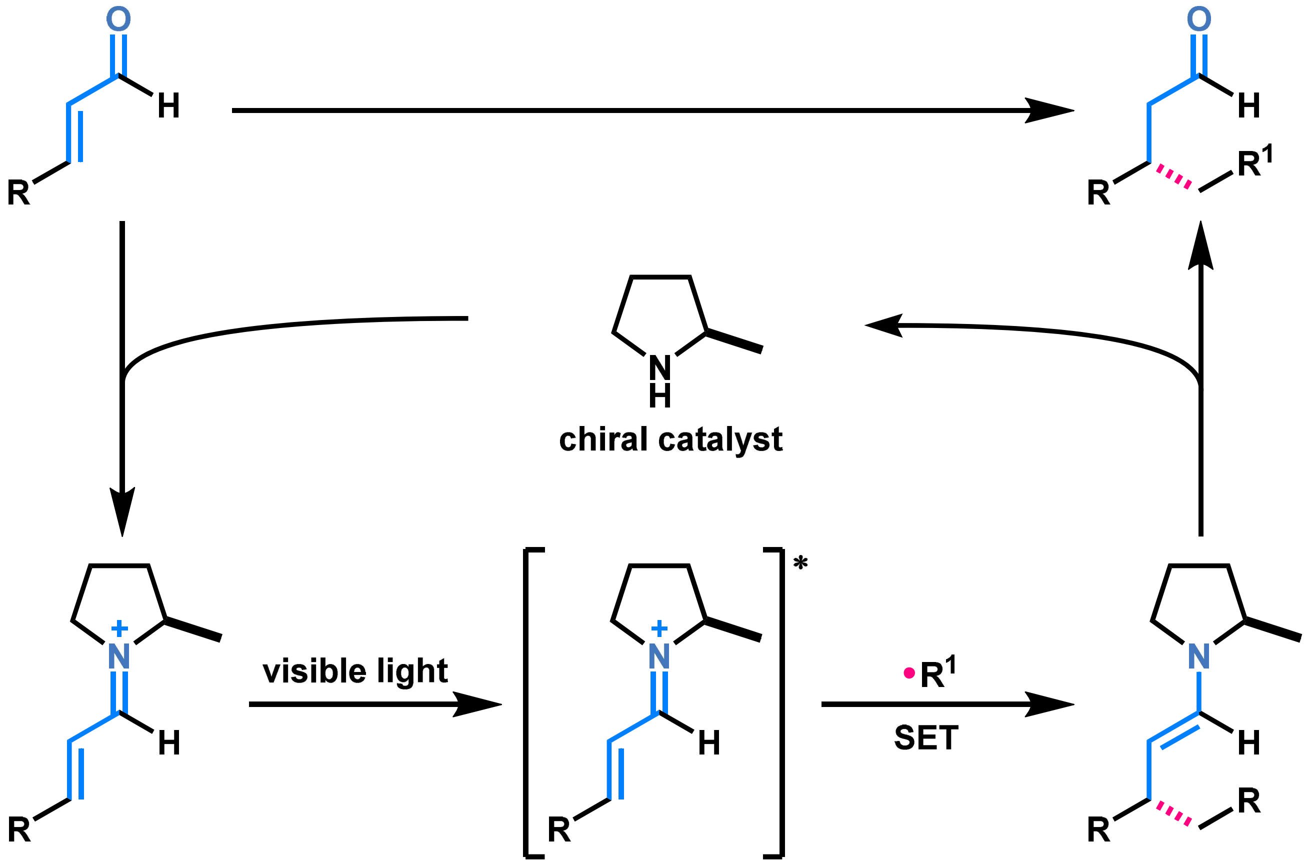
+

ii) Photo-organocatalysis and energy transfer

↓

Fundamental carbon-carbon bond-forming transformations in an environmentally respectful way

Organocatalysis



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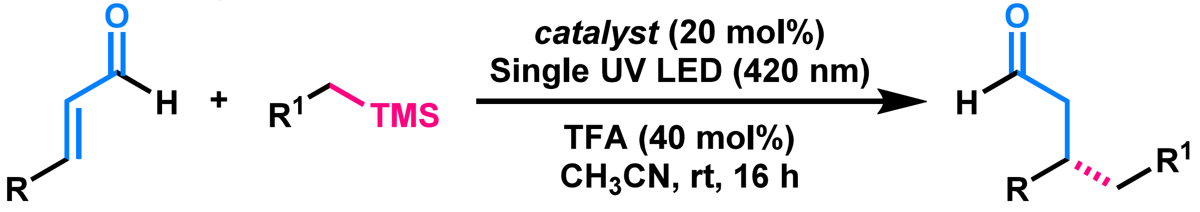
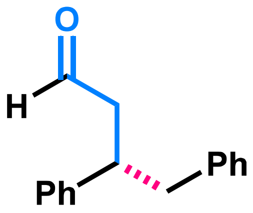
1) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem. in press*.

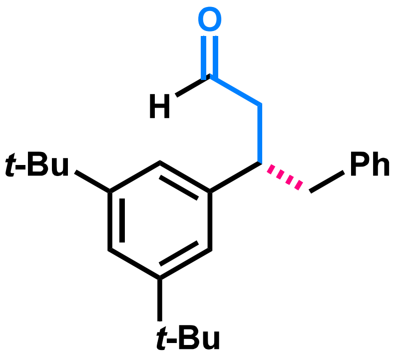
Asymmetric RCA to Enal



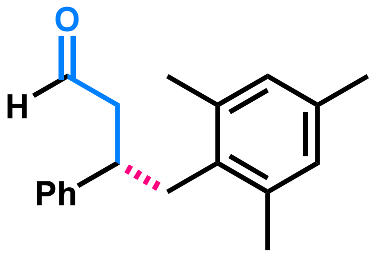
catalyst (20 mol%)
Single UV LED (420 nm)
TFA (40 mol%)
CH_3CN, rt, 16 h



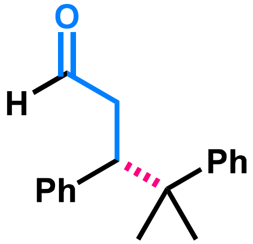
87% (88% ee)



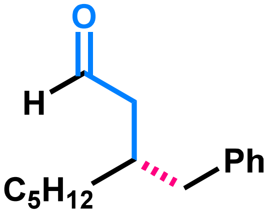
63% (68% ee)



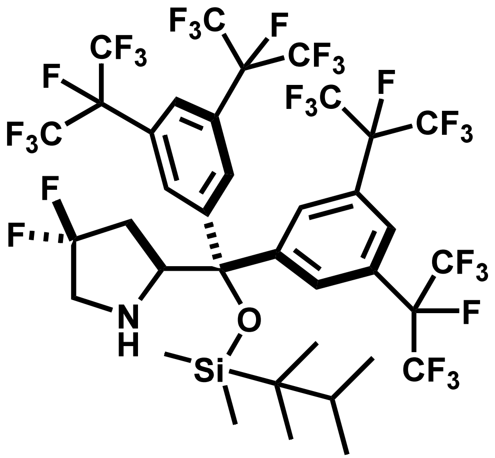
93% (93% ee)



46% (71% ee)



0%



catalyst

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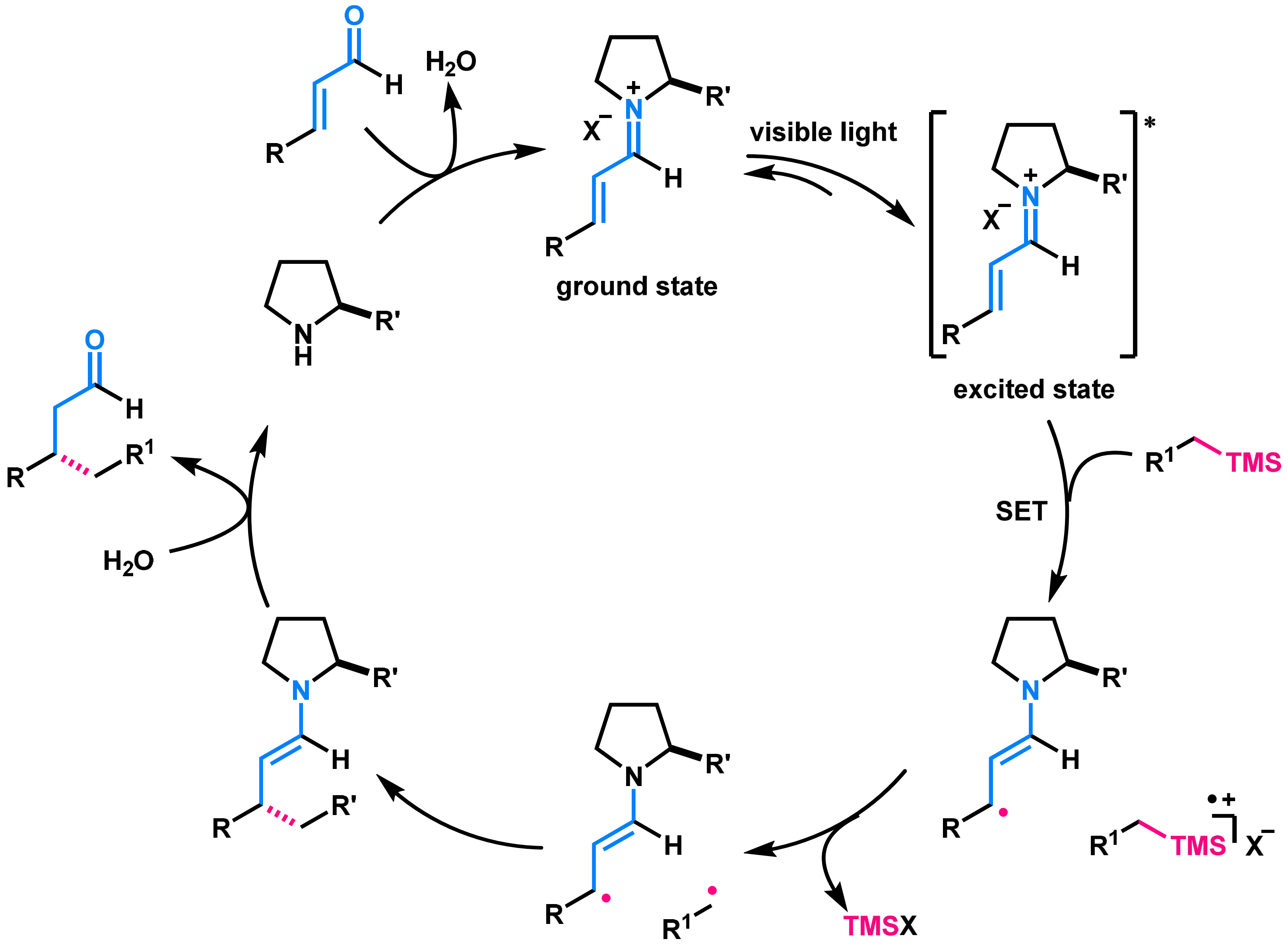
1) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem. in press*.

Catalytic Cycle



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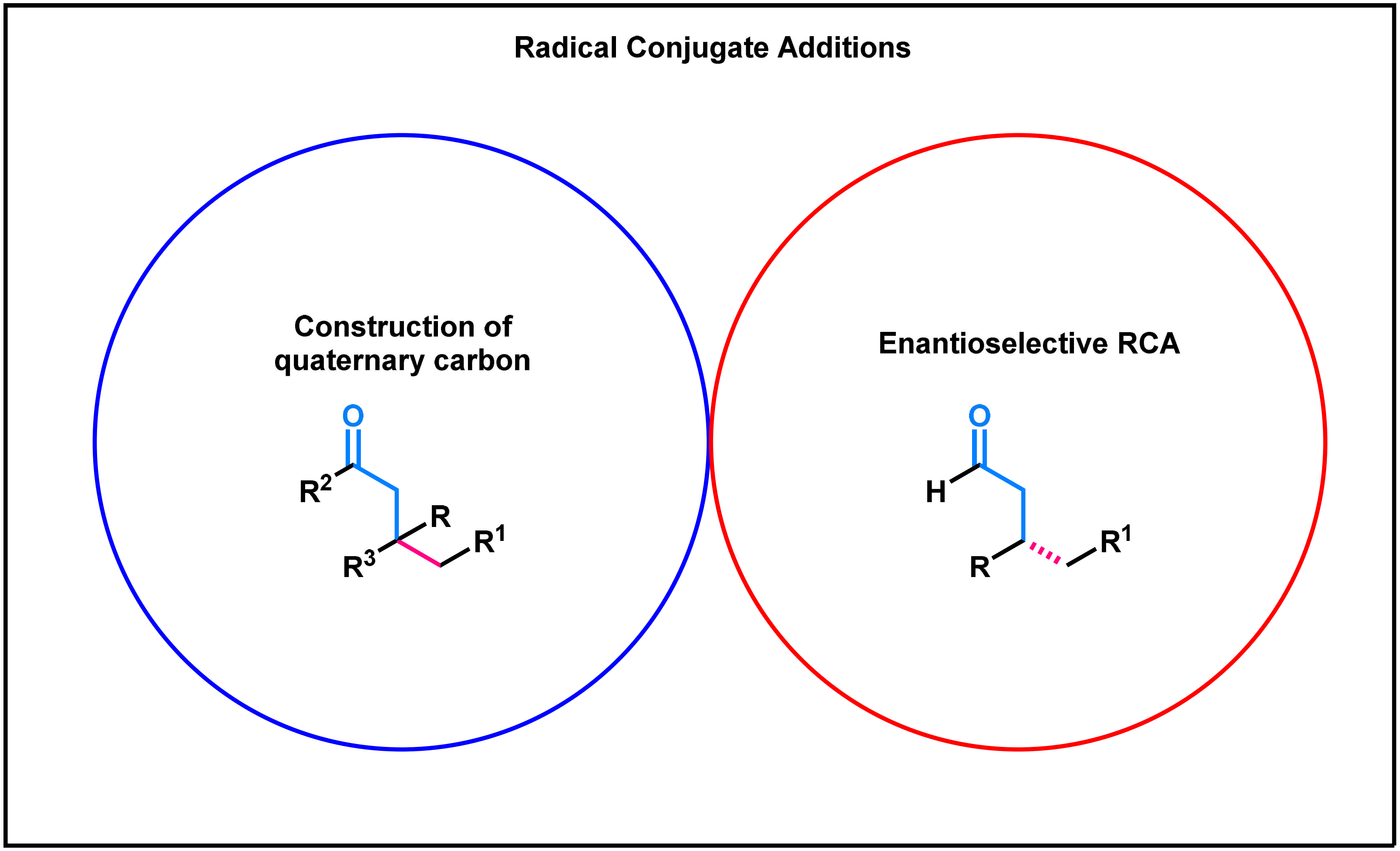
1) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem. in press*.

Short Summary

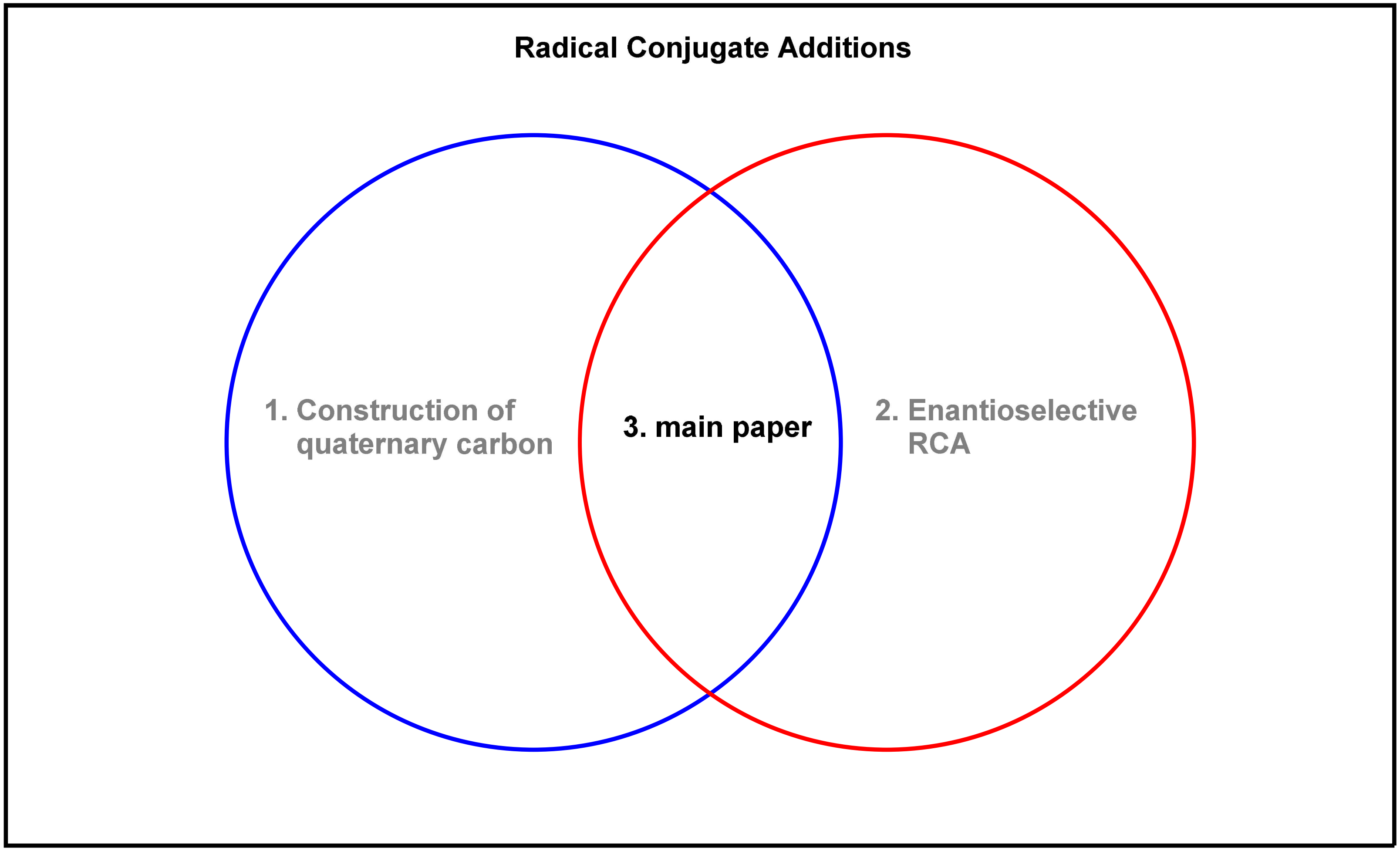


Radical Conjugate Additions

Construction of quaternary carbon

Enantioselective RCA

Contents



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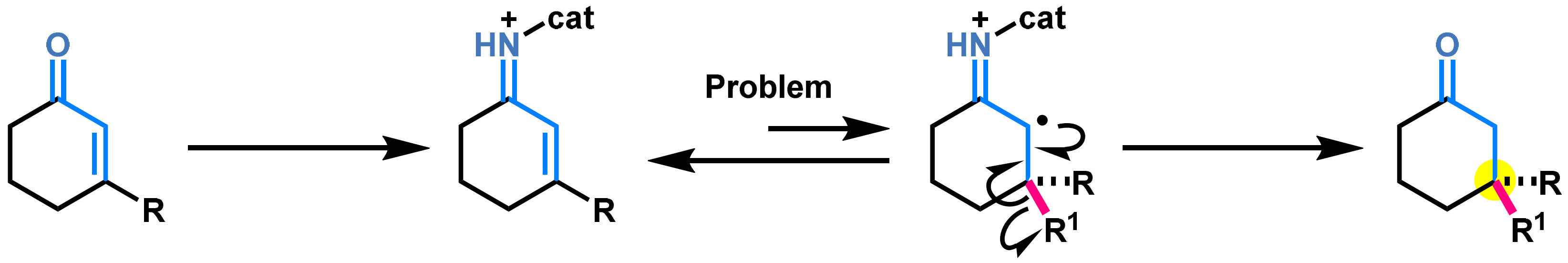
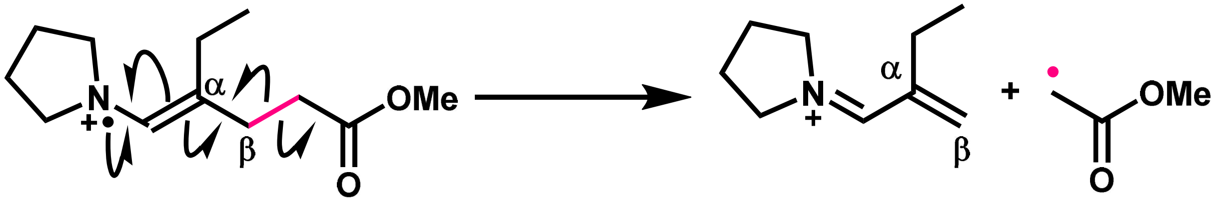
Iminium Ion Activation & Problem



Problem



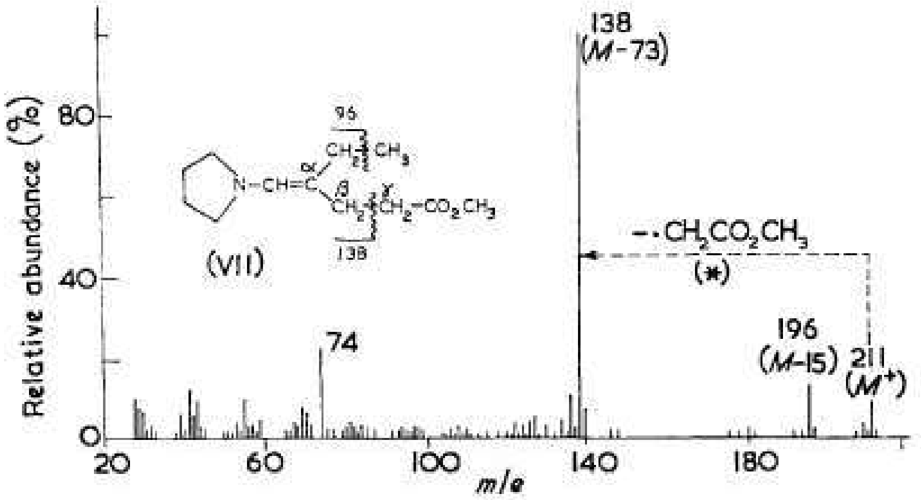


FIGURE 3

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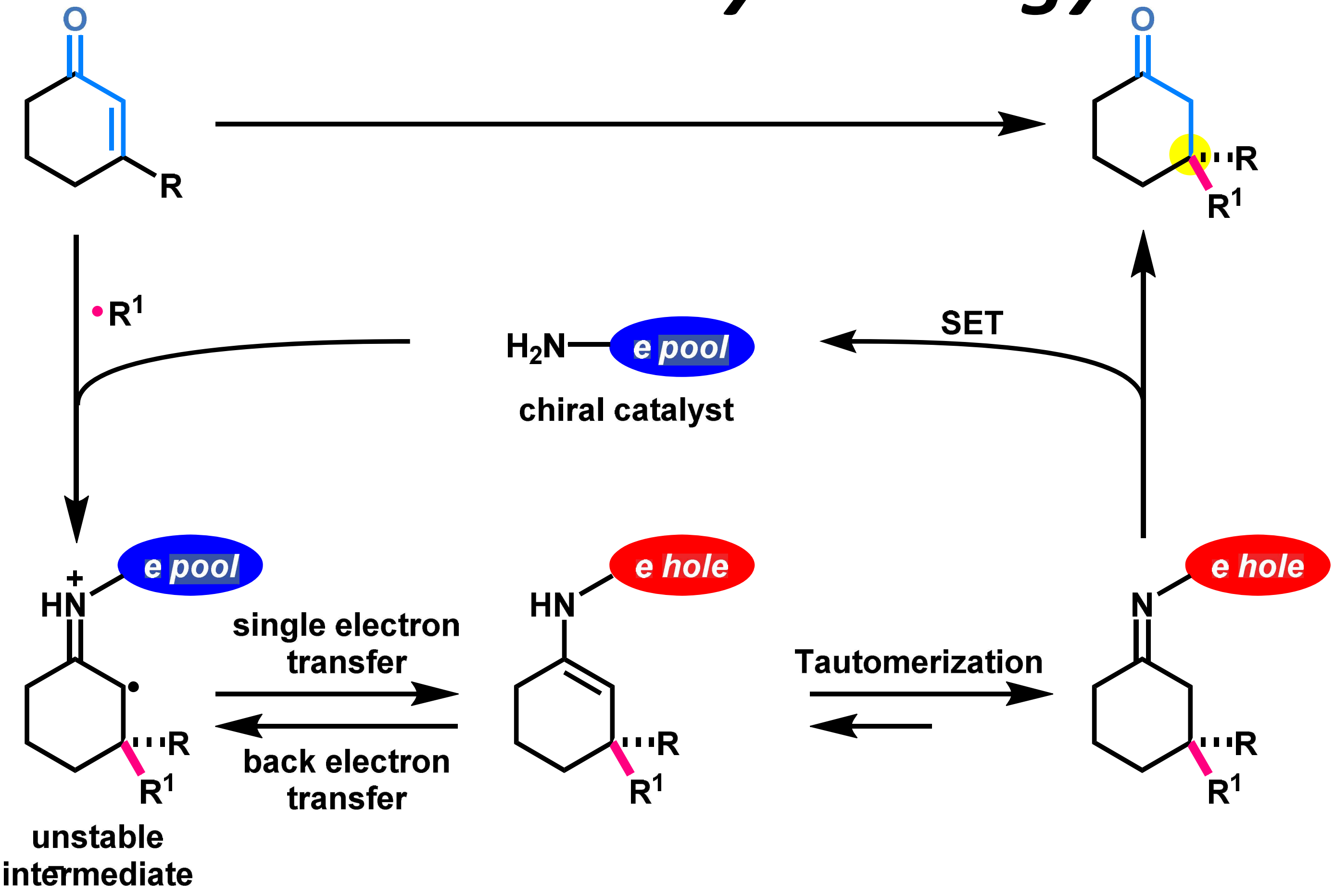
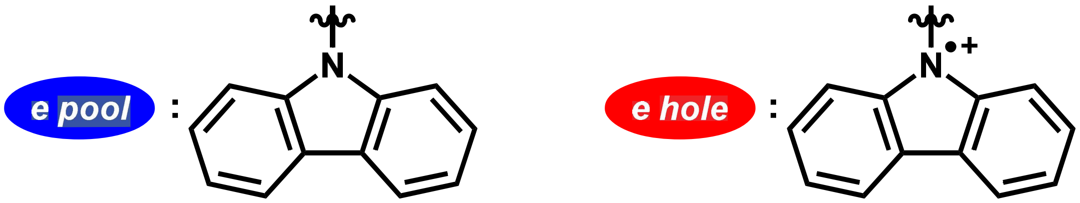
1) Jakobsen, H. J.; Lawesson, S.-O.; Marshall, J. T. B.; Schroll, G.; Williams, D. H. *J. Chem, Soc. B*. **1966**, 940.

Electron-Relay Strategy



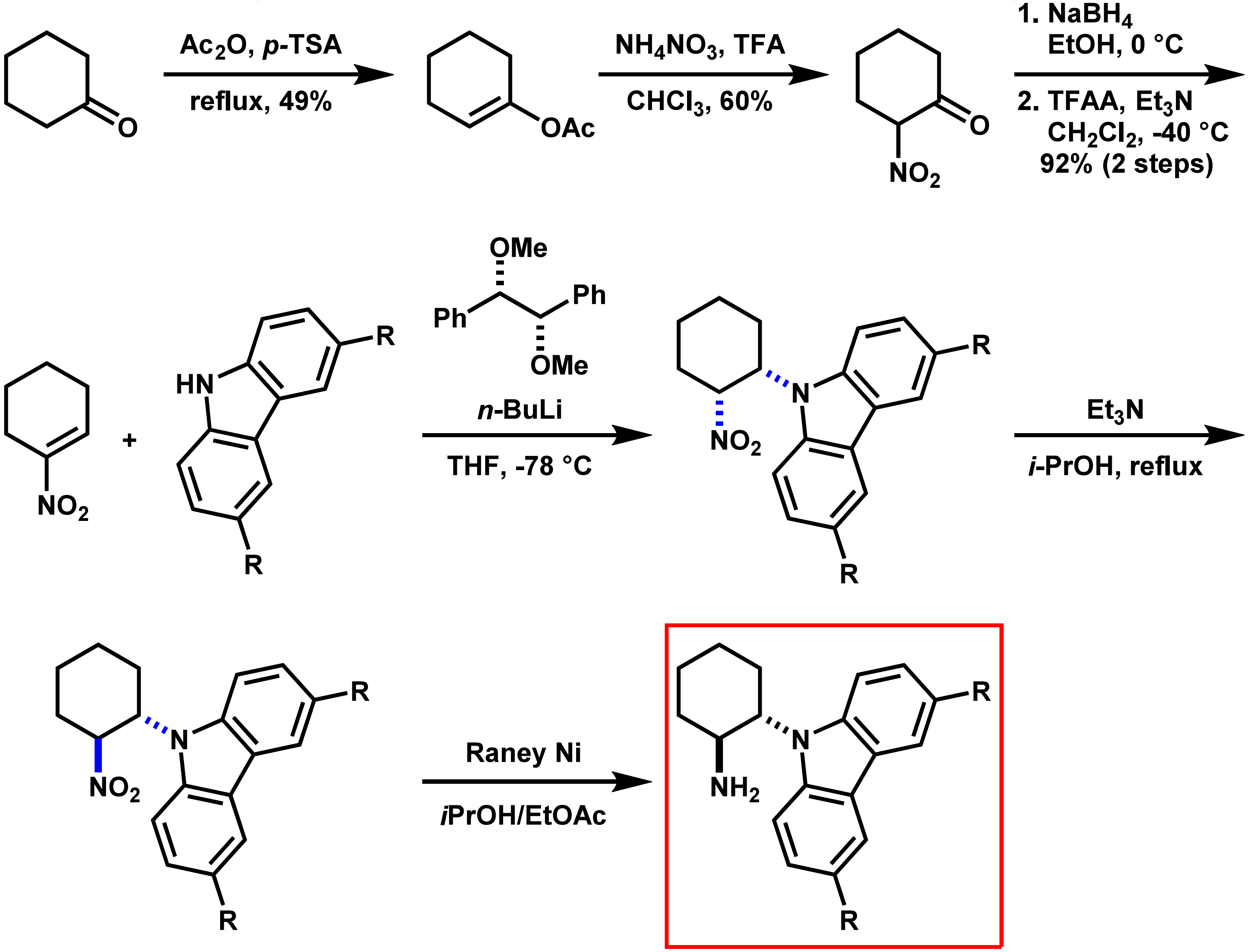


high electron donating capability

high stability

1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Preparation of Chiral Catalyst



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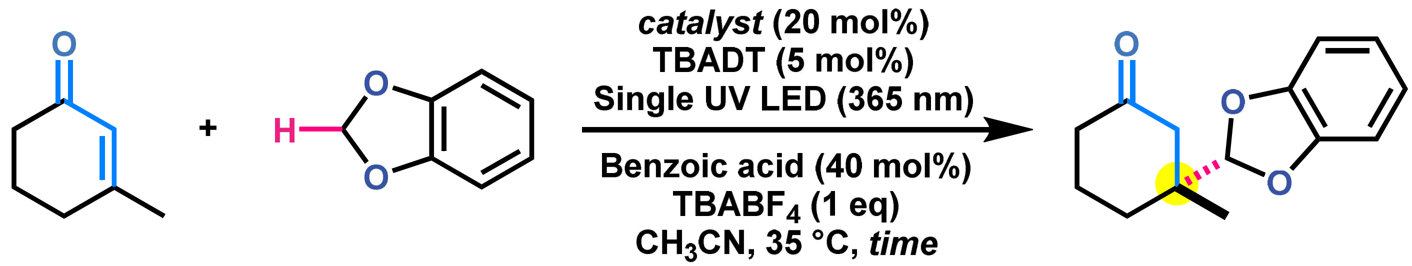
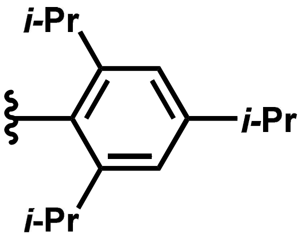
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Optimization of Catalyst

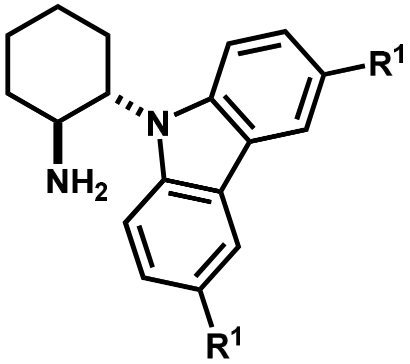


catalyst (20 mol%)
TBADT (5 mol%)
Single UV LED (365 nm)

Benzoic acid (40 mol%)
$TBABF_4$ (1 eq)
CH_3CN, 35 °C, *time*

entry	*catalyst* (R^1)	*time* (h)	reduction potential vs. Ag/AgCl (V)	yield (%)	ee (%)
1	H	48	+1.23	33	82
2	*t*-Bu	48	+1.16	35	84
3	CF_3	48	+1.68	52	77
4		48	+1.24	46	93
5		84	+1.24	75	93

catalyst



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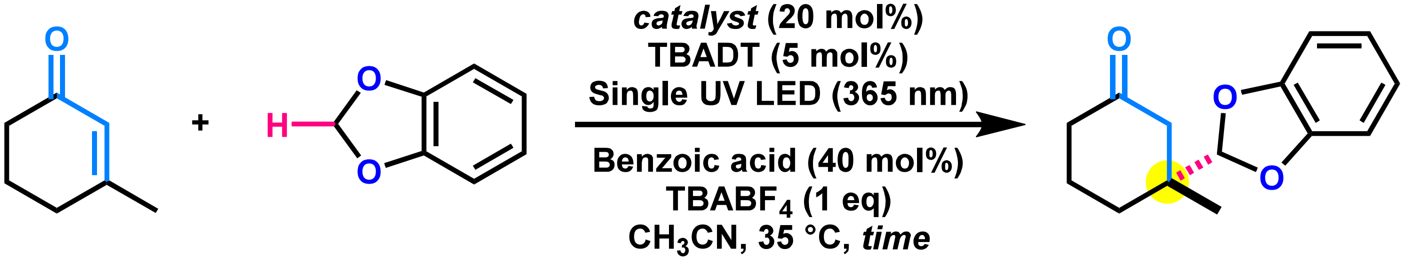
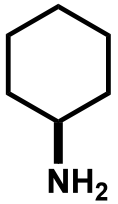
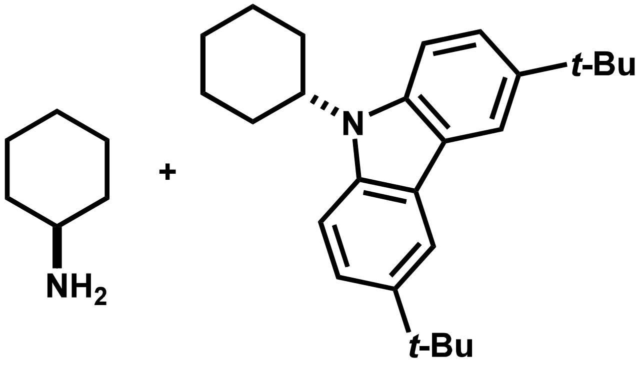
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Control Experiment



catalyst (20 mol%)
TBADT (5 mol%)
Single UV LED (365 nm)

Benzoic acid (40 mol%)
$TBABF_4$ (1 eq)
CH_3CN, 35 °C, *time*

entry	*catalyst*	*time* (h)	reduction potential vs. Ag/AgCl (V)	yield (%)	ee (%)
6	None	48	NA	trace	ND
7[a]		48	NA	4	0
8[a]		48	NA	5	0

a. **TFA (40 mol%) was used instead of benzoic acid.**

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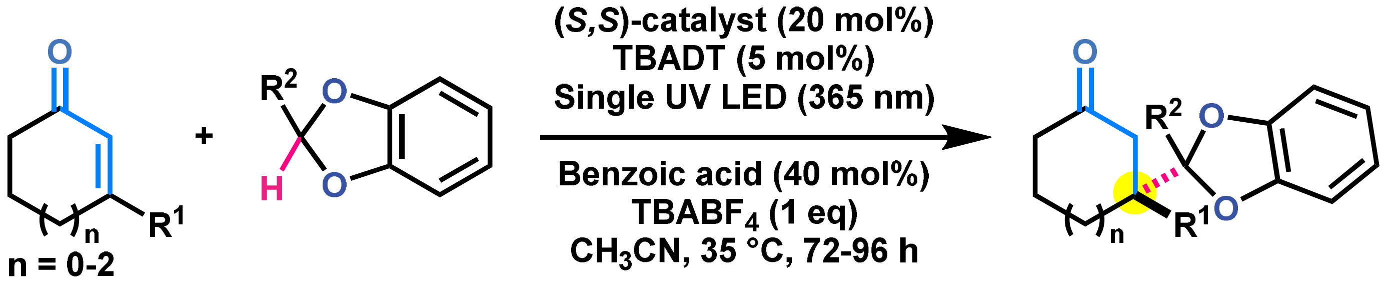
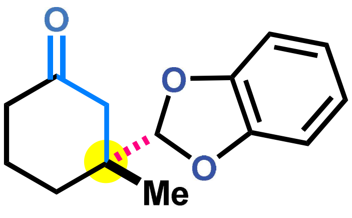
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Substrate Scope

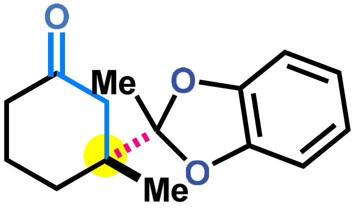


(*S,S*)-catalyst (20 mol%)
TBADT (5 mol%)
Single UV LED (365 nm)

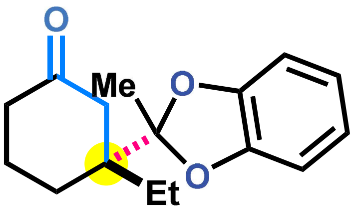
Benzoic acid (40 mol%)
TBABF$_4$ (1 eq)
CH_3CN, 35 °C, 72-96 h



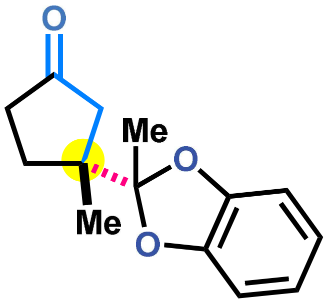
75% (93% ee)



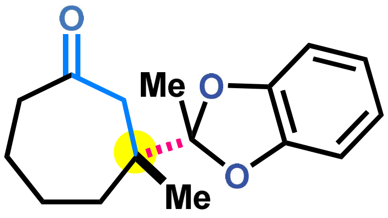
69% (97% ee)



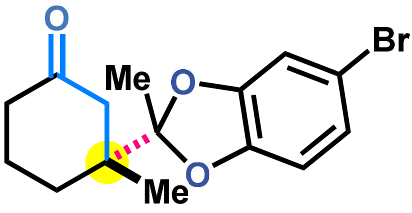
56% (96% ee)



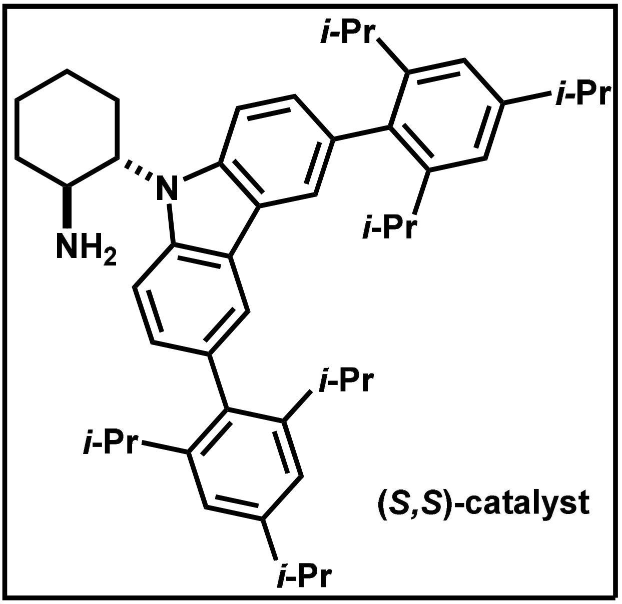
99% (88% ee)



70% (94% ee)



69% (dr 1.5:1, 97% ee)



(*S,S*)-catalyst

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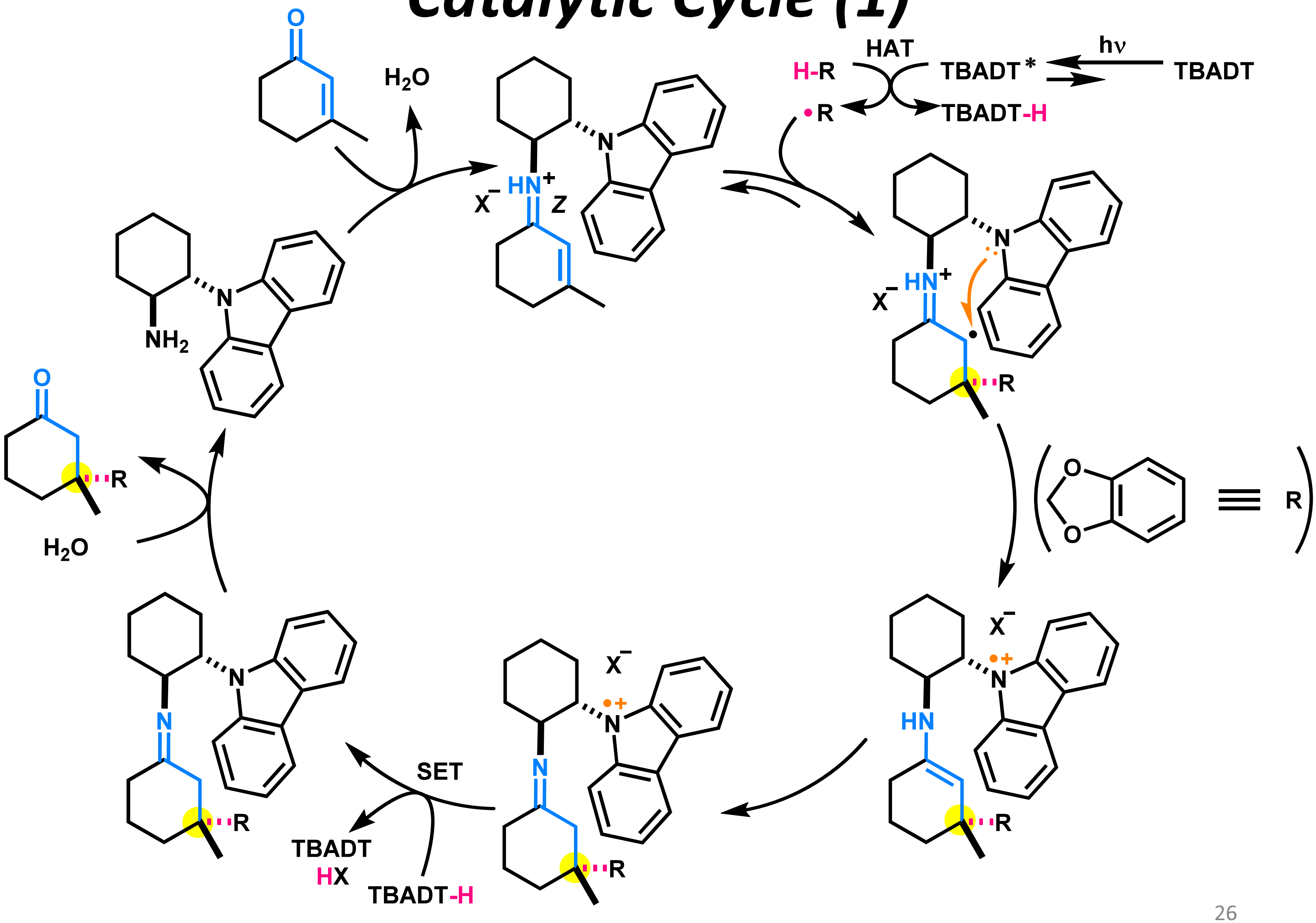
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Catalytic Cycle (1)



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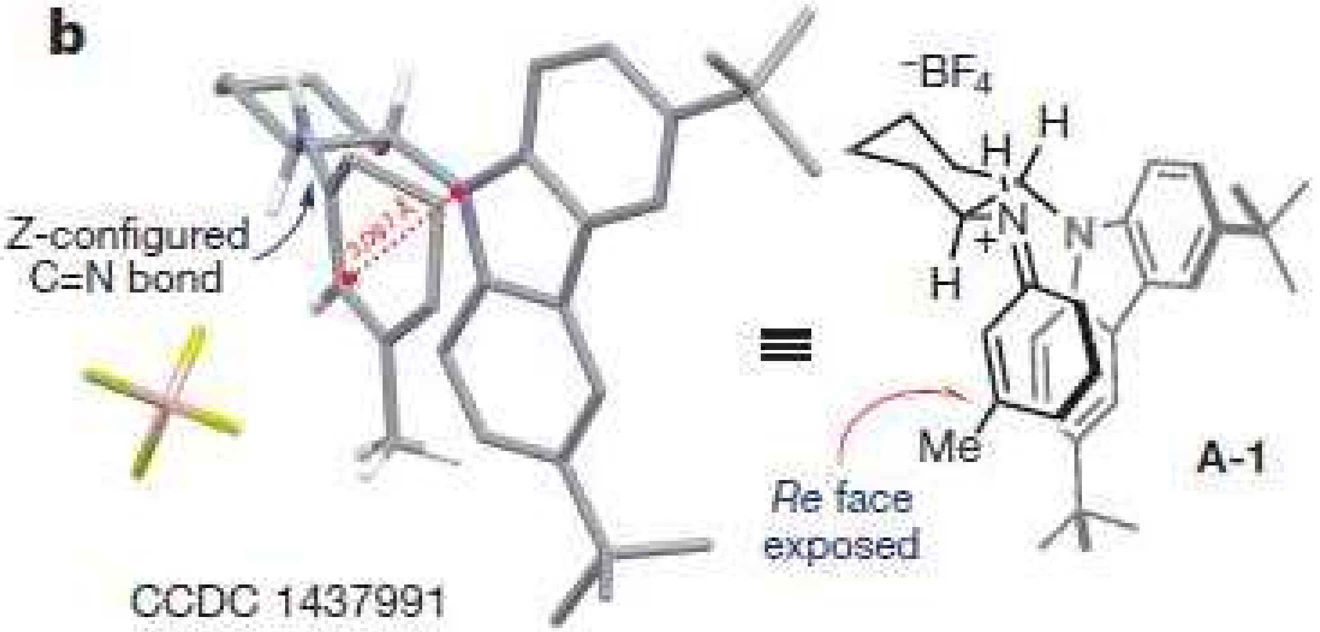
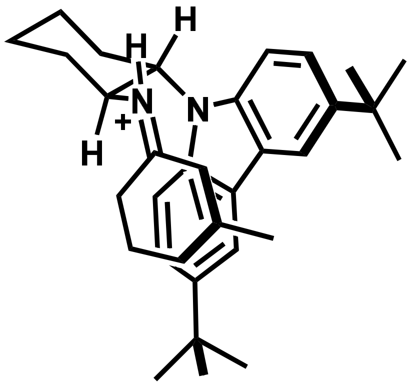
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Enantioselectivity



π-π interaction between iminium ion and carbazole makes *Z*-configuration.

cf. *E*-configured C=N bond



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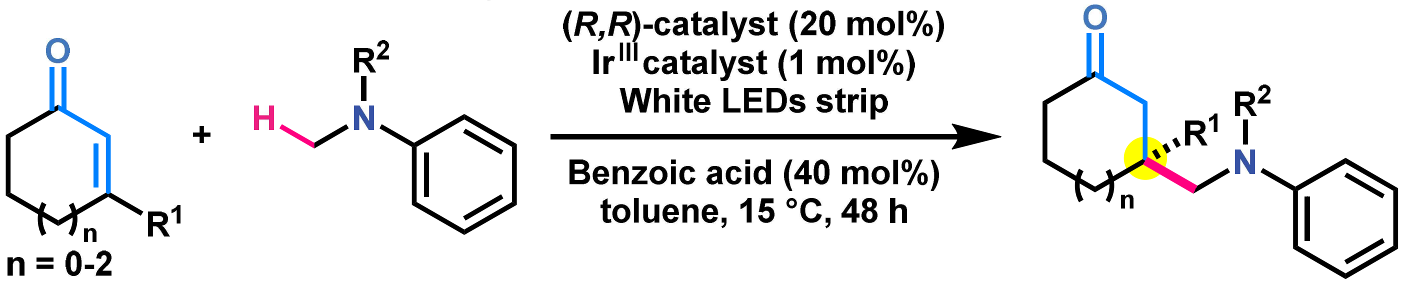
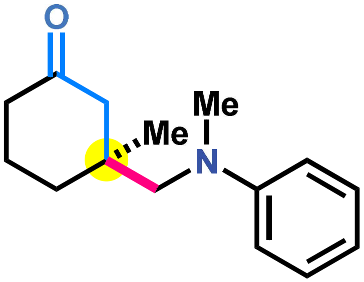
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Addition of α-Amino Radical

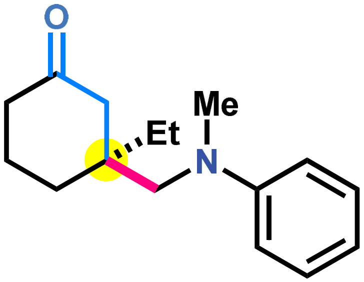


(*R,R*)-catalyst (20 mol%)
Ir^{III}catalyst (1 mol%)
White LEDs strip

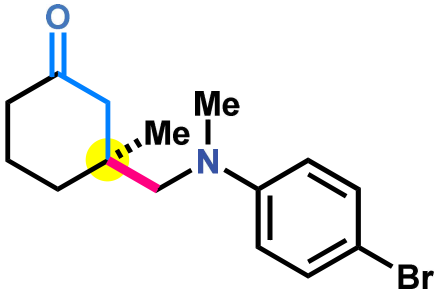
Benzoic acid (40 mol%)
toluene, 15 °C, 48 h



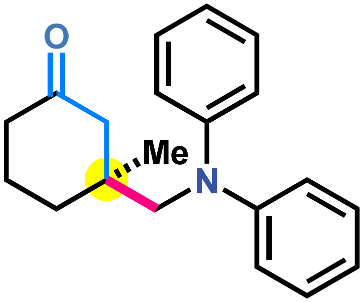
78% (88% ee)



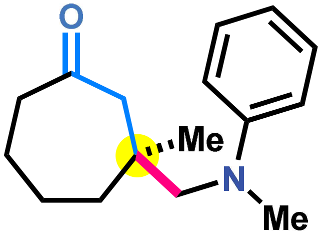
85% (84% ee)



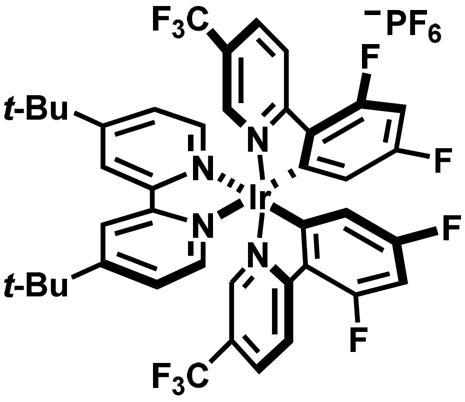
81% (80% ee)



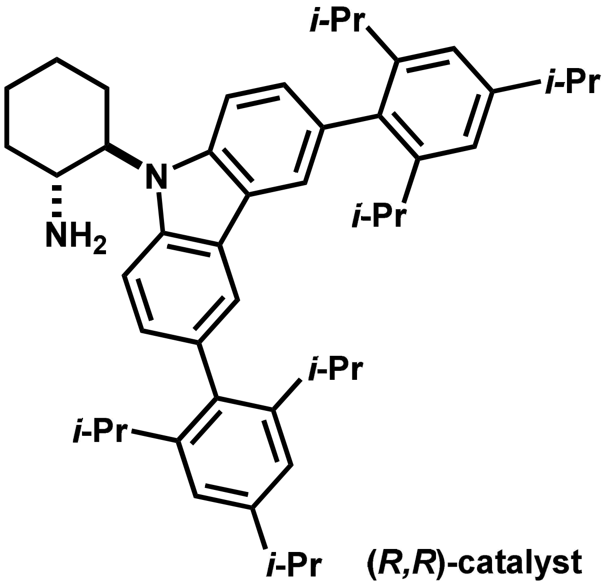
69% (87% ee)



92% (88% ee)



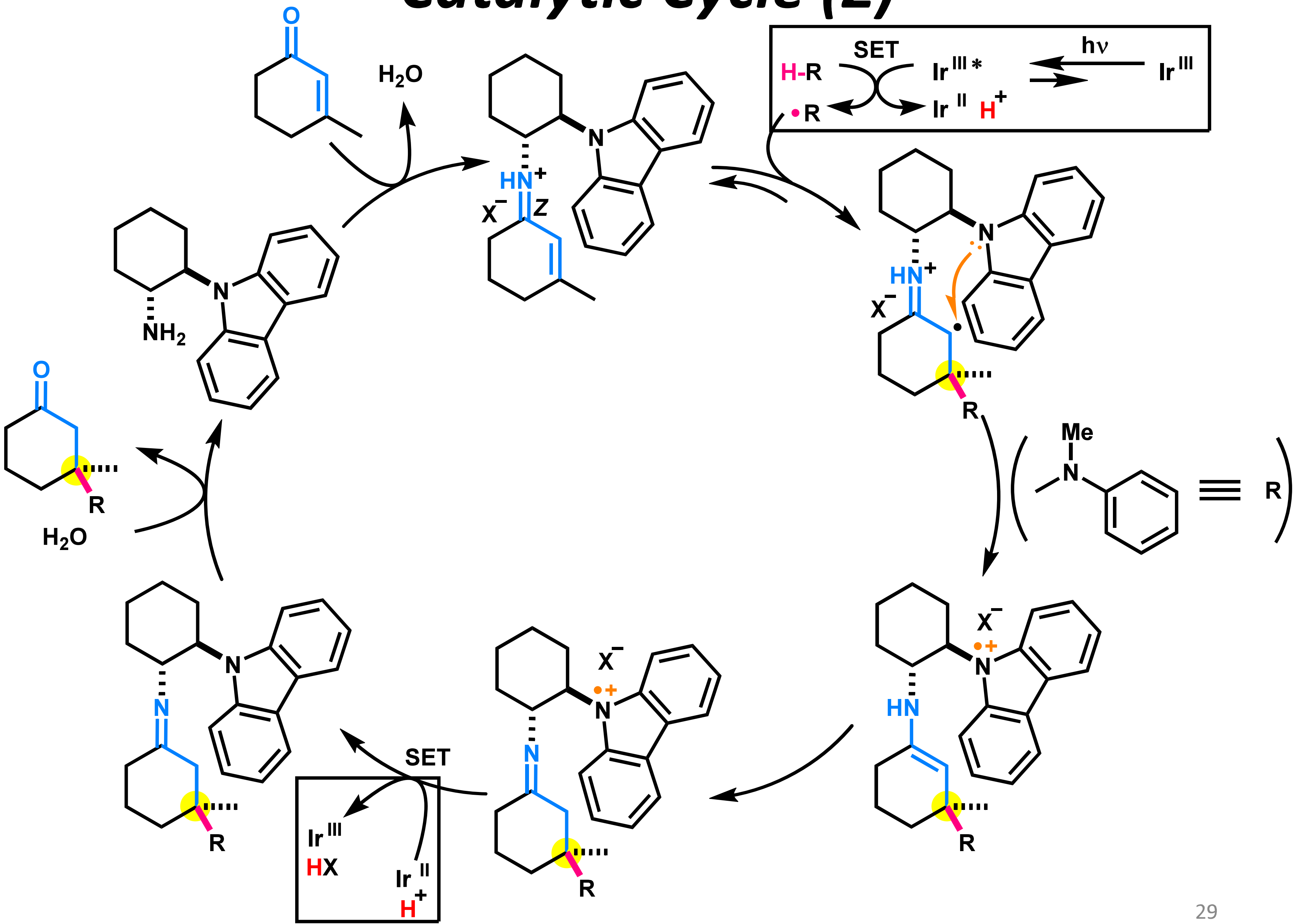
Ir^{III}catalyst



(*R,R*)-catalyst

1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

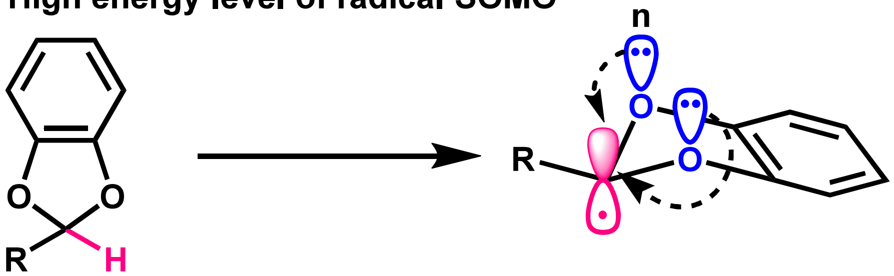
Catalytic Cycle (2)



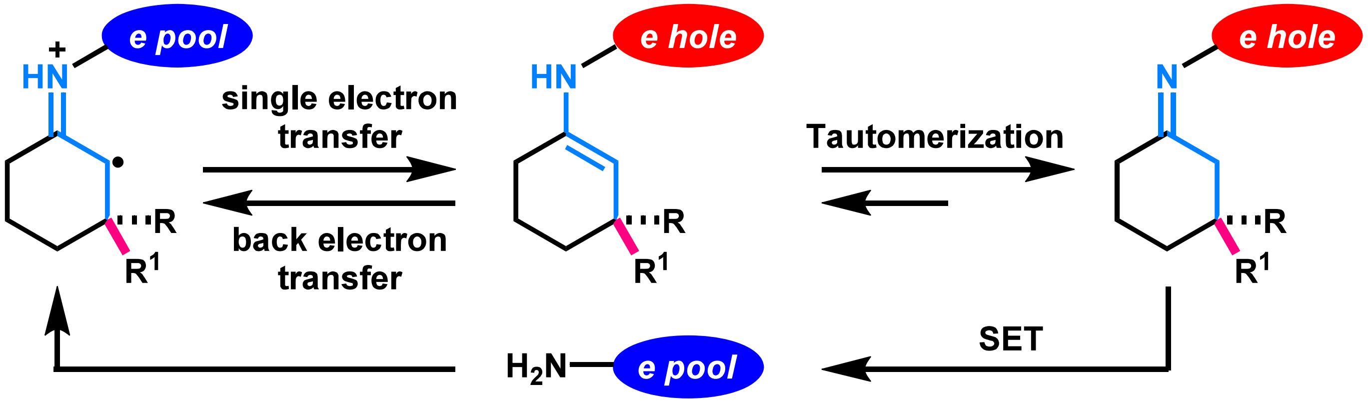
1) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218.

Summary

1. High energy level of radical SOMO



2. Low energy level of radical acceptor LUMO



single electron transfer

back electron transfer

Tautomerization

SET

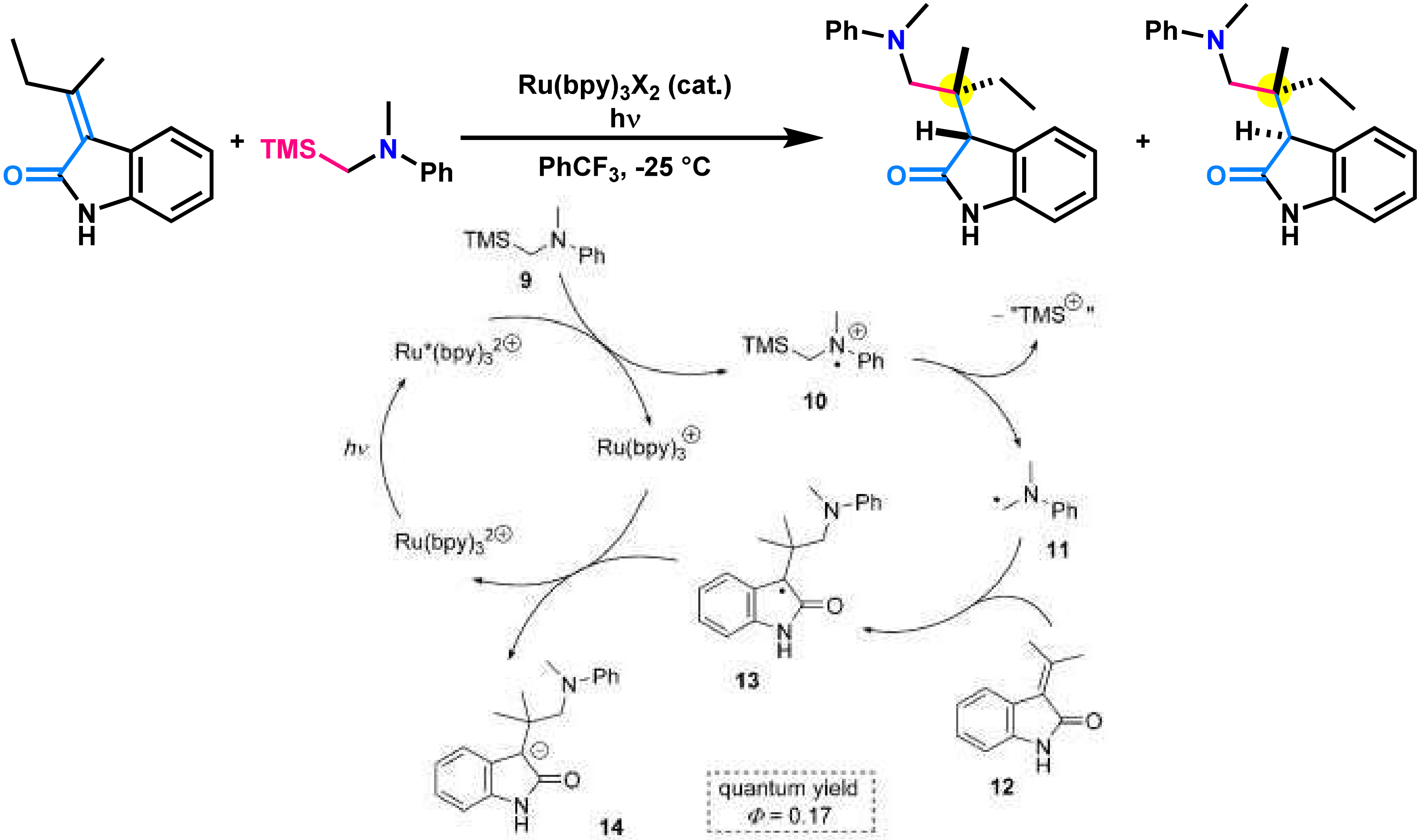
chiral organocatalyst + photoredox

○ Mild conditions
High yield and ee
Versatility (EWG is not necessary)

△ Long time
Application to total synthesis

Appendix

Mechanism of RCA to 3-alkylidene indolin-2-one



Scheme 3. Mechanistic model for the catalytic cycles involved in the photochemical addition of α-aminoalkyl radical **11** to 3-isopropylidene indolin-2-one (**12**).

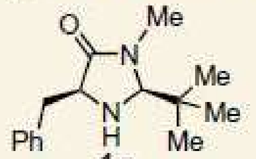
1) Lenhart, D.; Bauer, A.; Pöthig, A.; Bach, T. *Chem. Eur. J.* **2016**, *22*, 6519.

Catalyst Scope

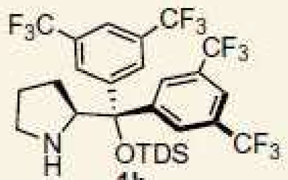
Table 1 | The model reaction and the chiral catalysts evaluated.

E_{ox} (**3a**$^{\bullet+}$/**3a**) = +1.74 V

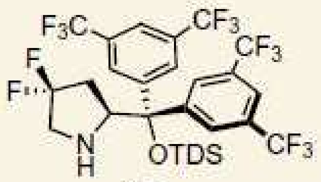
Catalysts used in this study


1a

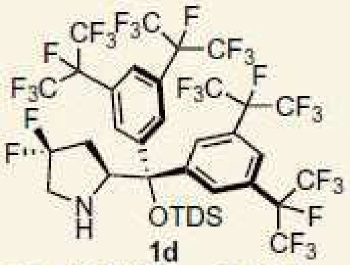
(E_{ox} (**1a**$^{\bullet+}$/**1a**) = +1.80 V)


1b

(E_{ox} (**1b**$^{\bullet+}$/**1b**) = +1.57 V)


1c

(E_{ox} (**1c**$^{\bullet+}$/**1c**) = +2.20 V)


1d

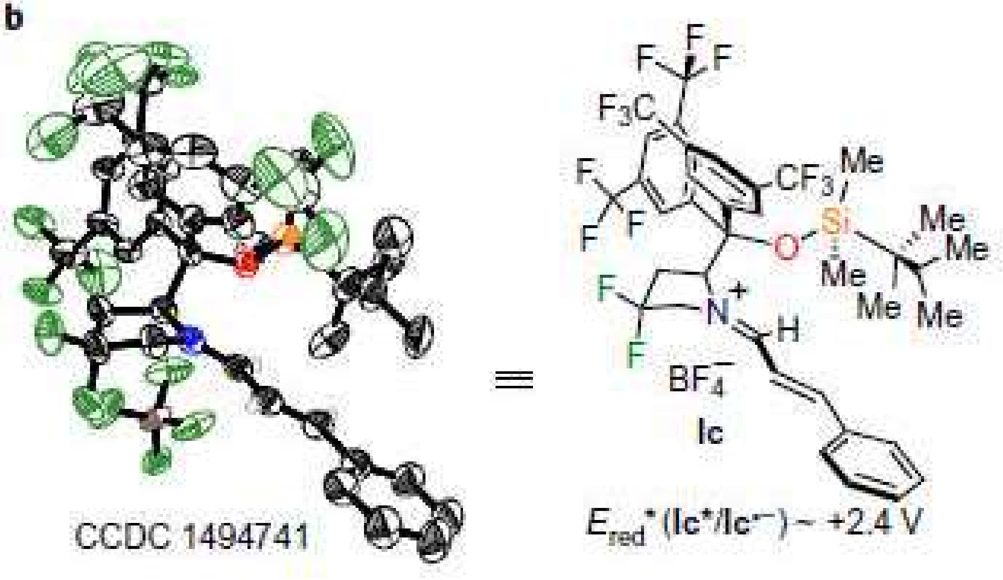
(E_{ox} (**1d**$^{\bullet+}$/**1d**) = +2.40 V)

Entry	Catalyst	Light	3a yield (%)	e.e. (%)
1	**1a**	On	79	30
2	None	On	0	-
3	**1a**	Off	0	-
4	**1b**	On	28	76
5	**1c**	On	83	85
6	**1d**	On	87	88

E_{ox} for catalysts 1 measured by cyclic voltammetry versus Ag/Ag$^+$ in CH$_3$CN.

1) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem. in press*.

Enantioselective Addition to Enal



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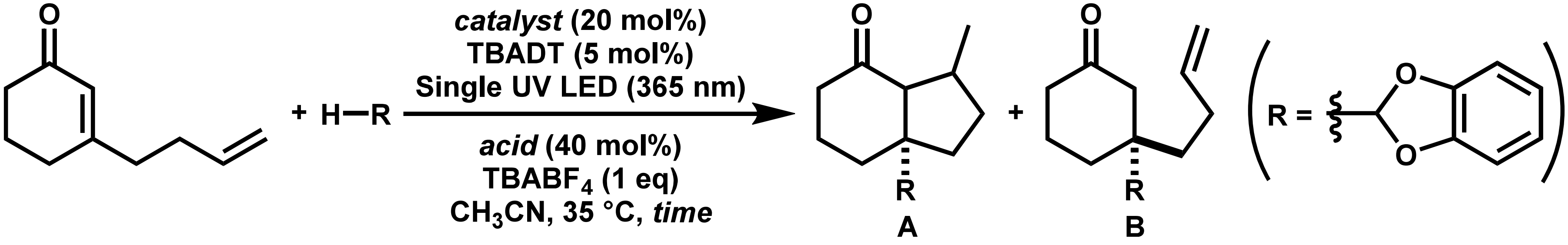
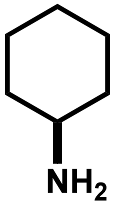
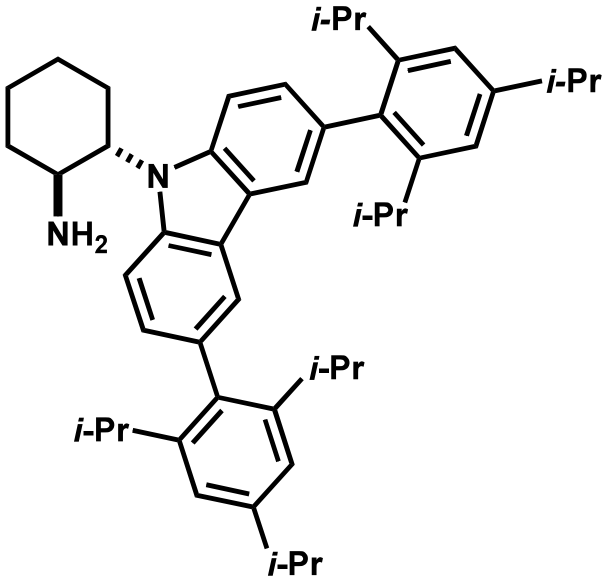
1) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem. in press*.

Cyclization Experiment



entry	*catalyst*	*acid*	A	B
1		TFA	6%	3%
2		benzoic acid	trace	40% (83% ee)

Additional research

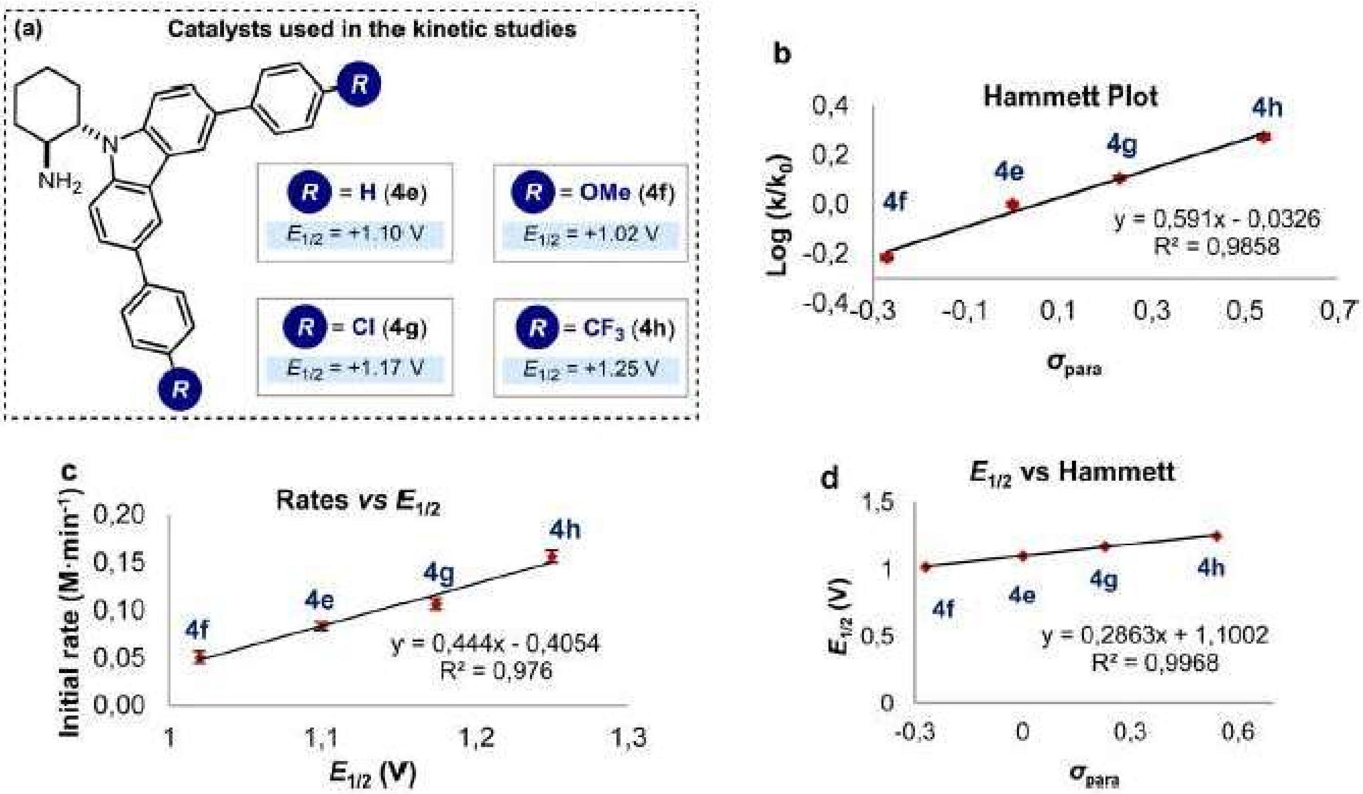


Figure 6. (a) A new family of chiral catalysts: *para*-substituted 3,6-aryl carbazole catalysts **4e**−**h**. They promoted the model reaction depicted in Scheme 1 inferring the same level of stereoselectivity (87−88% ee). $E_{1/2}$ is the reduction potential of the carbazole-based catalysts **4e**−**h** as measured by cyclic voltammetry vs Ag/Ag$^+$ in CH$_3$CN; the carbazole within **4** undergoes a reversible oxidation to produce the corresponding carbazoliumyl radical cation. (b) LFER correlating the Hammett σ value of the *para*-substituted aryl carbazole moiety with the initial rates for the model reaction depicted in Scheme 1 catalyzed by catalysts **4e**−**h**. (c) Correlations between the initial rates and the redox potentials measured for the different aminocatalysts **4e**−**h**. (d) Linear relationship between the redox potentials for the different aminocatalysts and the corresponding Hammett σ value of their aryl moiety. Reactions performed in CD$_3$CN under illumination by HP black LED, λ_{max} = 365 nm, with an irradiance of 60 ± 2 mW/cm^2. [**4**] = 0.1 M, [**1a**] = 0.5 M, [**2a**] = 1.5 M, [TBADT] = 0.025 M, [TBABF$_4$] = 0.5 M and [benzoic acid] = 0.1 M. The error bars in (c) represent the standard deviation.

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1) Bahamonde, A.; Murphy, J. J.; Savarese, M.; Bremond, E.; Cavalli, A.; Melchiorre, P. *J. Am. Chem. Soc.* **2017**, *139*, 4559.