Ti Mediated Coupling Reactions

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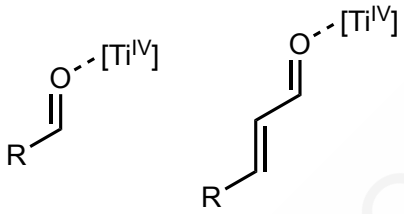
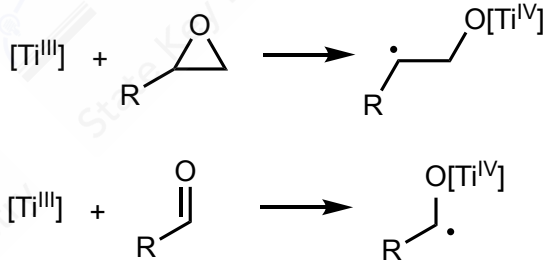
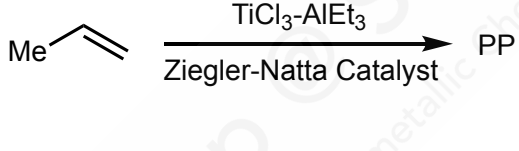
Common Activation Modes of Titanium



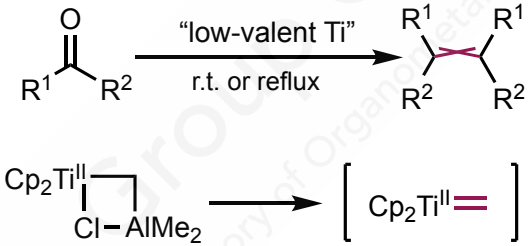
Tradictional Lewis acid



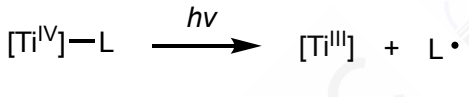
Radical reaction catalyst



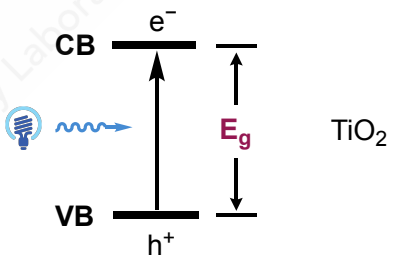
Coordination polymerization initiator



Reductive agent mediating cycloaddition or deoxygenation



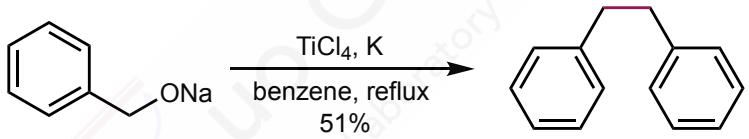
Photocatalyst in Photoinduced LMCT



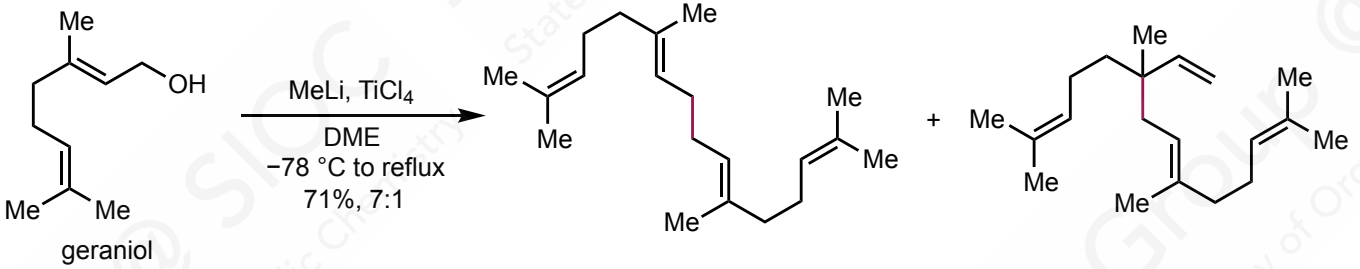
Semiconductor Photocatalyst

Early Examples of Ti Mediated Couplings

Reductive Coupling

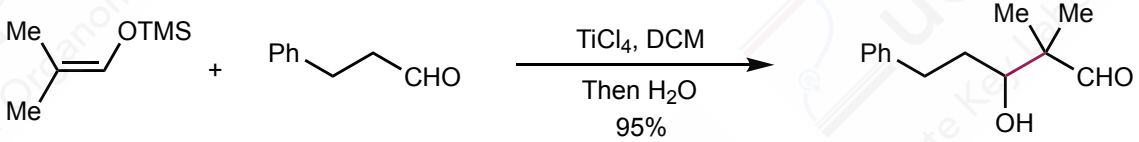


van Tamelen E. E. and Schwartz M. A. *J. Am. Chem. Soc.* **1965**, *87*, 3277–3278.



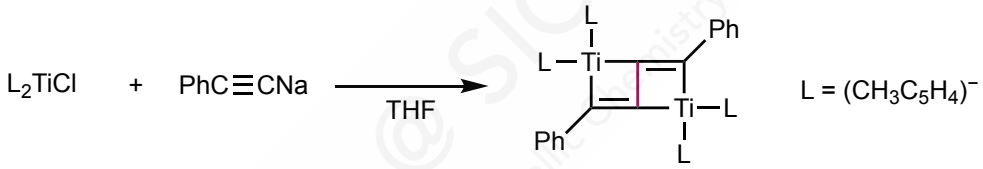
Sharpless, K. B. *et al. J. Am. Chem. Soc.* **1968**, *90*, 209–210.

Cross-Aldol Reaction



Narasaka, K. *et al. J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

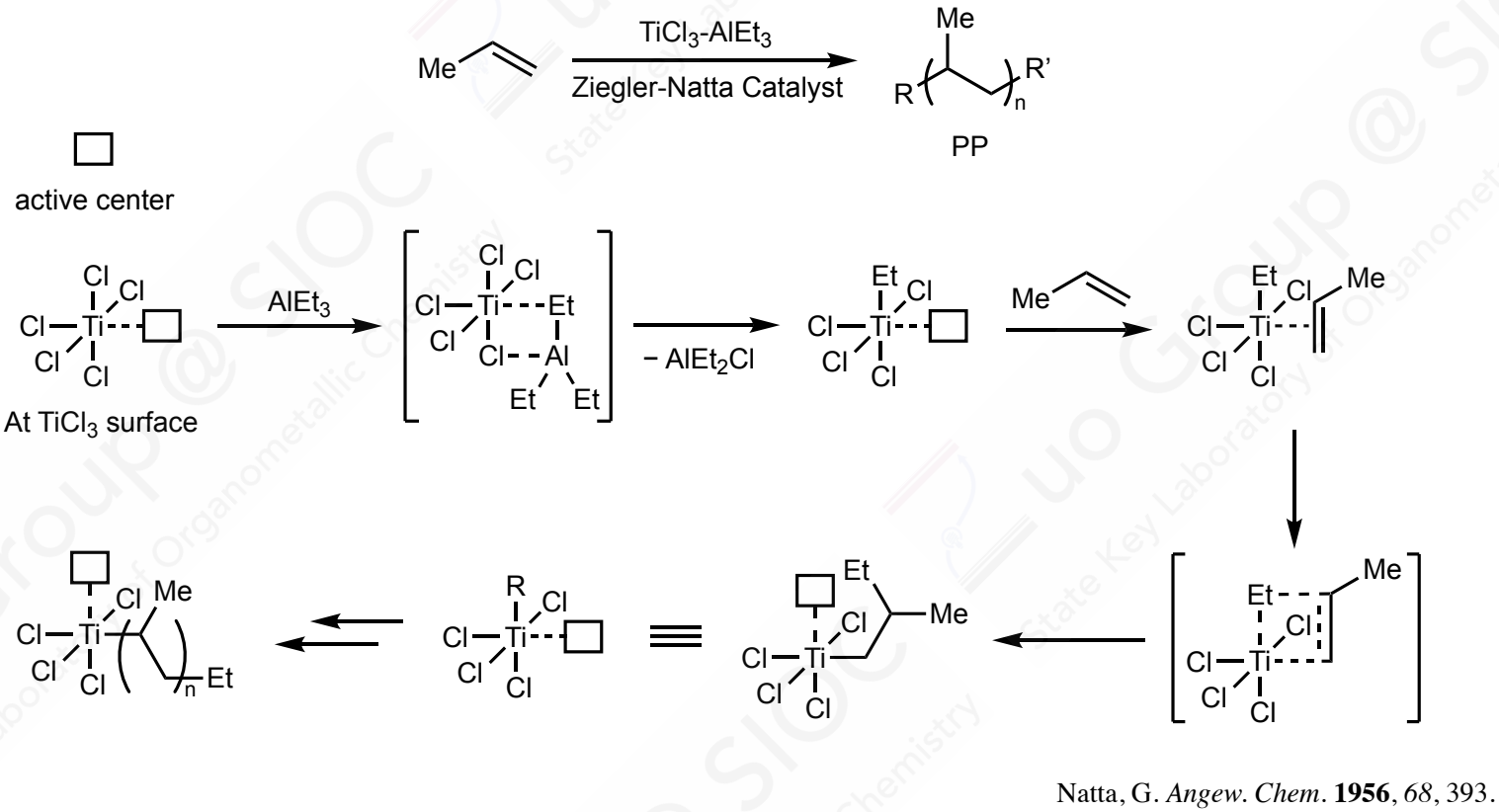
Oxidative Coupling



Sekutowski, D. G. and Stuck, G. D. *J. Am. Chem. Soc.* **1976**, *98*, 1376–1382.

Coordination Polymerization initiator

Ziegler-Natta Catalyst

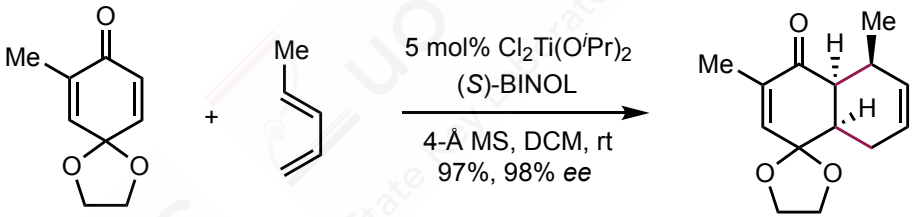


Natta, G. *Angew. Chem.* **1956**, *68*, 393.

Titanium Compounds as Lewis Acids

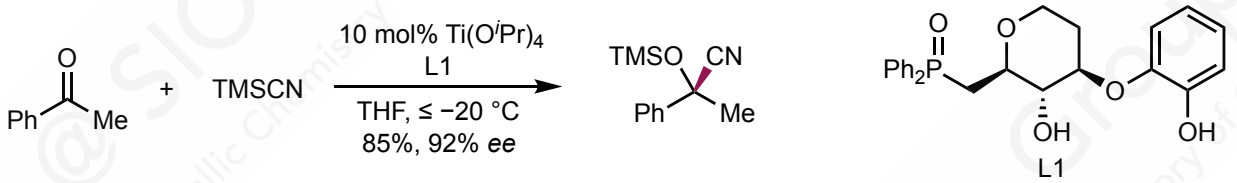
Ti Catalyzed Asymmetric Additions as Lewis Acid

Cycloadditon Reaction



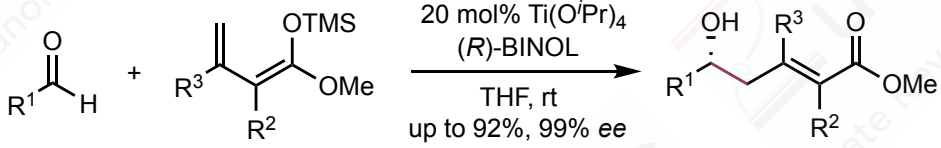
Breuning, M. and Corey, E. J. *Org. Lett.* **2001**, *3*, 1559–1562.

Cyanation



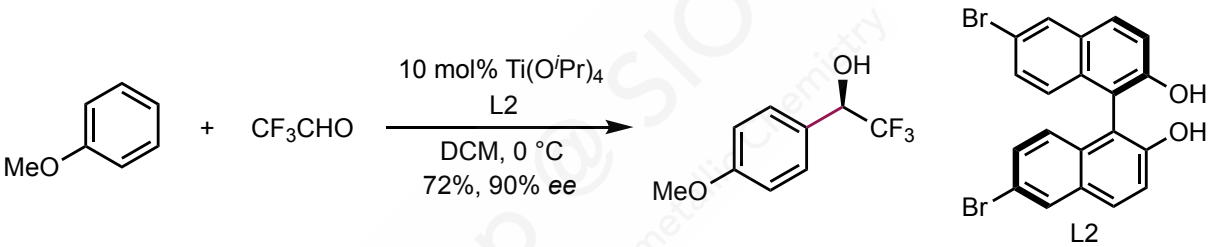
Shibasaki, M. *et al. J. Am. Chem. Soc.* **2000**, *122*, 7412–7413.

Aldol-Type Reaction



Scettri, A. *et al. Tetrahedron: Asymmetry* **2000**, *11*, 2255–2258.

Friedel-Crafts Reaction



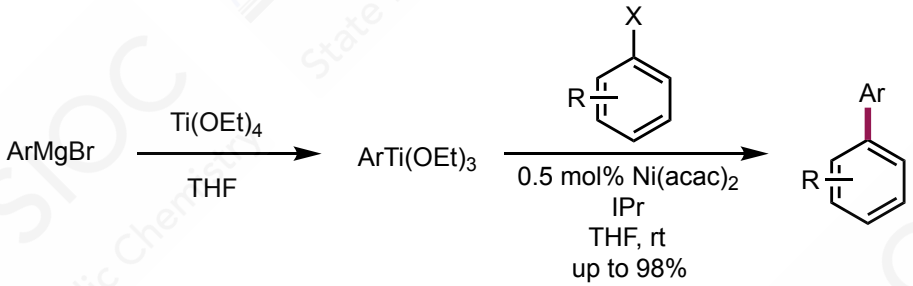
Mikami, K. *et al. J. Org. Chem.* **2000**, *65*, 1597–1599.

Titanium Compounds as Lewis Acids

Coupling Reactions of Organotitanium Reagents

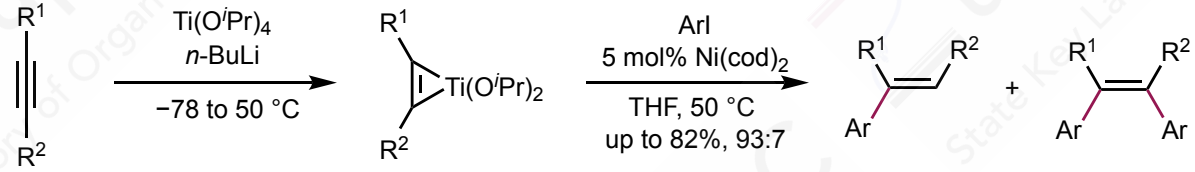
Herman, D. F. and Nelson, W. K. *J. Am. Chem. Soc.* **1952**, *74*, 2693.

■ **σ–Bonding**



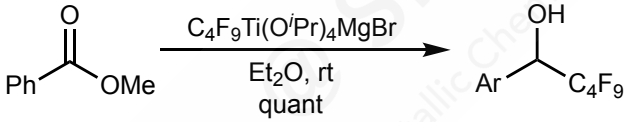
Knochel, P. *et al*. *Synlett*. **2007**, *13*, 2077–2080.

■ **π–Bonding**



Tsuji, Y. *et al*. *Chem. Commun*. **2003**, *50*, 2820–2821.

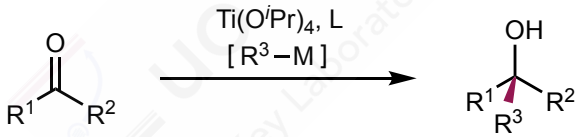
■ **Titanate Complexes**



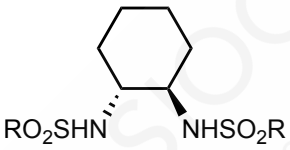
Itoh, Y. *et al*. *J. Am. Chem. Soc*. **2007**, *129*, 11686–11687.

Titanium Compounds as Lewis Acids

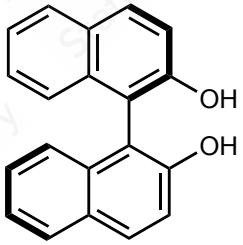
Ti Catalyzed Additions of Organometallic Reagents



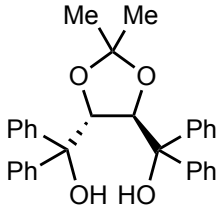
■ **Typical Ligands**



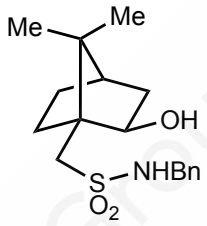
Sulfonamides
R = CF_3, 99%, 99% *ee*
Yoshioka-Ohno, **1989**



Binols
quant, 92% *ee*
Chan, **1997**

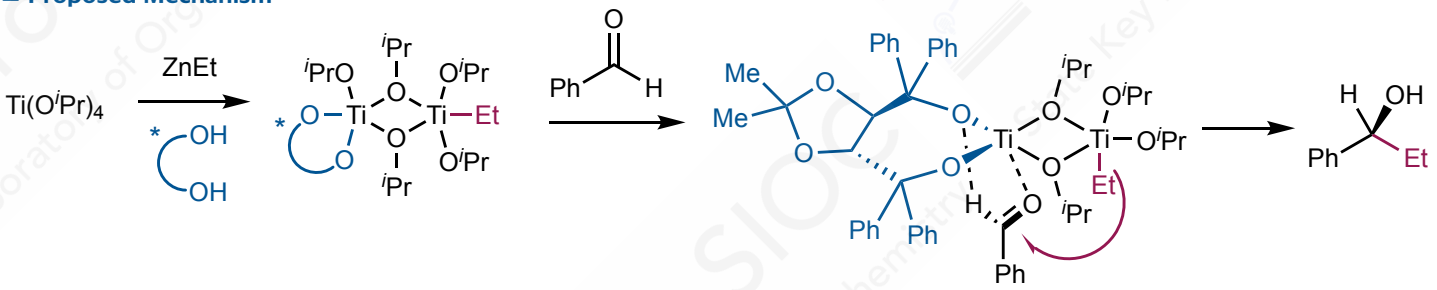


TADDOLs
93%, 98% *ee*
Seebach, **2001**



Hydroxysulfonamides
99%, 96% *ee*
Ramón, **2005**

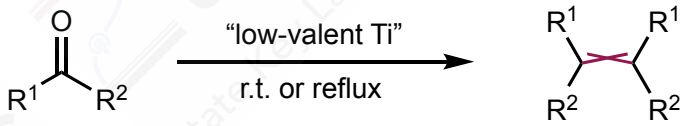
■ **Proposed Mechanism**



Ramón, D. J. and Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208.

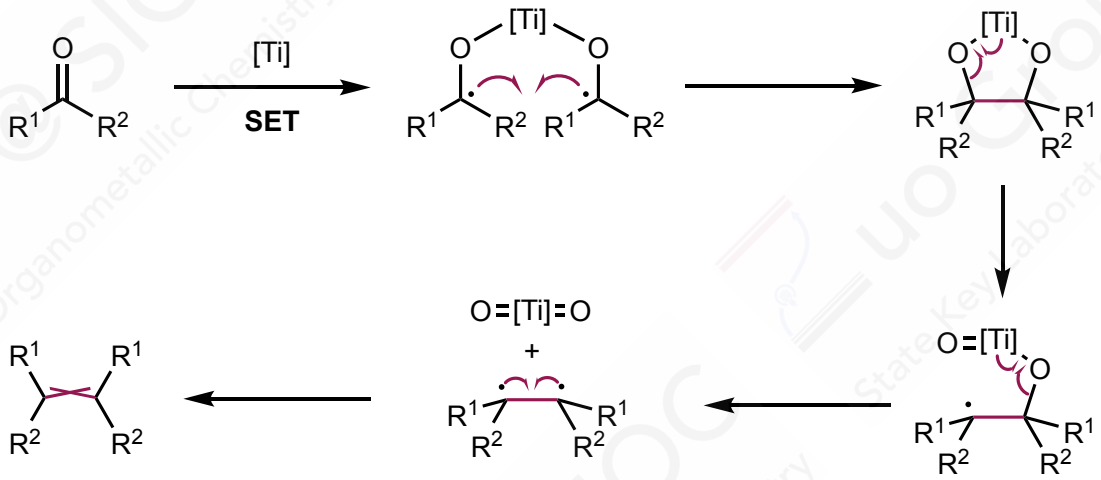
McMurry Reaction

McMurry Reaction



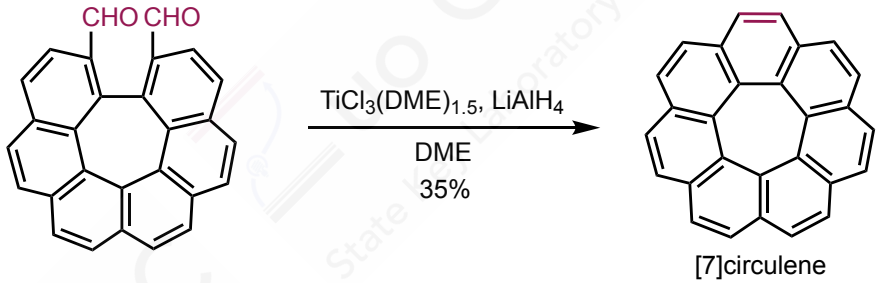
McMurry, J. E. and Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.

■ **Proposed Mechanism**



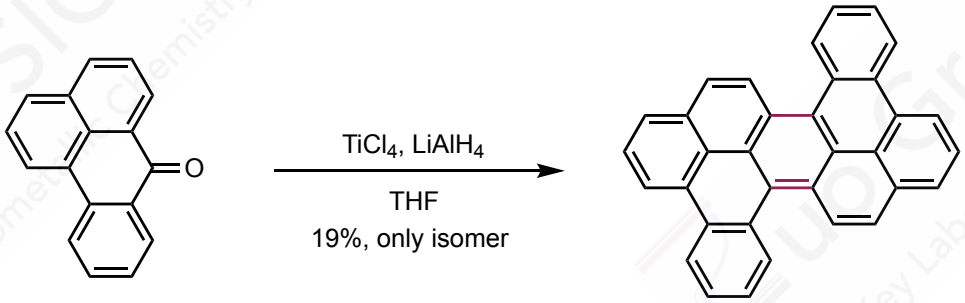
McMurry Reaction

Construction of Strained C=C Bonds

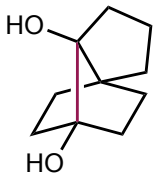


[7]circulene

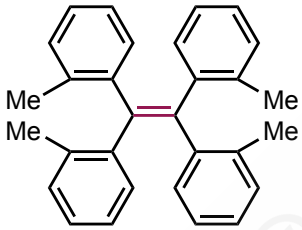
Nakazaki, M. and Kasai, N. *et al*. *J. Am. Chem. Soc.* **1983**, *105*, 7171–7172.



Agranat, I. and Pogodin, S. *Org. Lett.* **1999**, *1*, 1387–1390.

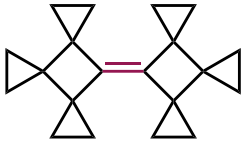


25%, Nyi, **1980**



15%, Geise, **1982**
40% pinacol

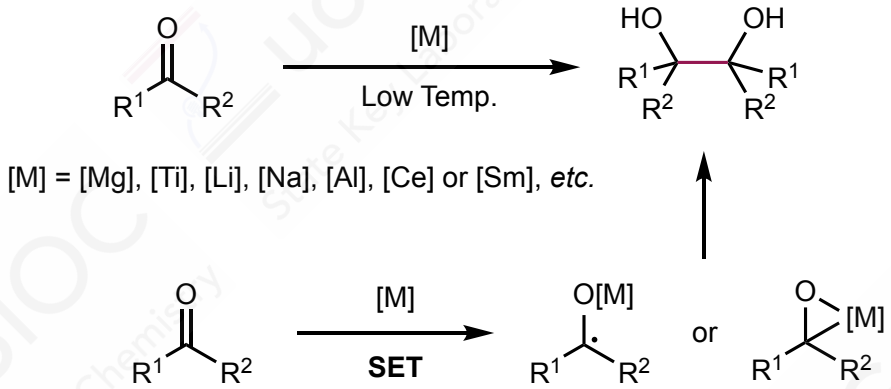
24%, McMury, **1984**



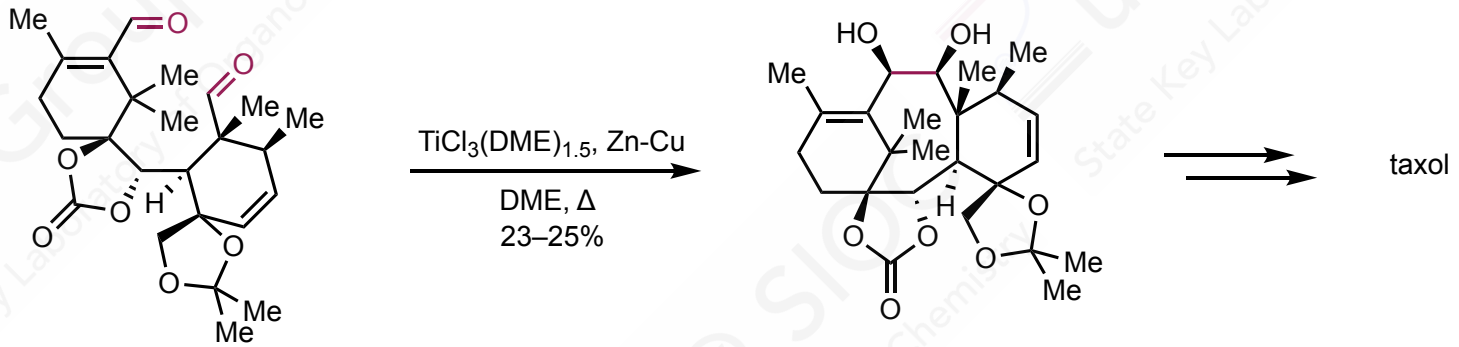
8%, Gleiter, **1986**
60% pinacol

Pinacol Coupling

Pinacol Coupling



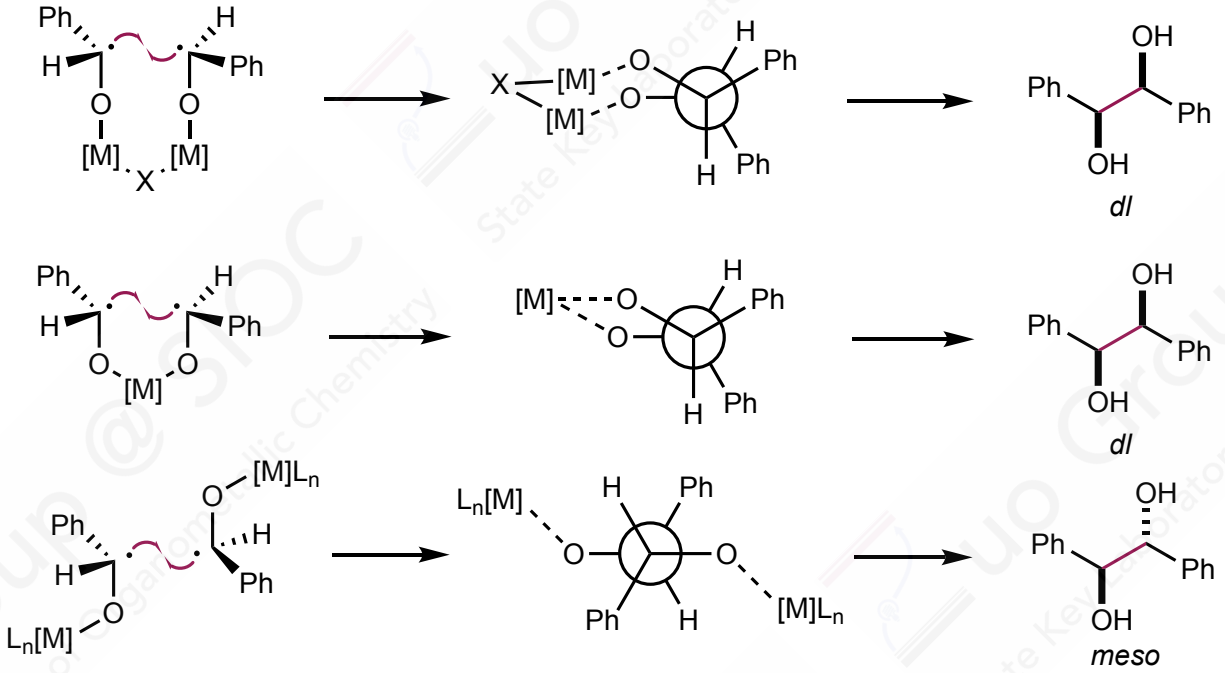
■ Key Steps in Total Synthesis



Nicolau, K. C. and Sorensen, E. J. *et al*. *Nature* **1994**, *367*, 630–634.

Pinacol Coupling

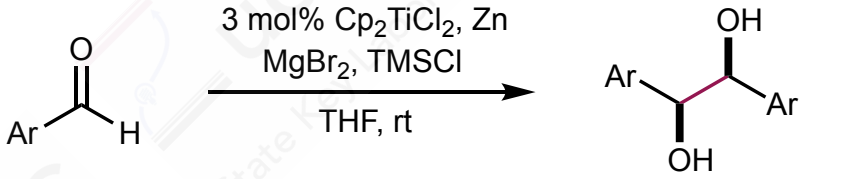
Diastereoselective Pinacol Coupling



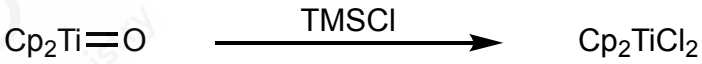
with $MgCl_2$-C_8K	*dl*/*meso* selectivity up to 3:1	Weidmann, **1988**
with ^{i}PrOH, *hv*	*dl*/*meso* selectivity up to > 99:1	Li, **2003**
with Li, PhBr, neat	*dl*/*meso* selectivity up to > 99:1	Guo, **2003**

Pinacol Coupling

Diastereoselective Pinacol Coupling



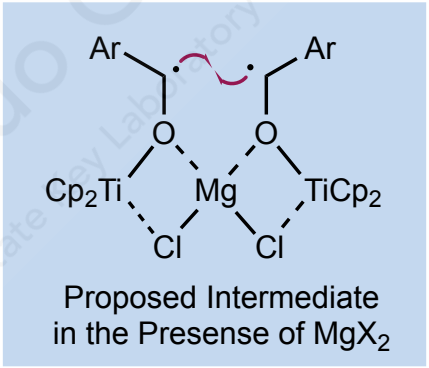
> 80% yield, > 10:1 *dr*



■ Condition Screening

Ar = Ph

Without $MgBr_2$	96% yield, 5.3:1 *dr*
Slow addition of ArCHO and TMSCl, without $MgBr_2$	88% yield, 8.1:1 *dr*
Slow addition of ArCHO and TMSCl	90% yield, 19:1 *dr*

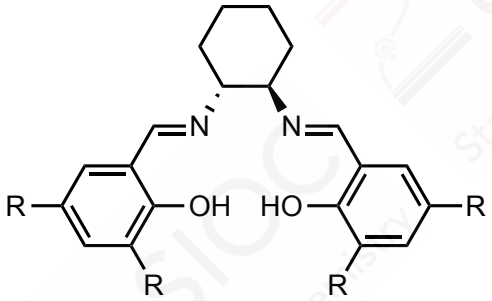


Proposed Intermediate in the Presense of MgX_2

Gansäuer, A. *Chem. Commun.* **1997**, 457–458.

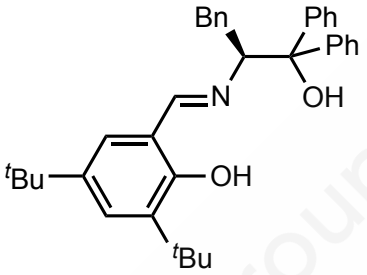
Pinacol Coupling

Ligands Used in Ti Catalysed Enantioselective Pinacol Coupling

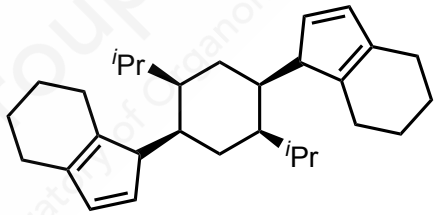


R = ^{t}Bu, 40%, 9:1 *dr*, **10% ee**, Umani-Ronchi, **1999**

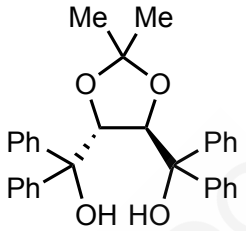
R = H, 94%, > 20:1 *dr*, **95% ee**, Joshi, **2003**



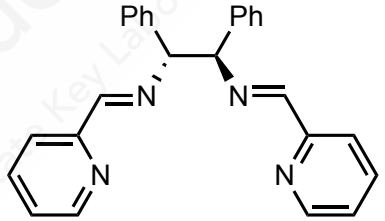
95%, > 20:1 *dr*, **64% ee**, Riant, **2001**



3.4:1 *dr*, **32% ee**, Nicholas, **2000**



up to 93%, > 99:1 *dr*, **74% ee**, You, **2006**

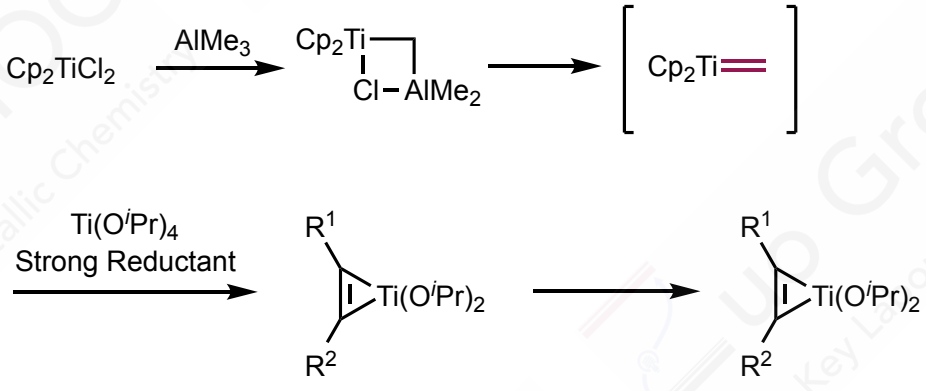


96%, 19:1 *dr*, **90% ee**, You, **2004**

*All *dr*s are *dl*/*meso*.

Ti(II) Mediated Couplings

[Ti^{II}] Mediated Couplings

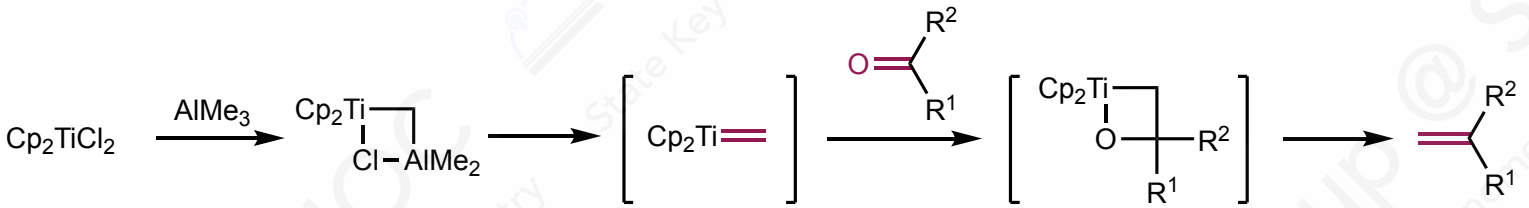


- Metal-ligand Multiple Bonds
- Cycloadditions

Ti(II) Mediated Couplings

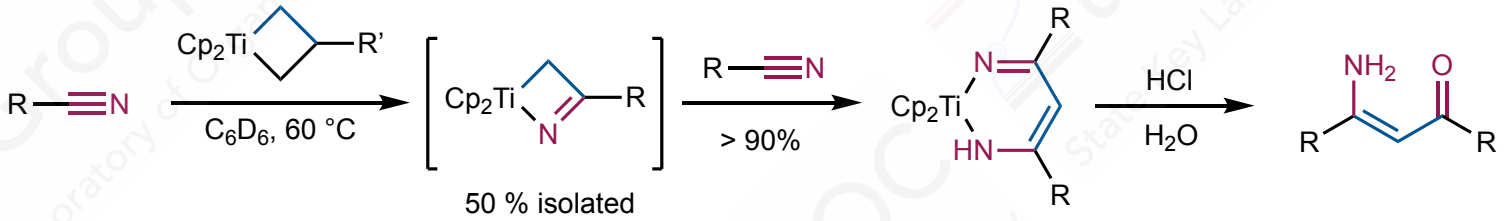
Stoichiometric [Ti^{II}] Mediated Couplings

■ Tebbe Olefination



Tebbe, F. N. *et al*. *J*. *Am*. *Chem*. *Soc*. **1978**, *100*, 3611–3613.

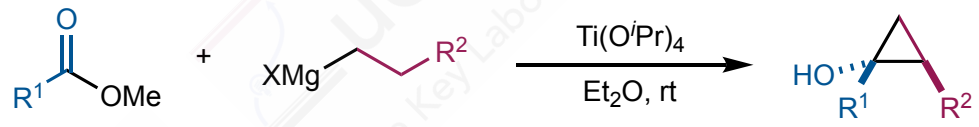
■ Coupling of Nitriles



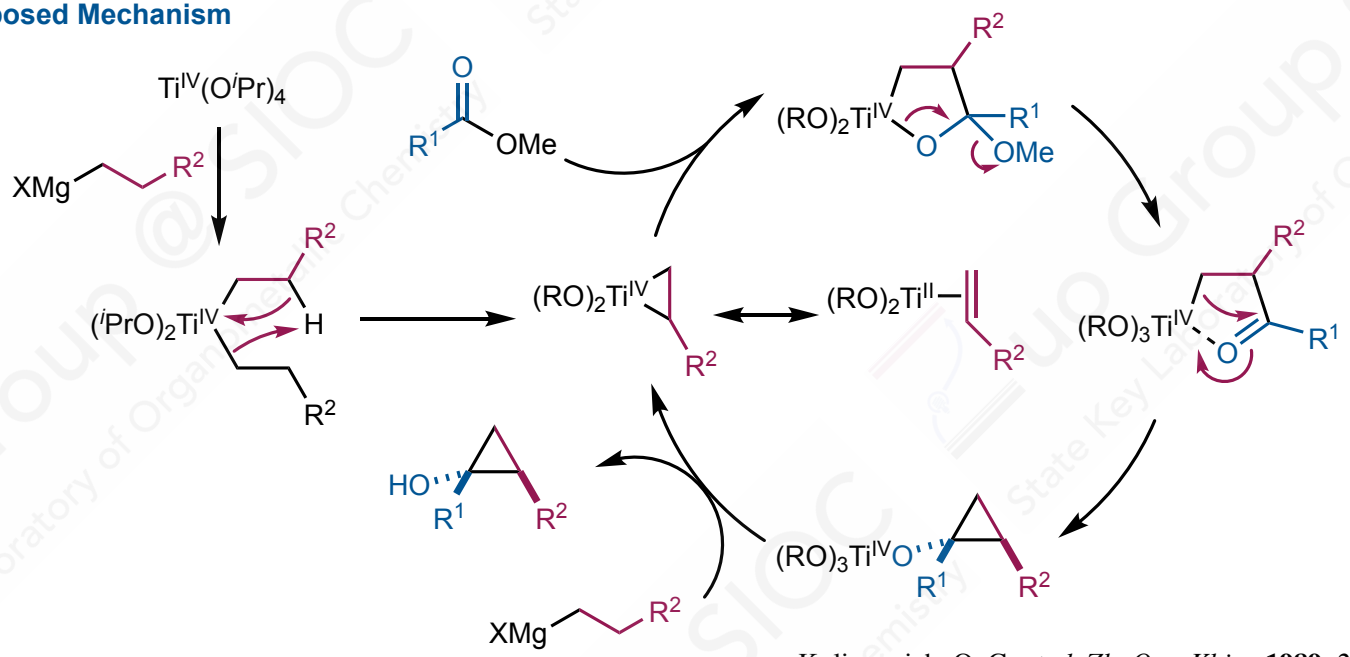
Doxsee, K. M. and Farahi, J. B. *J*. *Am*. *Chem*. *Soc*. **1988**, *110*, 7239–7240.

Ti(II) Mediated Couplings

Kulinkovich Cyclopropanation



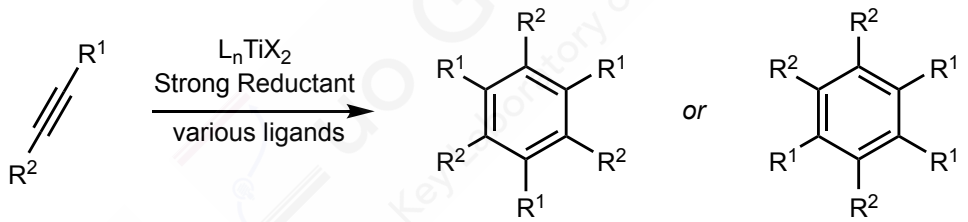
■ **Proposed Mechanism**



Kulincovich, O. G. *et al*. *Zh*. *Org*. *Khim*. **1989**, *25*, 2244–2245.

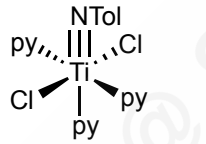
Ti(II) Mediated Couplings

Alkyne Cyclotrimerization

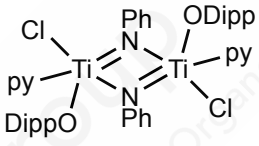


■ **Ligands**

R^1 = ^{n}Bu, R^2 = H



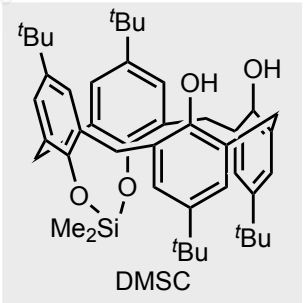
quant.
A:B = 27:73



quant.
A:B = 31:69

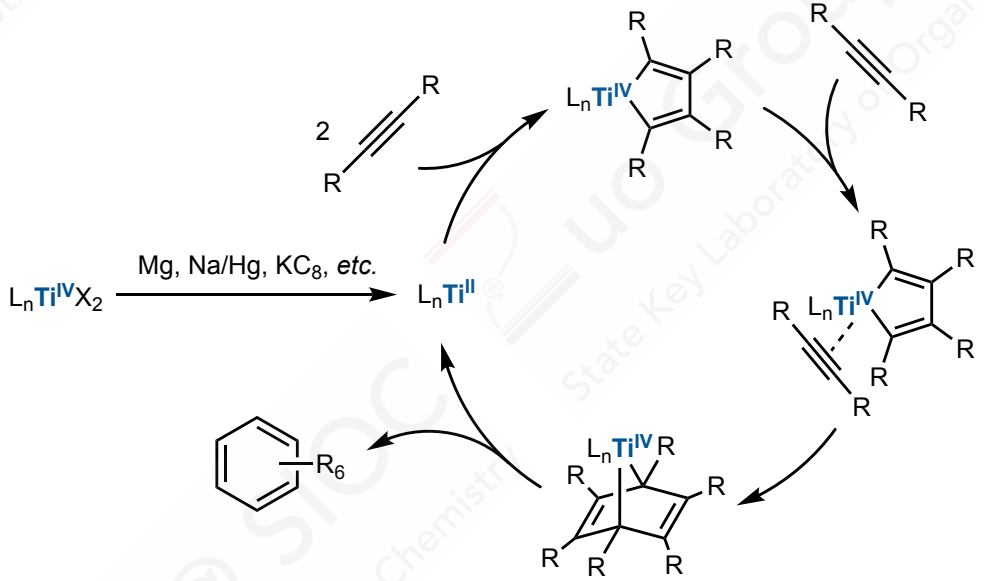
(DMSC)Ti

quant.
A:B = 2:98
Ladipo, **2000**



DMSC

■ **Proposed Mechanism**

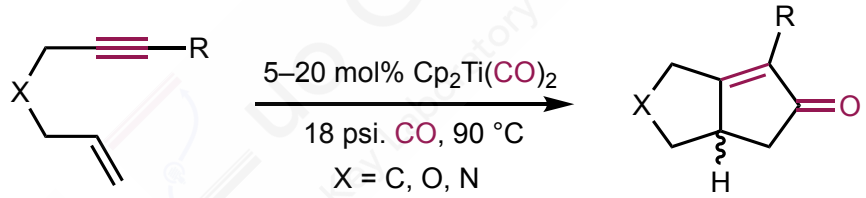


Ladipo, F. T., *et al*. *J. Am. Chem. Soc*. **2000**, *122*, 6423–6431.

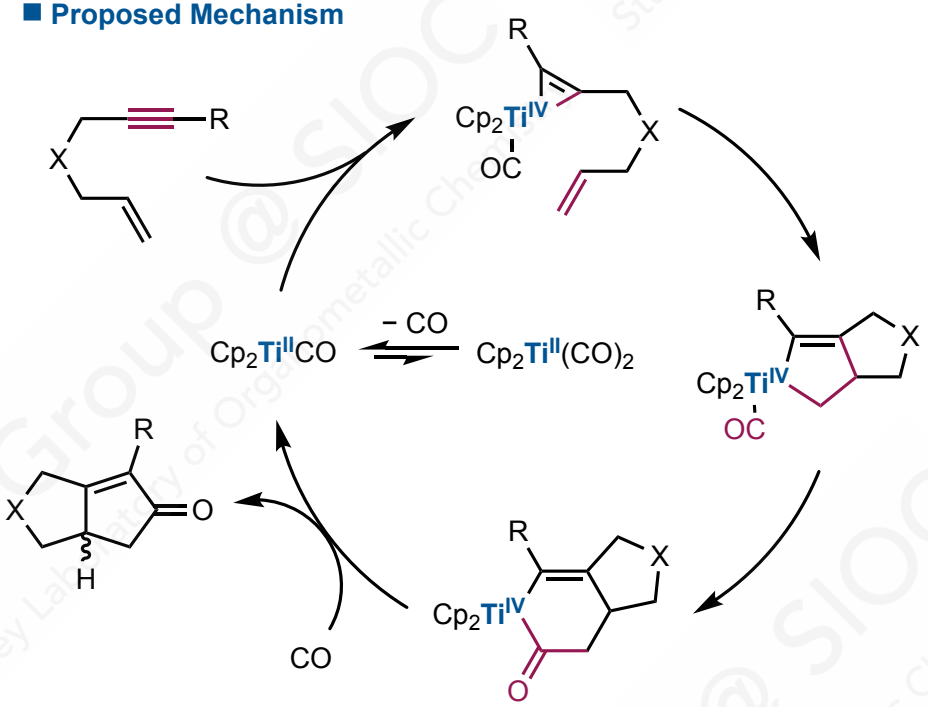
Tonks, I. A., *et al*. *Organometallics* **2017**, *36*, 1383–1390.

Ti(II) Mediated Couplings

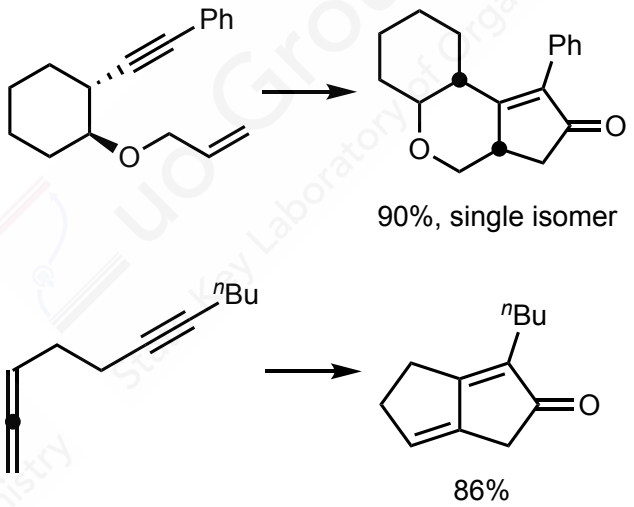
Pauson-Khand Reaction



■ **Proposed Mechanism**



■ **Selected Scope**

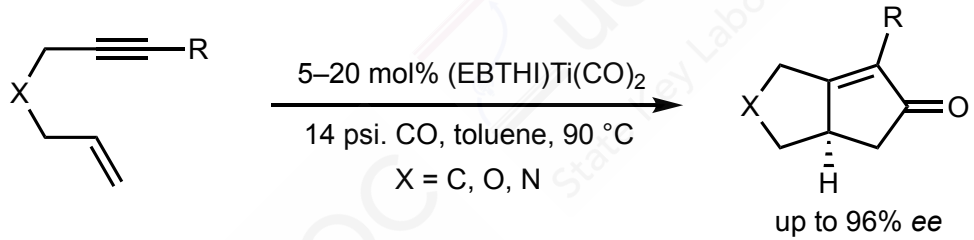


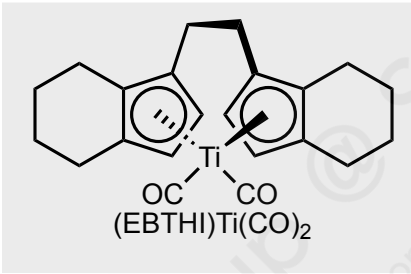
Buchwald, S. L. *et al*. *J. Am. Chem. Soc*. **1996**, *118*, 9450–9451.

Ti(II) Mediated Couplings

Pauson-Khand Reaction

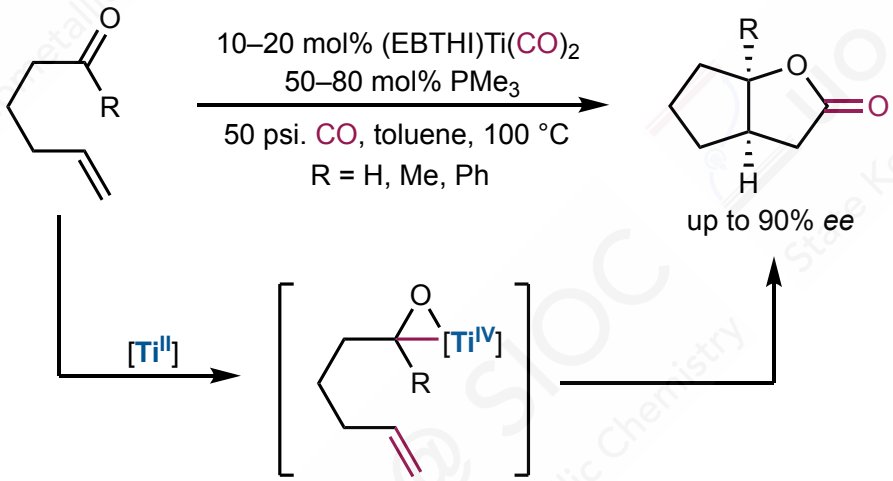
■ Enantioselective Version





Hicks, F. A. and Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688–11689.

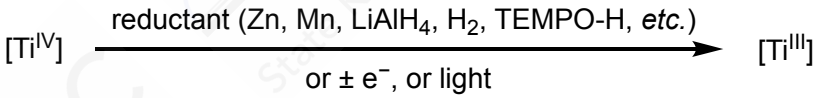
■ O-Hetero Version



Crowe, W. E. *et al*. *J. Am. Chem. Soc*. **2001**, *123*, 6457–6458.

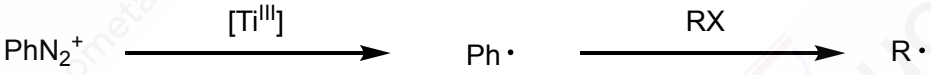
Ti(III) Mediated Radical Reactions

[Ti^{III}] Generation



$E^{\ominus}_{Ti(IV)/Ti(III)}$ = +0.10 V (TiO^{2+})

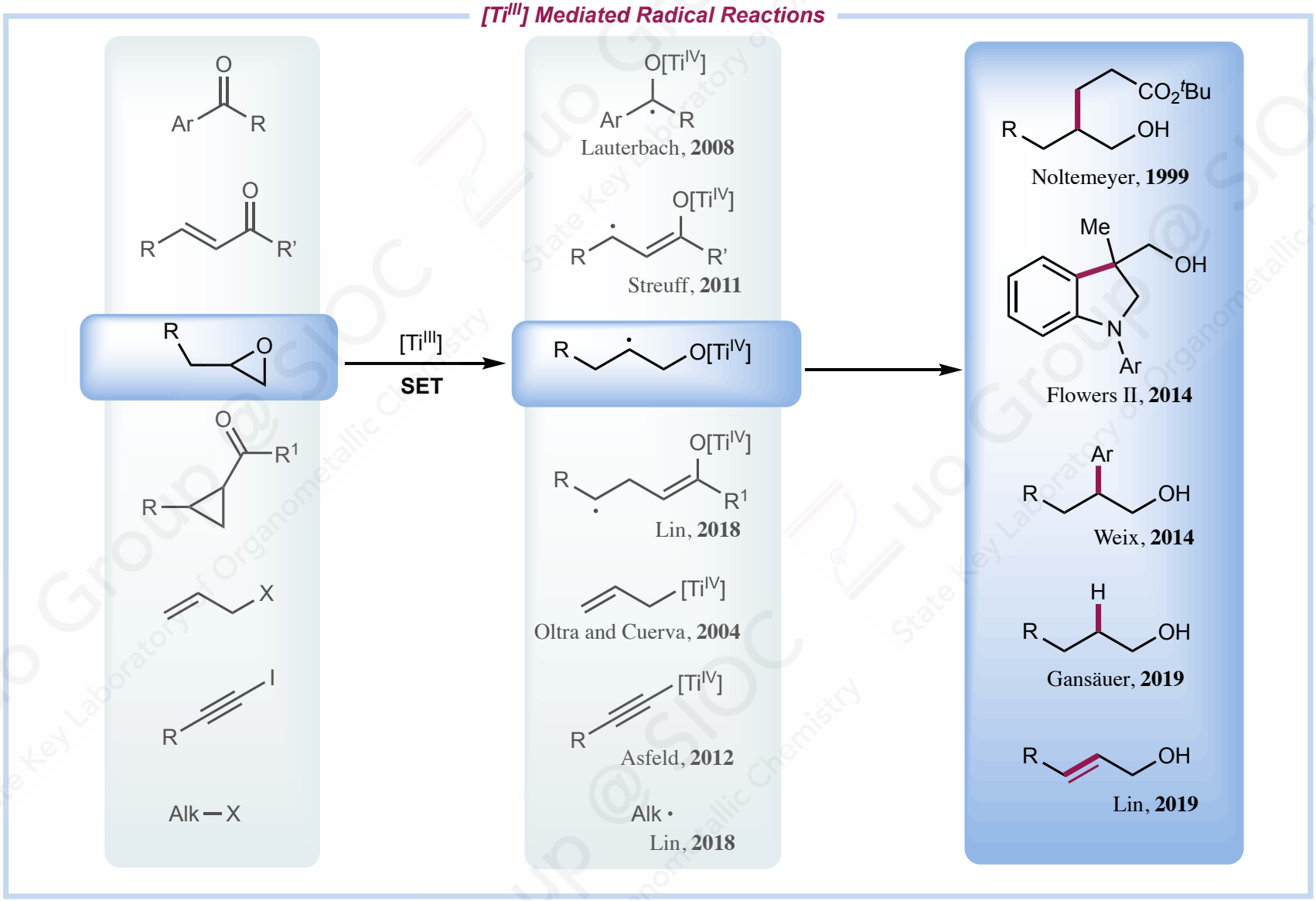
Early [Ti^{III}] Promoted Radical Generation



Clerici, A. and Porta, O. *Tetrahedron Lett*. **1990**, *31*, 2069–2072.

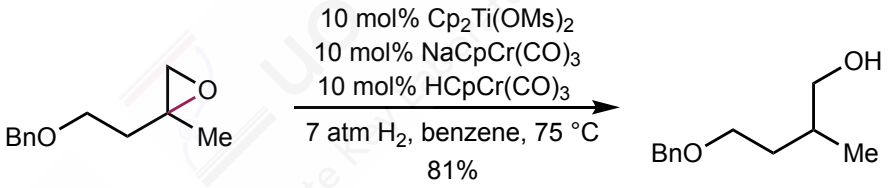
Porta, O., *et al*. *Tetrahedron* **2006**, *62*, 5986–5994.

Ti(III) Mediated Radical Reactions

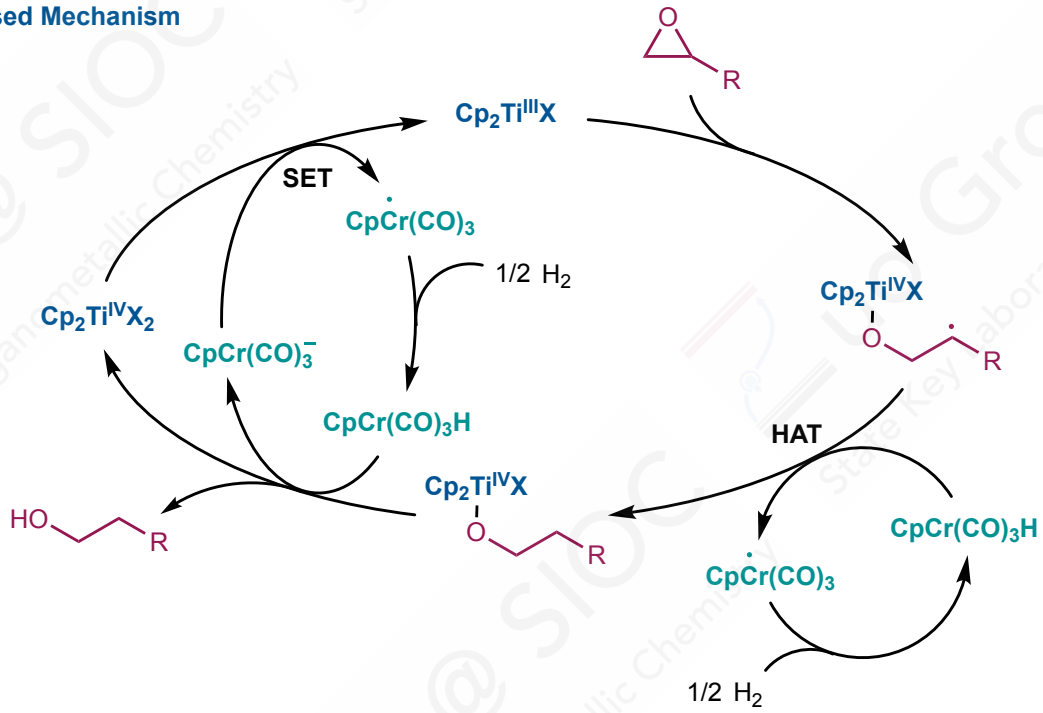


Ti(III) Mediated Radical Reactions

Anti-Markovnikov Epoxide Hydrogenation



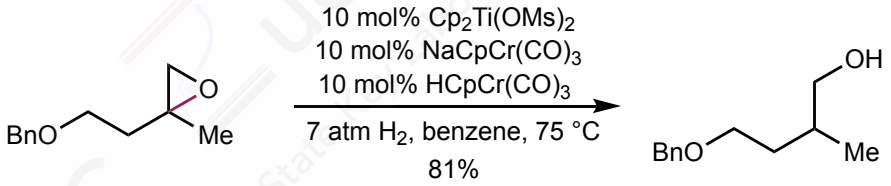
■ **Proposed Mechanism**



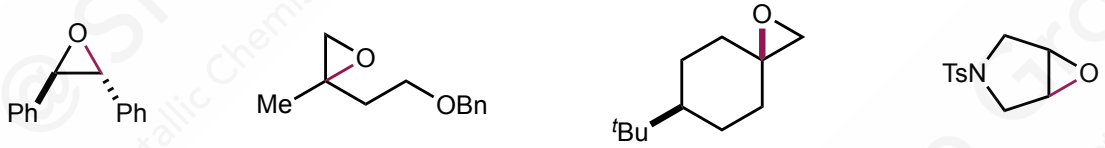
Gansäuer, A. and Norton, J. *et al*. *Science* **2019**, *364*, 764–767.

Ti(III) Mediated Radical Reactions

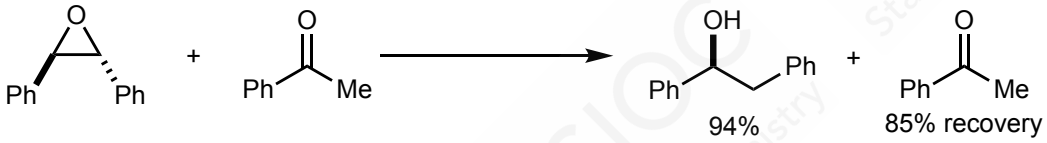
Anti-Markovnikov Epoxide Hydrogenation



■ **Selected Scope**



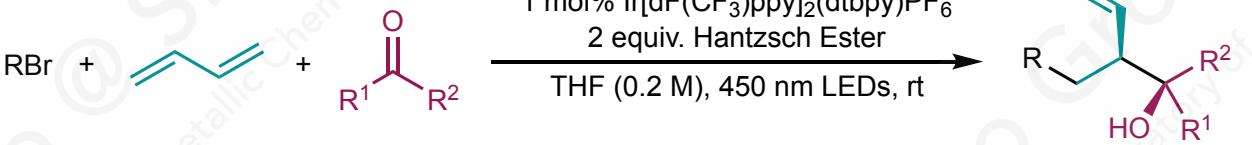
96% | 81% | 48%, *trans*:*cis* = 54:46, 10% allylic alcohol | 49%



Gansäuer, A. and Norton, J. *et al*. *Science* **2019**, *364*, 764–767.

Merging Titanocene Catalysis with Photoredox Catalysis

Photoinduced Addition of π-Allyltitanium Complexes



Shi, L., *et al*. *Angew. Chem. Int. Ed*. **2021**, *60*, 1561–1566.

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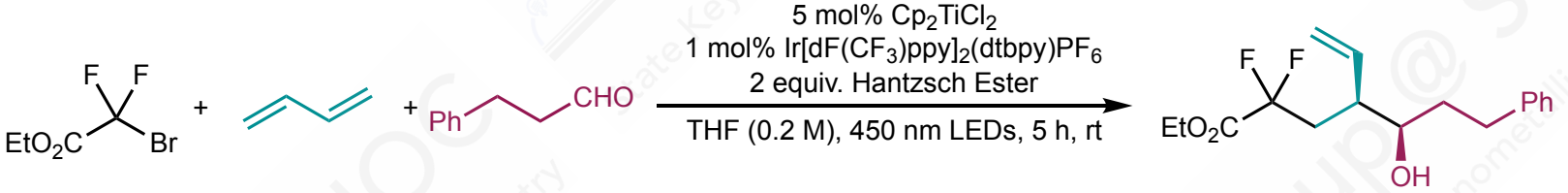

Entry	Variations from standard conditions	Pdt[a]
1	none	89%
2	4CzIPN instead of [Ir] cat.	85%
3	$Ru(bpy)_3(PF_6)_2$ instead of [Ir] cat.	N.R.
4	DIPEA istead of Hantzsch Ester	N.R.
5	$CoCl_2$, $NiCl_2$, $ZnCl_2$, $FeCl_3$, $TiCl_4$, instead of Cp_2TiCl_2	N.R.

[a]Determined by ^1H NMR analysis versus an internal standard.

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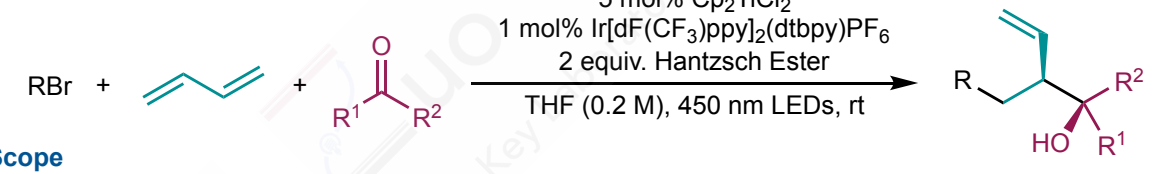
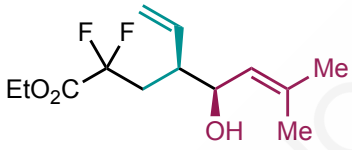
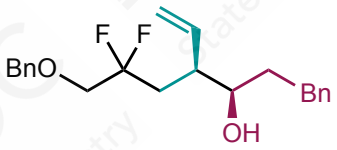


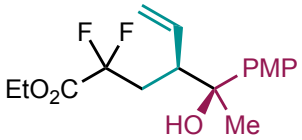
■ **Selected Scope**



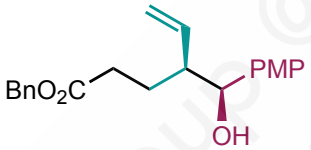
74%, > 20:1 *dr*



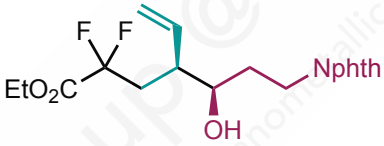
55%, > 20:1 *dr*



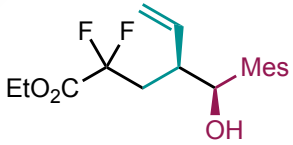
55%, 12:1 *dr*



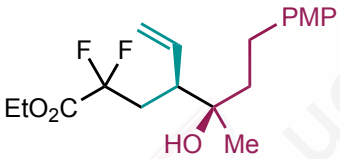
62%, > 20:1 *dr*



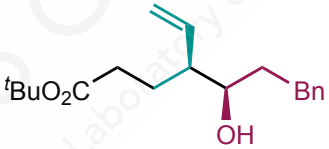
71%, > 20:1 *dr*



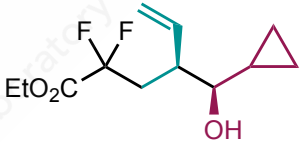
74%, > 20:1 *dr*



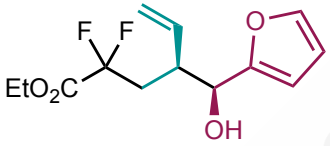
60%, 5:1 *dr*



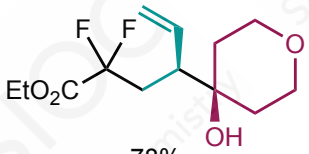
58%, > 20:1 *dr*



71%, > 20:1 *dr*



74%, > 20:1 *dr*



78%

PMP = *p*-methoxyphenyl

Nphth = phthalimido

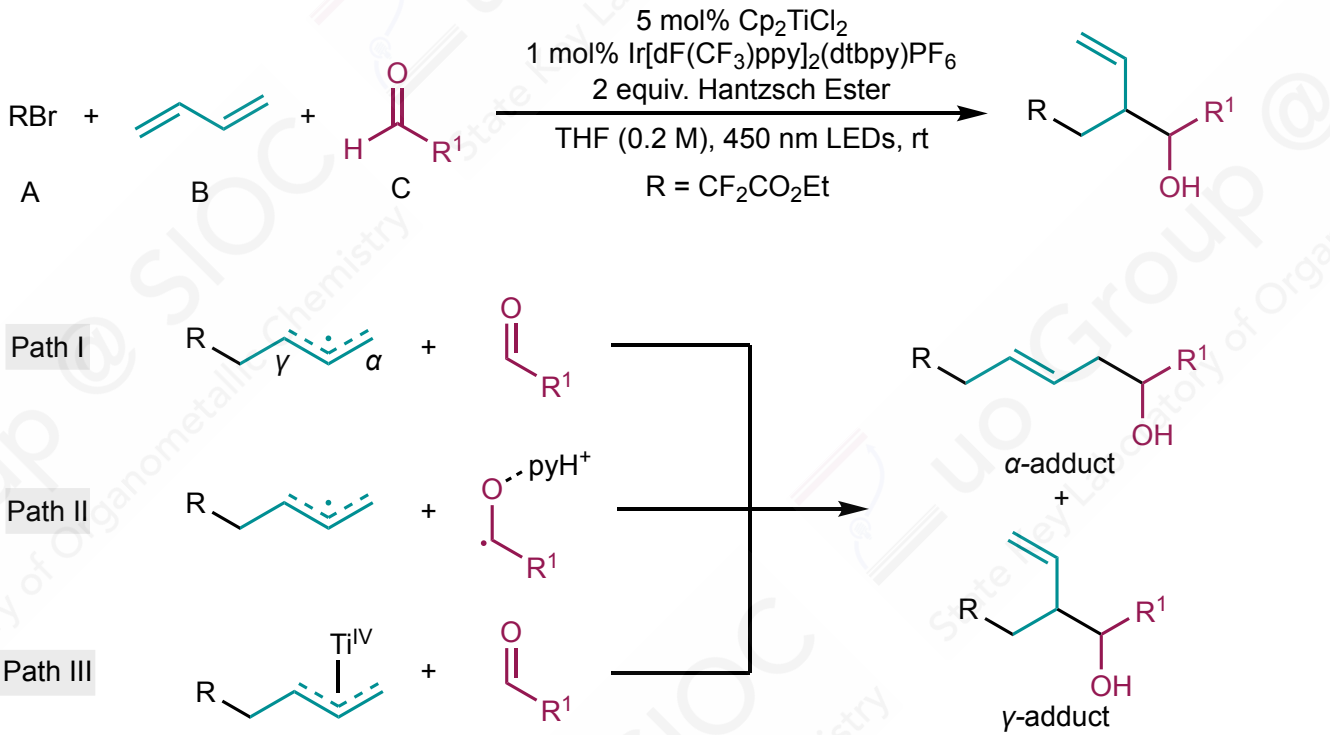
Mes = 2,4,6-trimethylphenyl

Shi, L., *et al*. *Angew. Chem. Int. Ed*. **2021**, *60*, 1561–1566.

Merging Titanocene Catalysis with Photoredox Catalysis

Photoinduced Addition of π-Allyltitanium Complexes

■ **Mechanistic Studies**



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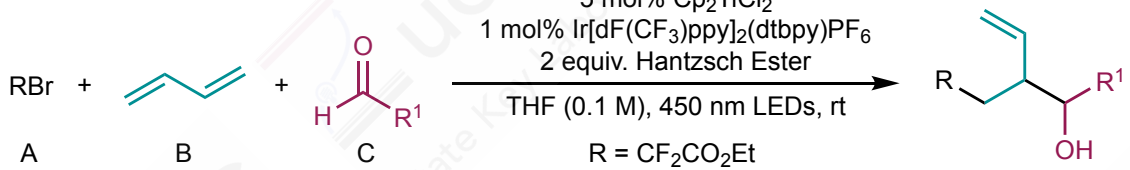
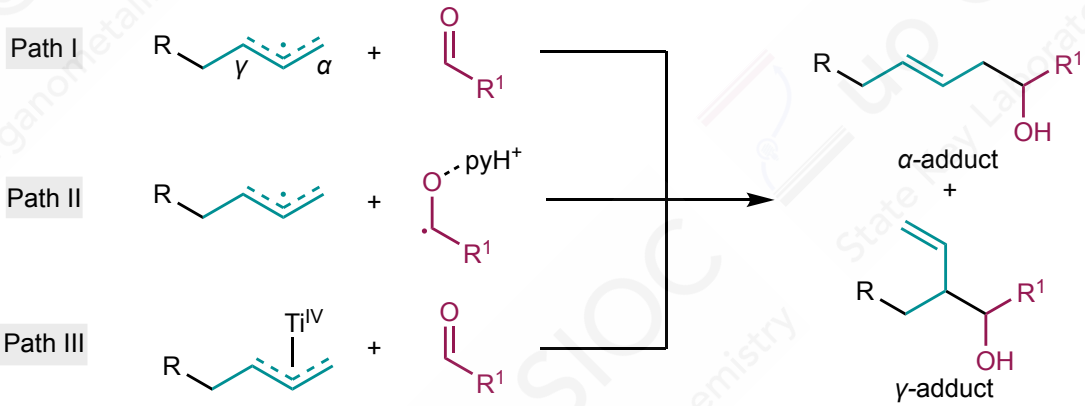
■ **Mechanistic Studies**





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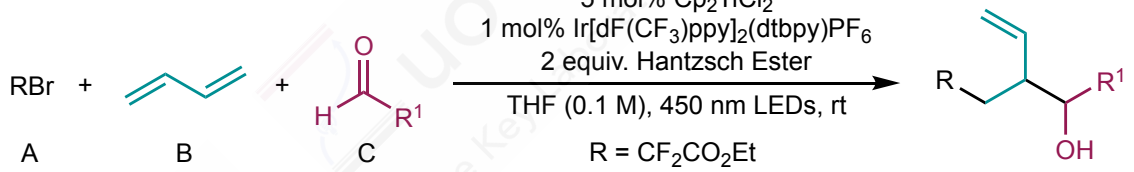

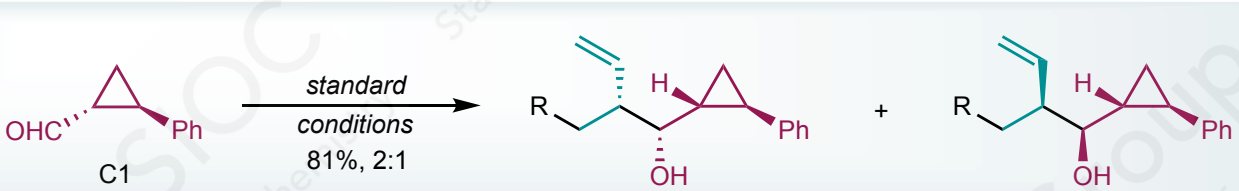

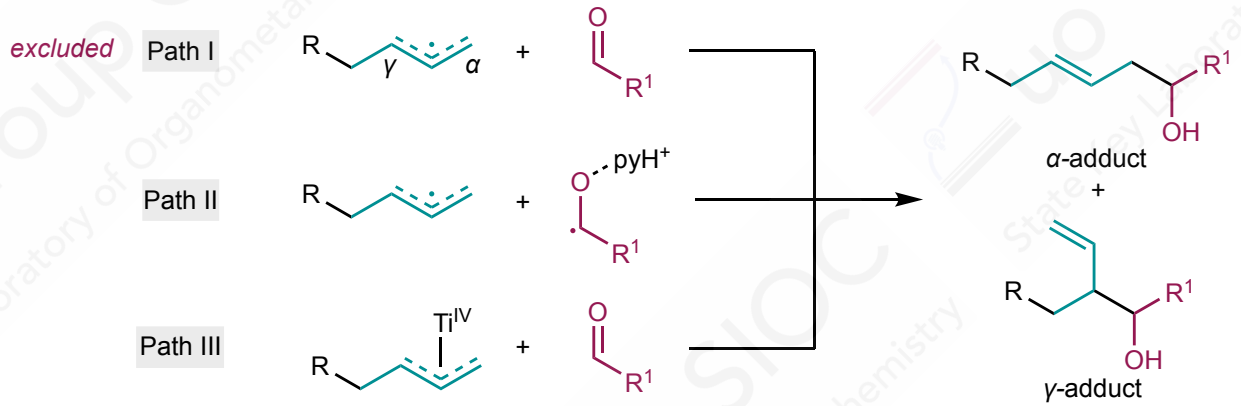

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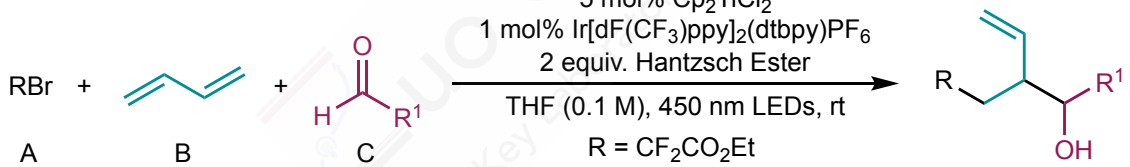
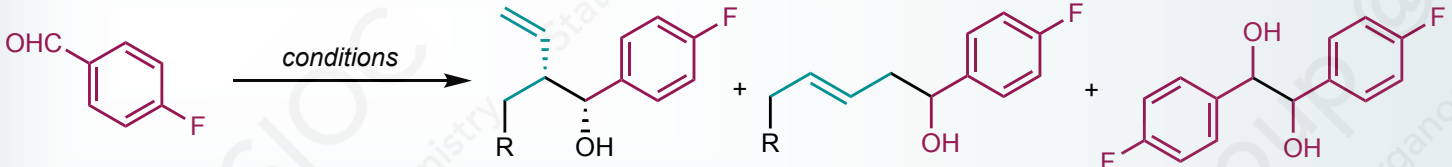
Merging Titanocene Catalysis with Photoredox Catalysis

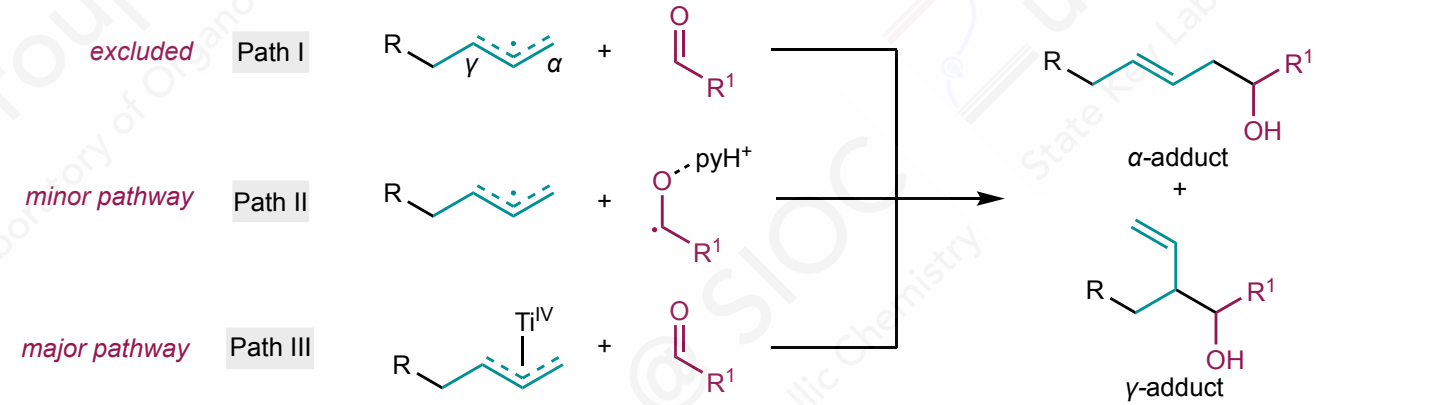
Photoinduced Addition of π-Allyltitanium Complexes

■ **Mechanistic Studies**





conditions	γ-adduct	α-adduct	pinacol
no Cp_2TiCl_2	8%	23%	36%
Cp_2TiCl_2	52%	11%	17%
Cp_2TiCl_2, LiCl	86%	trace	trace



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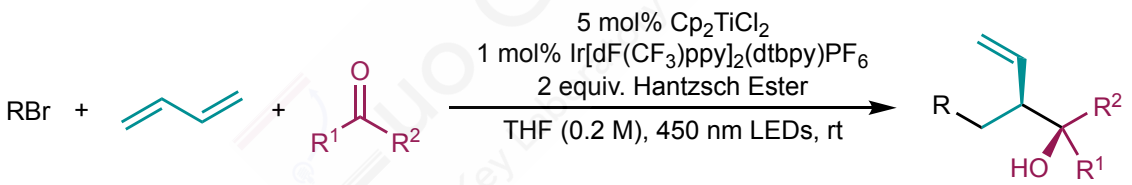
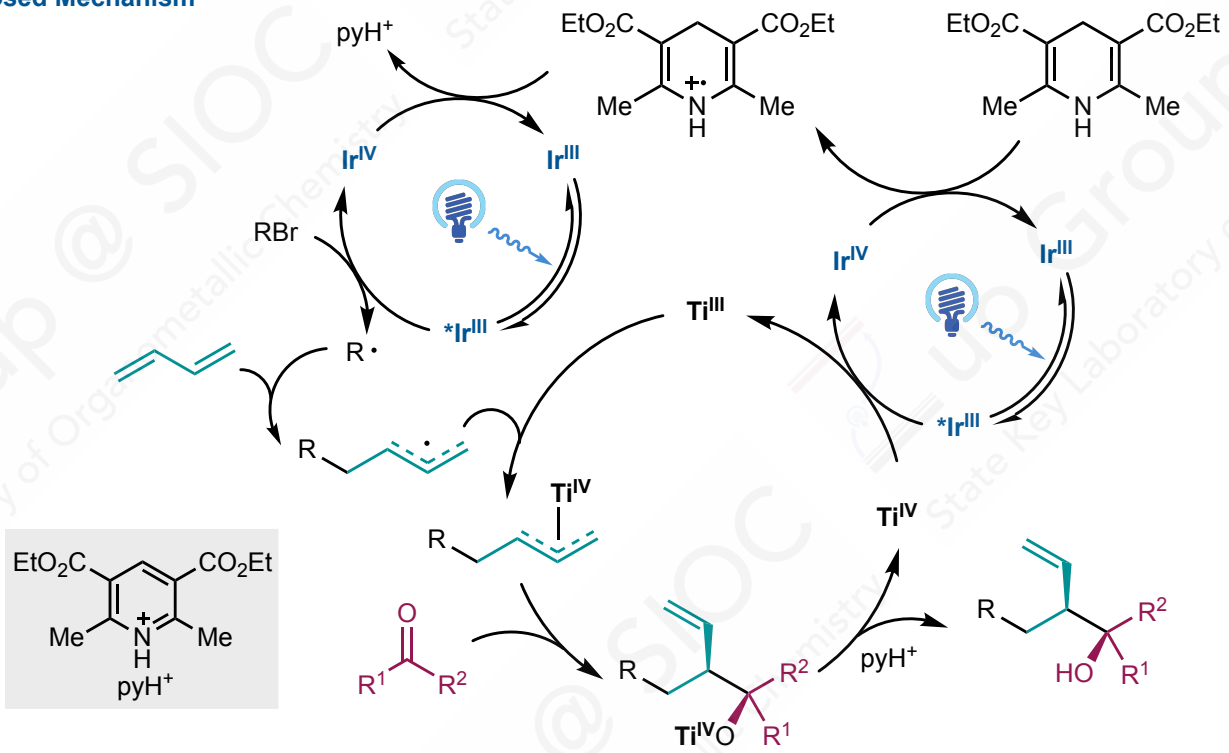


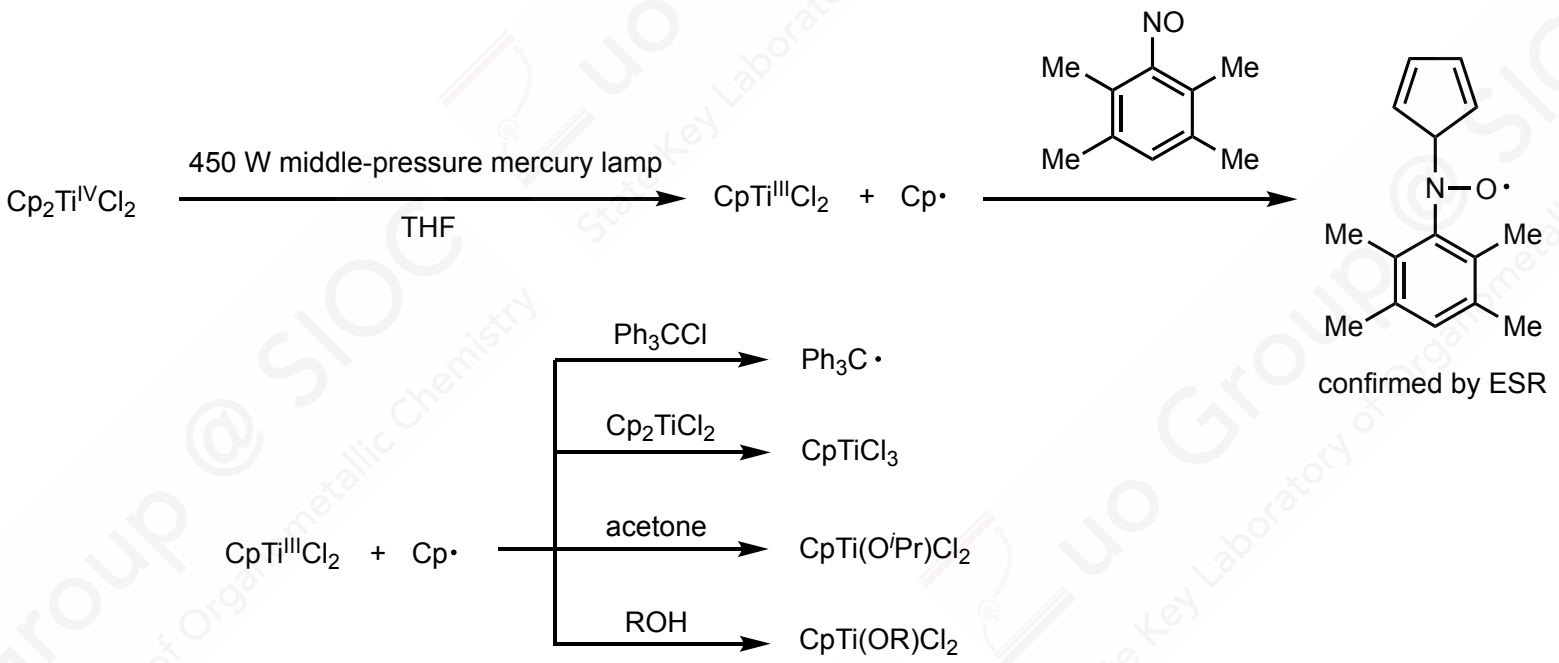
■ **Proposed Mechanism**



Shi, L., *et al*. *Angew. Chem. Int. Ed.* **2021**, *60*, 1561–1566.

Ti(IV) Species as Photocatalysts

Photolysis of Cp_2TiCl_2



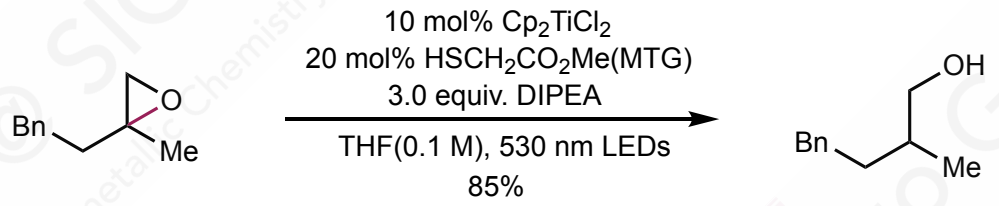
Cp_2TiCl_2 absorption bands(in MeCN): **250, 392, 522 nm**

Middle-pressure mercury lamp(MPML) Main irradiation bands: 300, 303, 313, 334, 366, 405, 436, 546, 578 nm

Tsai, Z.-T. and Brubaker, Jr. C. H. *J. Organomet. Chem.* **1979**, *166*, 199–210.

Ti(IV) Species as Photocatalysts

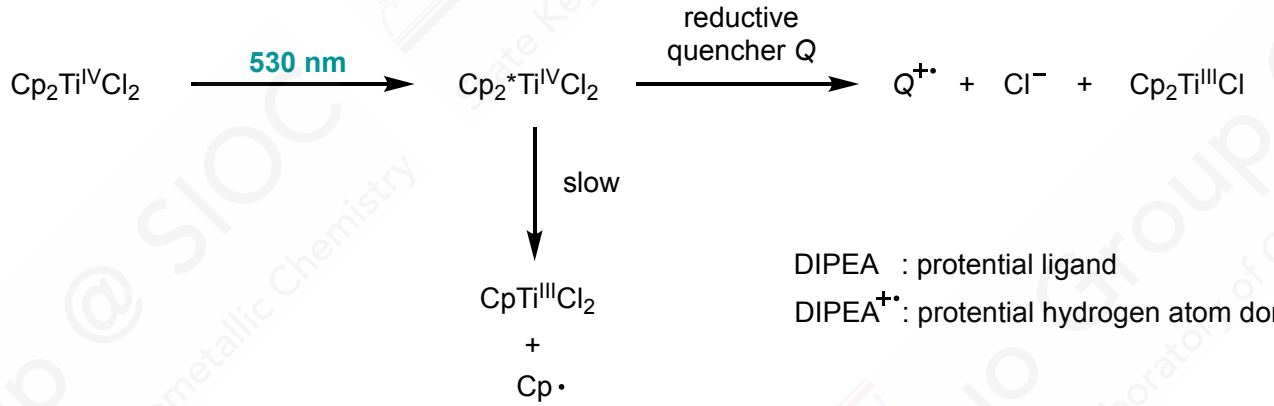
Cp_2TiCl_2 as Photocatalyst

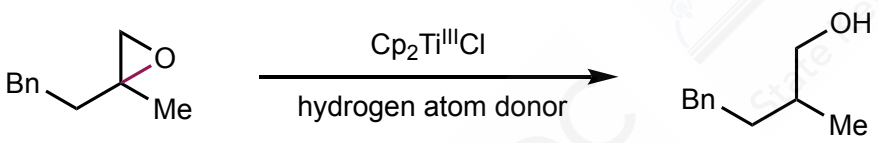


Flowers II, R. A. and Gansäuer, A., *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

Cp_2TiCl_2 as Photocatalyst

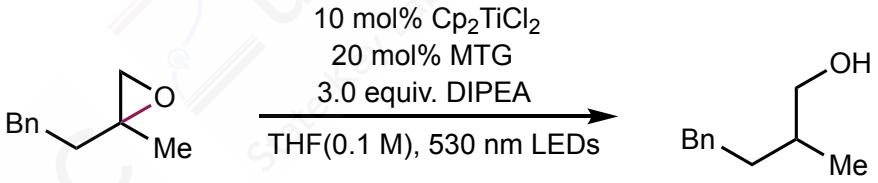




Flowers II, R. A. and Gansäuer, A., *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

Cp_2TiCl_2 as Photocatalyst

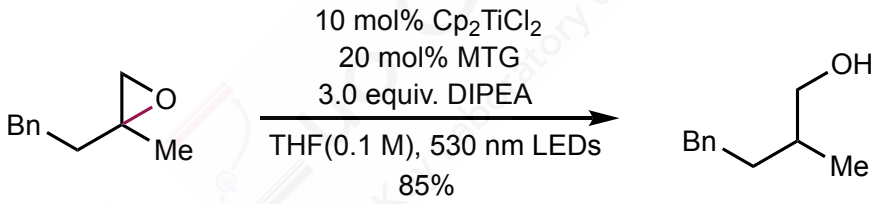


Entry	Variations from standard conditions	Pdt
1	none	85%
2	no $HSCH_2CO_2Me$	N.R.
3	NEt_3 instead of DIPEA	49%
4	no light	N.R.
5	no [Ti]	N.R.
6	no DIPEA	N.R.
7	$Cp_2Ti(OMs)_2$ instead of Cp_2TiCl_2	N.R.

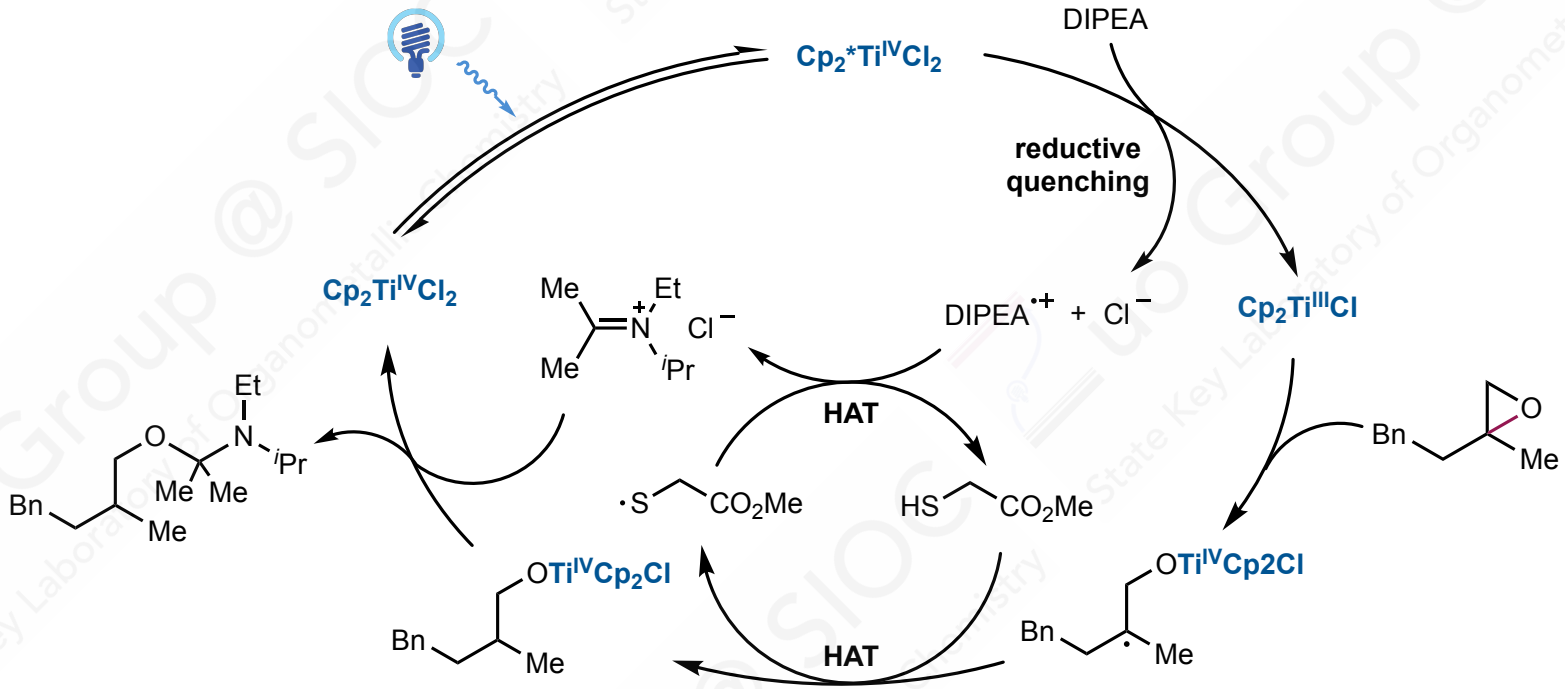
Flowers II, R. A. and Gansäuer, A., *et al*. *Angew. Chem. Int. Ed*. **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

Cp_2TiCl_2 as Photocatalyst



■ **Proposed Mechanism**

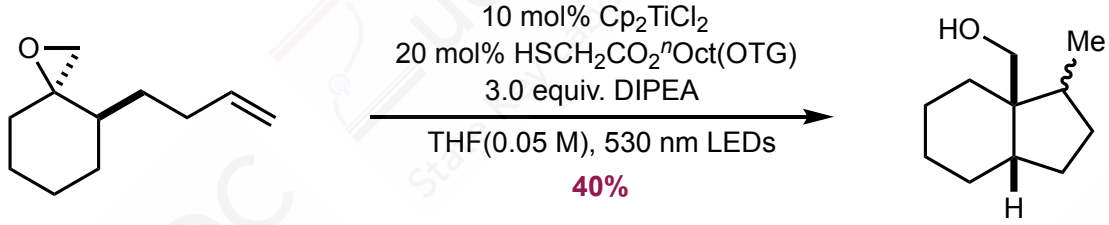


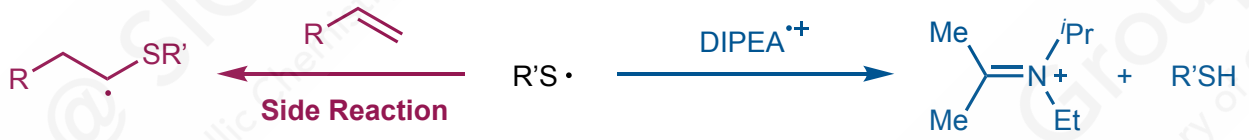
Flowers II, R. A. and Gansäuer, A., *et al*. *Angew*. *Chem*. *Int*. *Ed*. **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

Cp_2TiCl_2 as Photocatalyst

■ **Side Reaction 5-*exo* Cyclization**





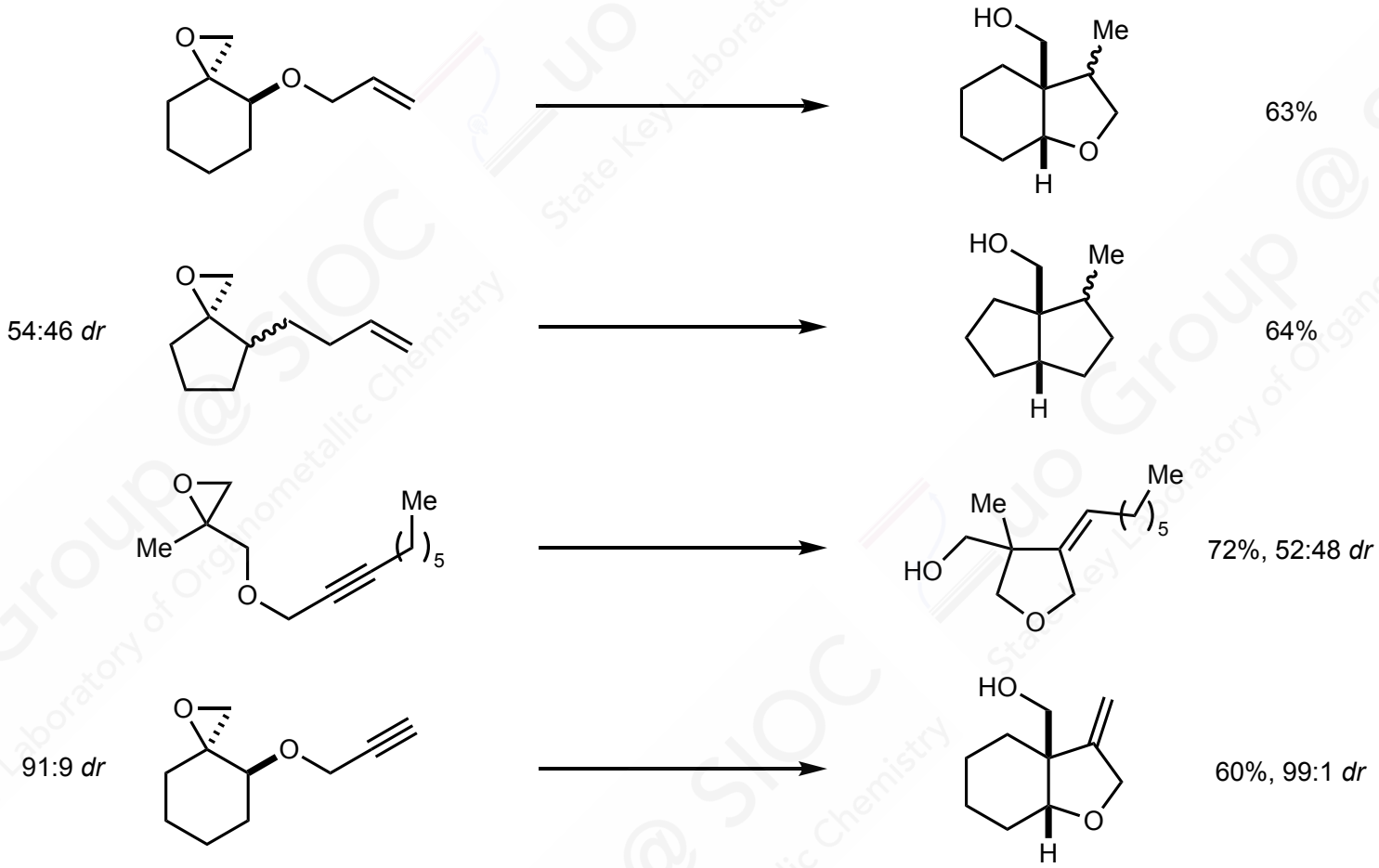
Entry	Variations from standard conditions	Pdt
1	none	40%
2	0.5 equiv. $PhSiH_3$	75%
3	**2.5 equiv. $PhSiH_3$**	**80%**
4	2.5 equiv. $PhSiH_3$, MTG instead of OTG	68%

Flowers II, R. A. and Gansäuer, A., *et al*. *Angew. Chem. Int. Ed.* **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

Cp_2TiCl_2 as Photocatalyst

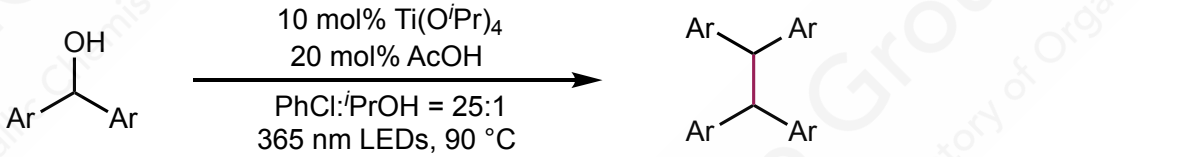
■ **Selected Scope of 5-*exo* Cyclization**



Flowers II, R. A. and Gansäuer, A., *et al*. *Angew. Chem. Int. Ed*. **2020**, *59*, 9355–9359.

Ti(IV) Species as Photocatalysts

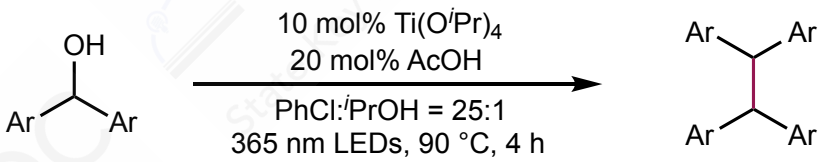
Ti(O^iPr)$_4$ as Photocatalyst



Iwasawa, N. *et al*. *Eur. J. Org. Chem*. **2021**, 2474–2478.

Ti(IV) Species as Photocatalysts

Ti(O^{i}Pr)$_4$ as Photocatalyst

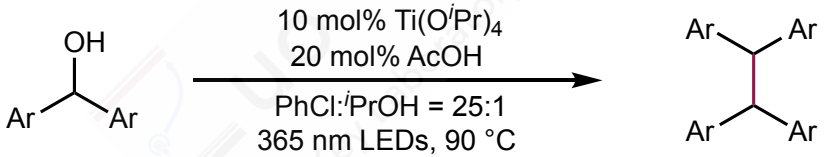


Entry	Variations from standard conditions	Pdt
1	none	55%
2	no AcOH	N.R.
3	no AcOH, no ^{i}PrOH	12%
4	no light	N.R.
5	no [Ti]	N.R.
6	425 nm LEDs	N.R.

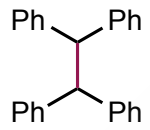
Iwasawa, N. *et al*. *Eur. J. Org. Chem*. **2021**, 2474–2478.

Ti(IV) Species as Photocatalysts

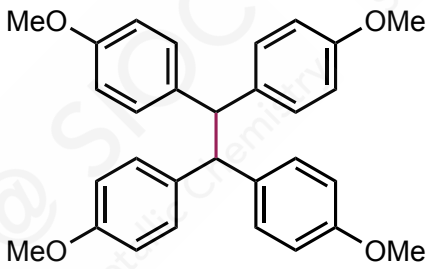
Ti(O^{i}Pr)$_4$ as Photocatalyst



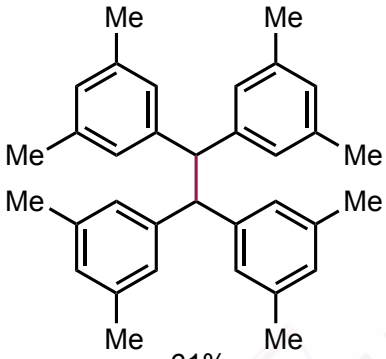
■ **Selected Scope**



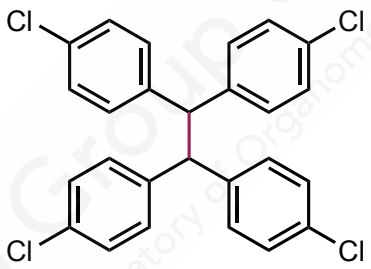
71%



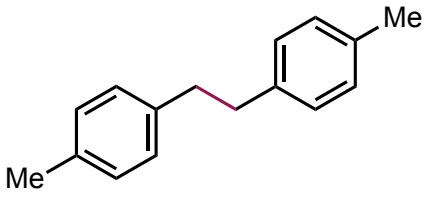
71%



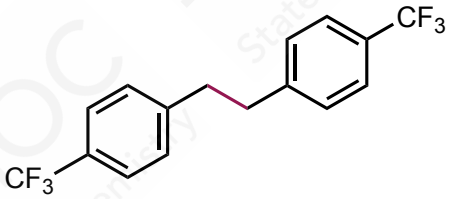
61%



63%



24%
5 equiv. AcOH, no ^{i}PrOH,120 °C



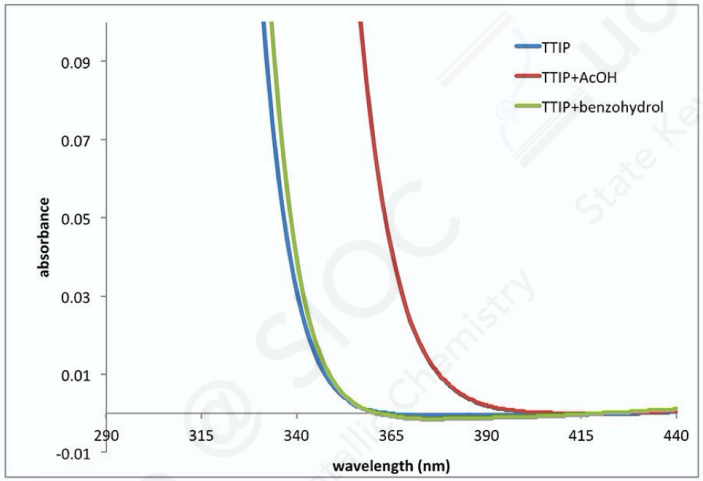
20%
5 equiv. AcOH, no ^{i}PrOH,120 °C

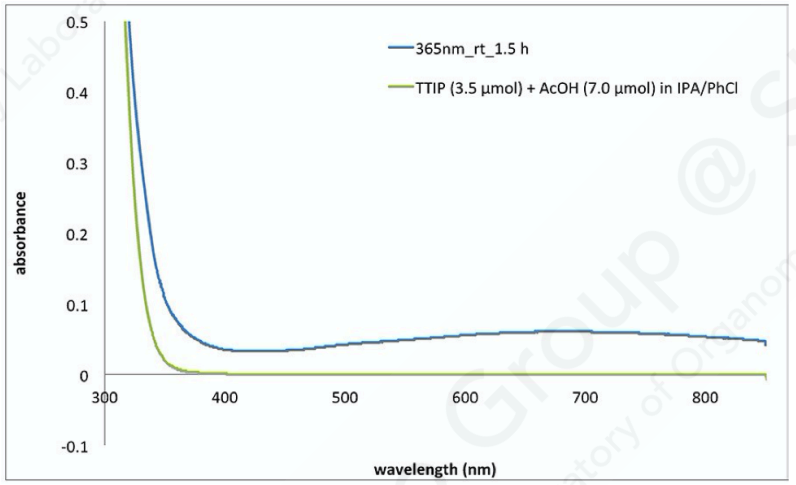
Iwasawa, N. *et al*. *Eur. J. Org. Chem*. **2021**, 2474–2478.

Ti(IV) Species as Photocatalysts

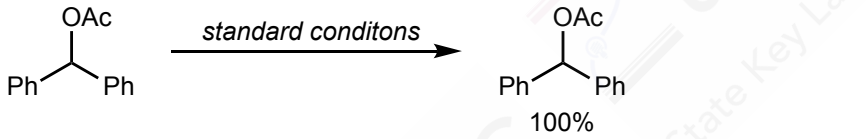
Ti(O^{i}Pr)$_4$ as Photocatalyst

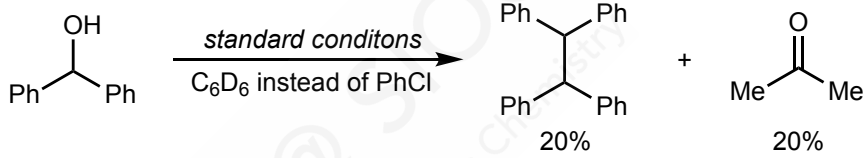
UV Spectra





Mechanistic Studies

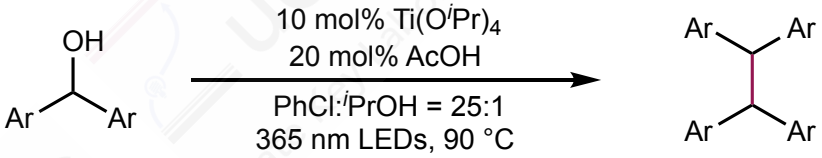




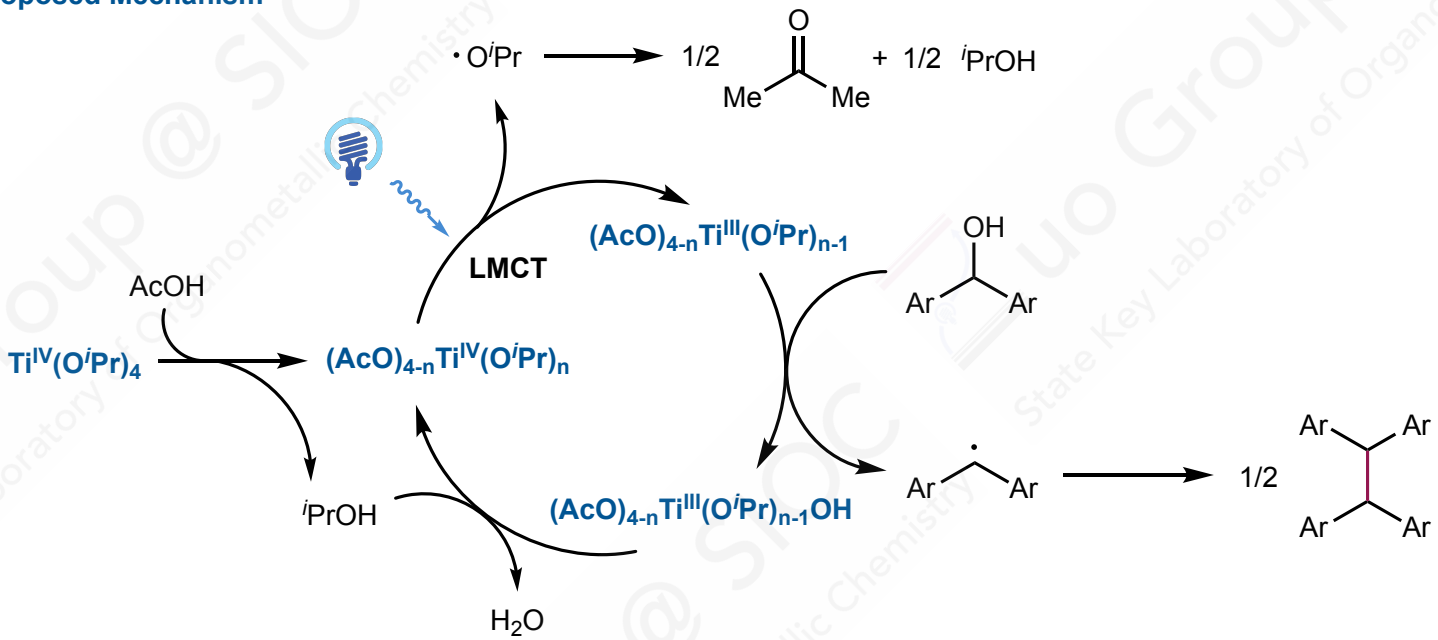
Iwasawa, N. *et al*. *Eur. J. Org. Chem*. **2021**, 2474–2478.

Ti(IV) Species as Photocatalysts

Ti(O^{i}Pr)$_4$ as Photocatalyst



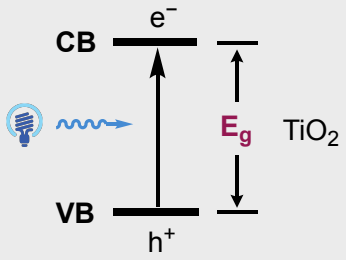
■ **Proposed Mechanism**



Iwasawa, N. *et al*. *Eur. J. Org. Chem*. **2021**, 2474–2478.

Heterogeneous Catalysis

TiO_2 as Photocatalyst



$E_{g(rutile)}$ = 3.05 eV λ = 407 nm

$E_{g(anatase)}$ = 3.2 eV λ = 388 nm

Fujishima, **2008**

$$H_2O \xrightarrow{TiO_2(rutile),\ hv} 1/2\ O_2 + H_2$$

via

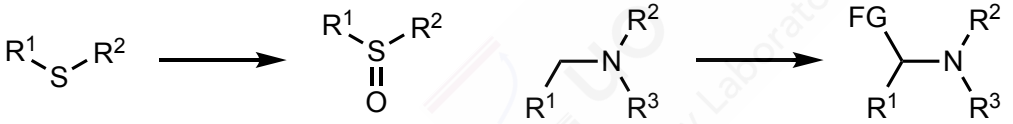
$$H_2O \xrightarrow[-\ e^-]{h^+} H^+ + {}^{\bullet}OH$$

Fujishima, A. and Honda, K. *Nature* **1972**, *238*, 37–38.

$$R^1{-}X{-}R^2 \xrightarrow[-\ e^-]{h^+} R^1{-}X^{+\bullet}{-}R^2$$

X = NR^3, O, S, *etc.*

■ **Oxidations**



broad band gap

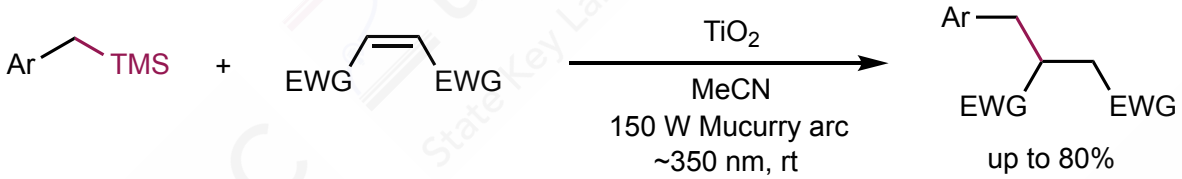
poor selectivity

low sunlight utilization

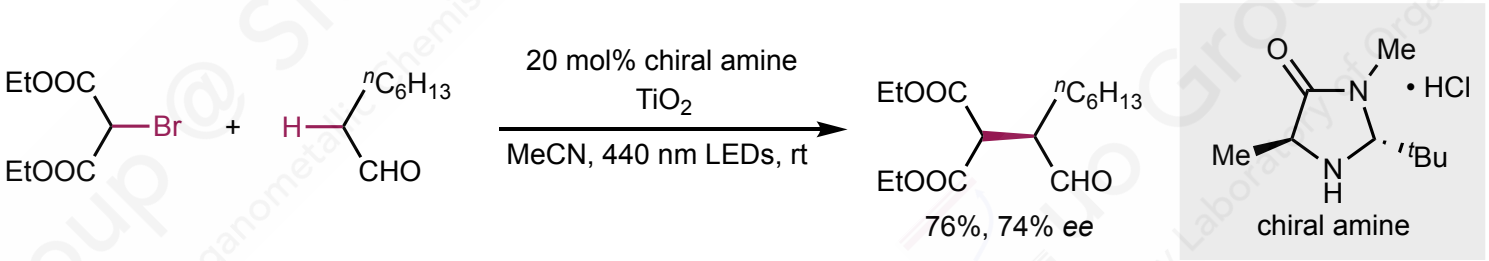
Dye-sensitization	AR-TiO_2	PPP-TiO_2	eosin Y-TiO_2
M-TiO_2 Composite	Pt-TiO_2	Sm_xO_y-TiO_2	NiO-TiO_2
TiO_2-ion	Ru^{II}-TiO_2 polyazine complex		Ti^{3+} doped TiO_2
Nonmetal Doping	Si-TiO_2	B_{12}-TiO_2	

Heterogeneous Catalysis

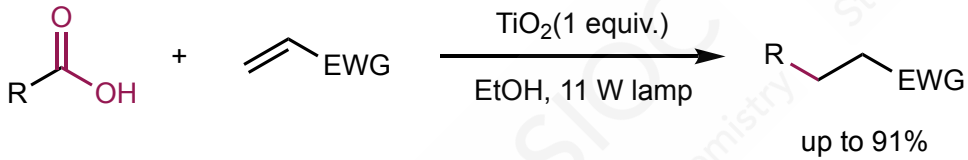
TiO_2 as Photocatalyst



Albini, A. *et al*. *Tetrahedron* **1998**, *54*, 2575–2582.



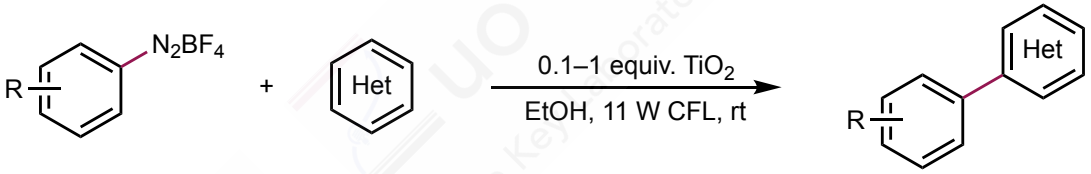
König, B. *et al*. *Angew. Chem. Int. Ed*. **2012**, *51*, 4062–4066.



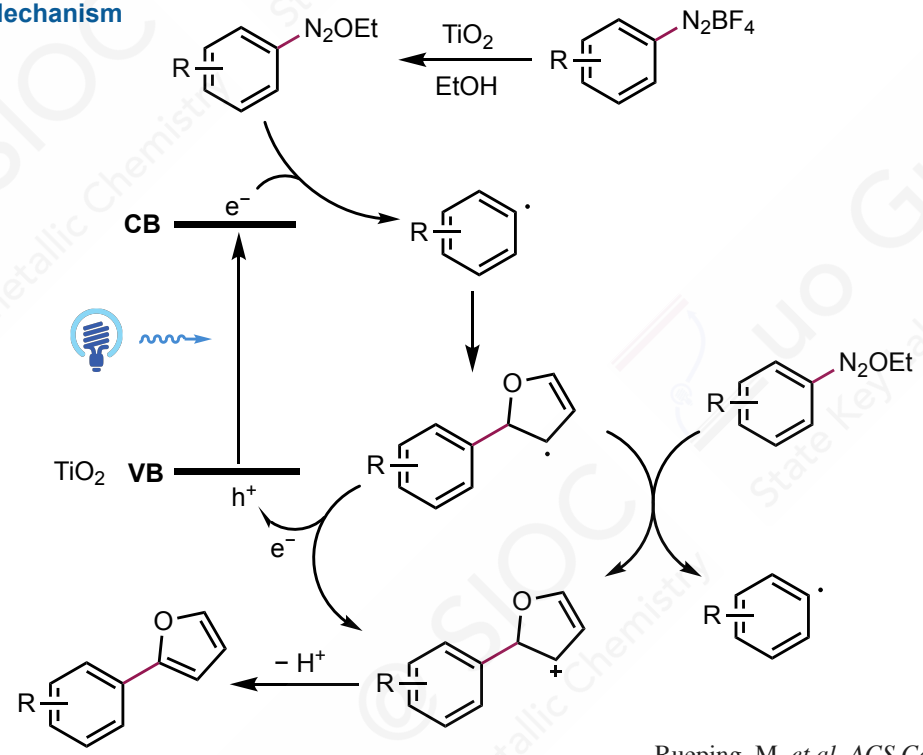
Zhu, Q. and Nocera, G. *J. Am. Chem. Soc*. **2020**, *142*, 17913–17918.

Heterogeneous Photocatalysis

TiO_2 as Photocatalyst



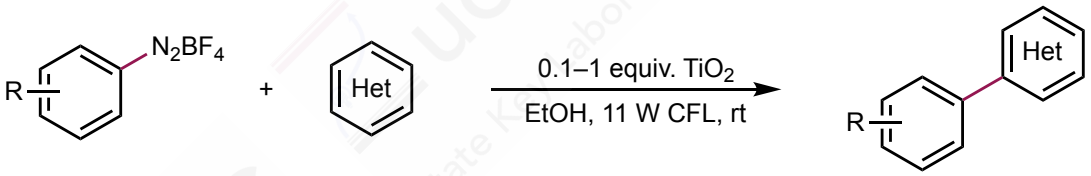
■ **Proposed Mechanism**



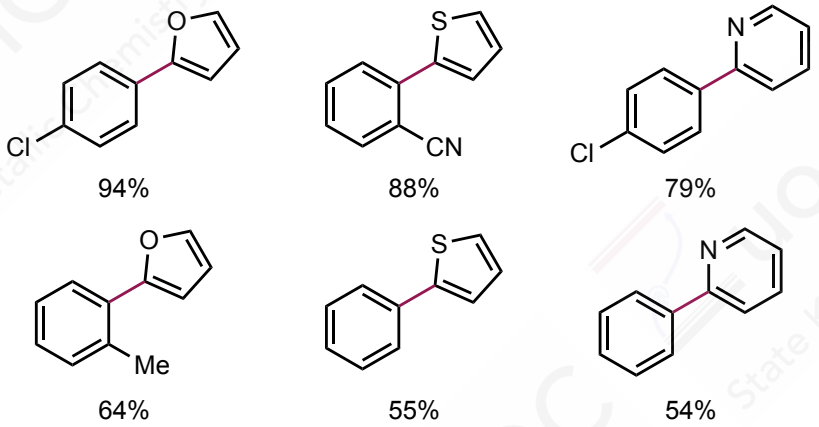
Rueping, M. *et al*. *ACS Catal*. **2015**, *5*, 3900–3904.

Heterogeneous Photocatalysis

TiO_2 as Photocatalyst



■ **Selected Scope**

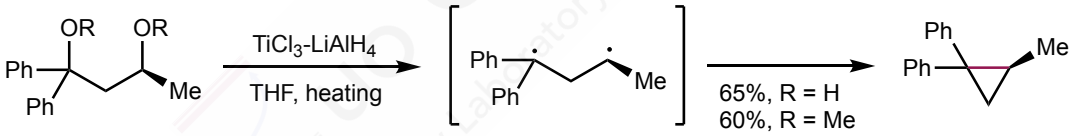


Yield depends on radical properties

Rueping, M. *et al*. *ACS Catal*. **2015**, *5*, 3900–3904.

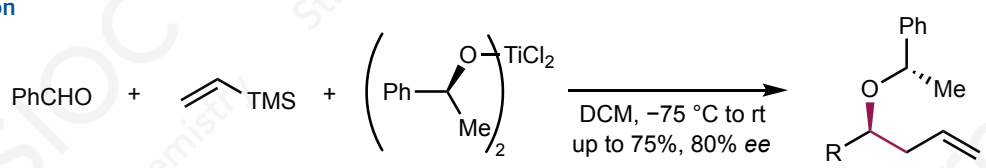
Other Couplings

Coupling of 1,3-diols



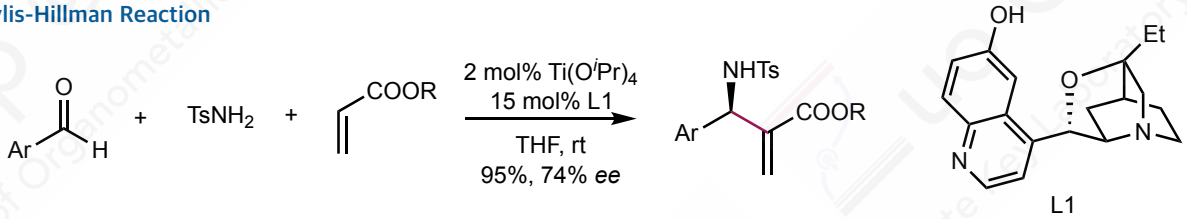
Hehre, W. J. and Taft, R. W. *et al*. *J*. *Am*. *Chem*. *Soc*. **1980**, *102*, 426–428.

Sakurai Reaction



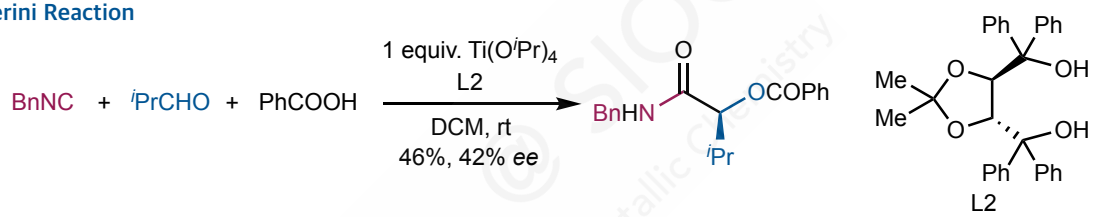
Seebach, D. *et al*. *Angew*. *Chem*. *Int*. *Ed*. **1985**, *24*, 765–766.

Baylis-Hillman Reaction



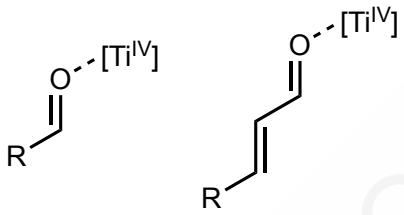
Balan, D. and Adolfsson, H. *Tetrahedron Lett*. **1999**, *28*, 257–258.

Passerini Reaction

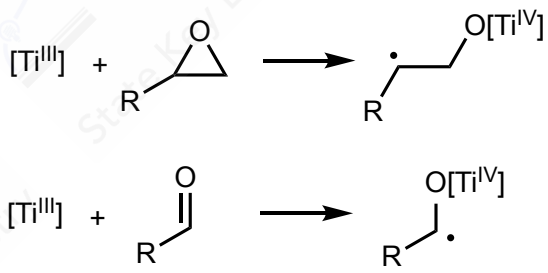


Dömling, A. *et al*. *Org*. *Lett*. **2003**, *5*, 4021–4024.

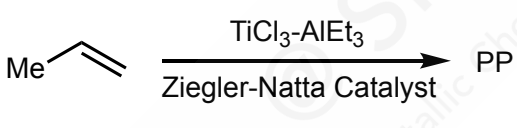
Summary



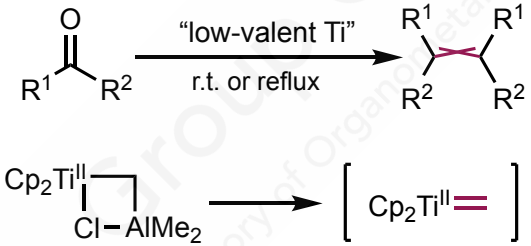
Tradictional Lewis acid



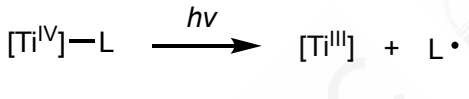
Radical reaction catalyst



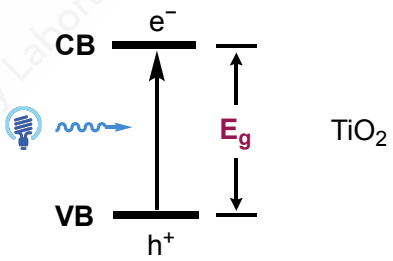
Coordination polymerization initiator



Reductive agent mediating cycloaddition or deoxygenation



Photocatalyst in Photoinduced LMCT



Semiconductor Photocatalyst