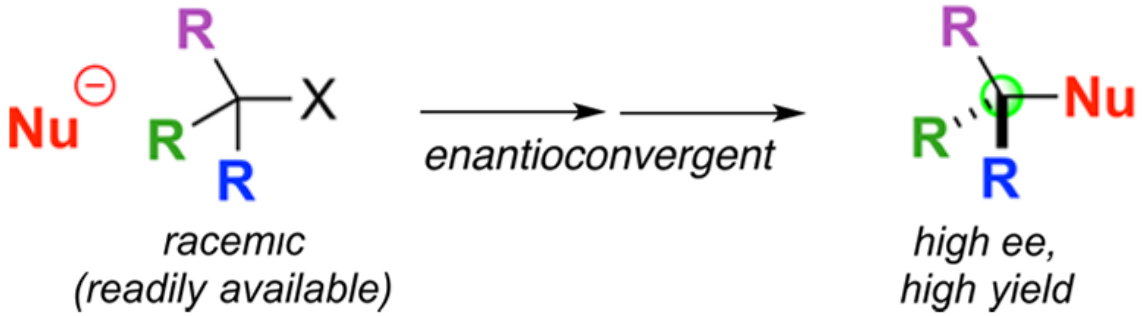
Enantioconvergent functionalization of racemic tertiary alkyl halides via catalytic strategies

Literature seminar 2025/11/27

B4 Kana Furukawa



Fu, G.C. *ACS Cent. Sci.* **2017**, *3*, 692–700

Introduction -Theme and its significance

Enantioconvergent functionalization of racemic tertiary alkyl halides via catalytic strategies

C-H/C-X functionalization

Consider cases where the reaction occurs at an C(sp^3) stereocenter

①Simple alkyl compounds or alkyl halides as SM

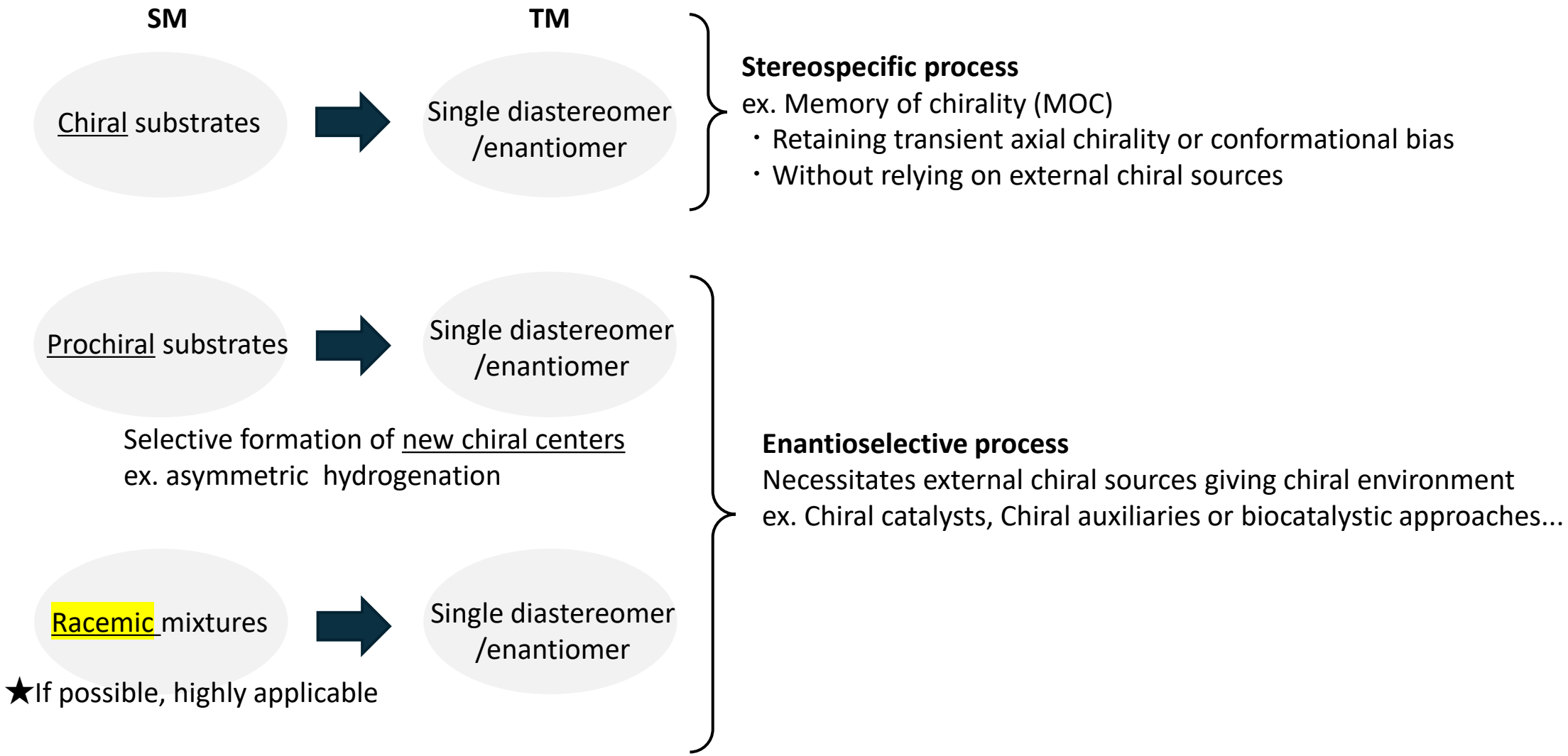
- Commercially available
- Simple Subsitution

②Creation of chiral quaternary carbon centers is challenging.

- Steric congestion
- Enantio-differentiation of three distinct carbon substituents of prochiral tertiary radicals

What does “enantioconvergent” means? >>>

Introduction -Chirality induction

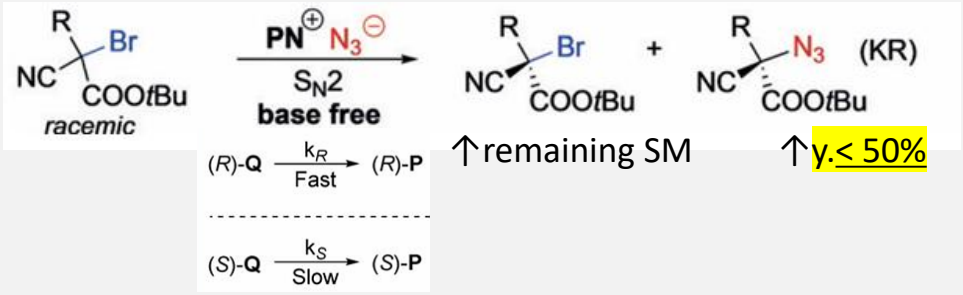


Introduction -Enantioconvergent reactions

✗Not enantioconvergent

①Kinetic resolution (KR)

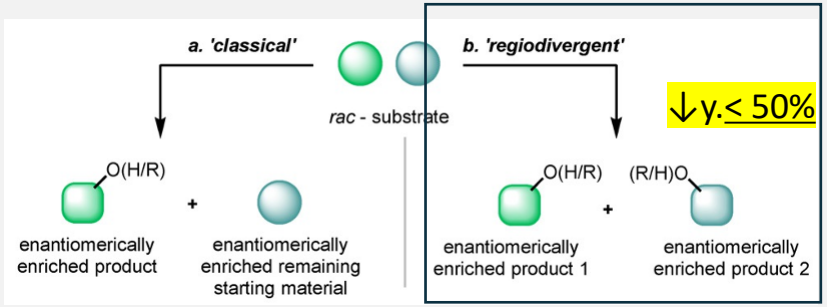
▲y.< 50%



↑remaining SM ↑y.< 50%

②cf. “Stereodivergent”

Parallel Kinetic Resolution (PKR)



For the improvement of yield,

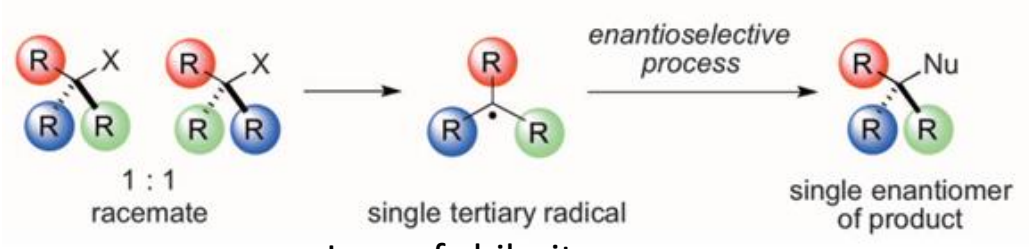
➡Need to convert the other half enantiomer...

➡Enantioconvergent process

Yus, M., Nájera, C., Foubelo, F. *et al. Chem. Rev*. **2023**, 123, 11817–11893

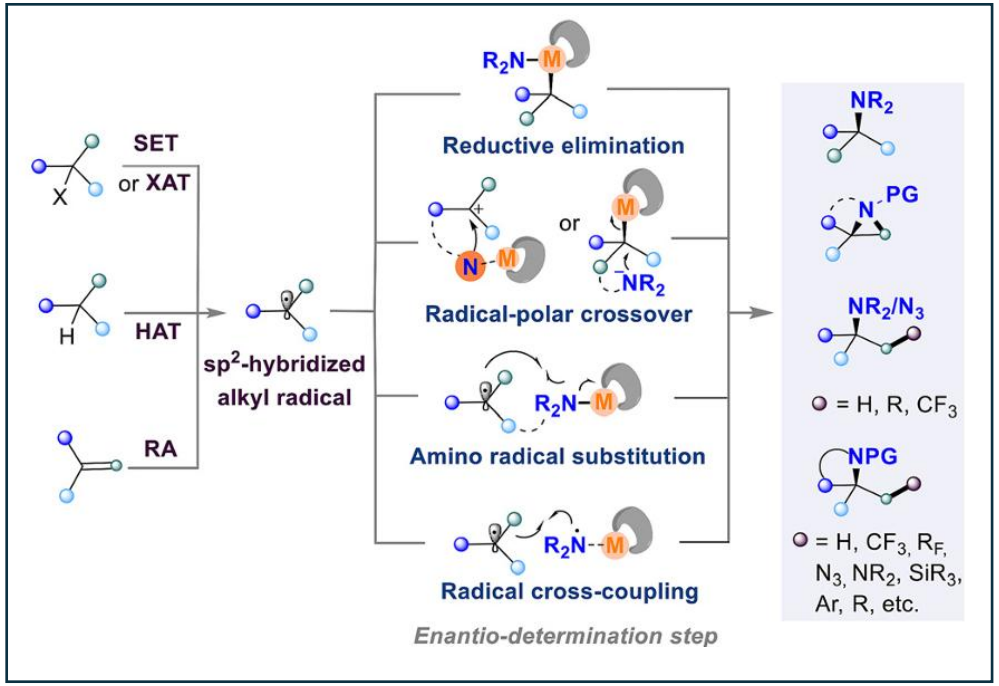
Enanticonvergent process

=Enantioselective transformation from racemic mixture



Loss of chilarity

ex.



Sun, J., Zheng, G., Zhang, G. *et al. Org. Chem. Front*. **2025**, 12, 1671

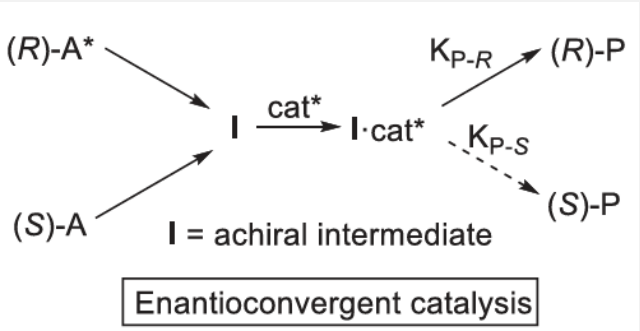
Introduction -Enantioconvergent reactions

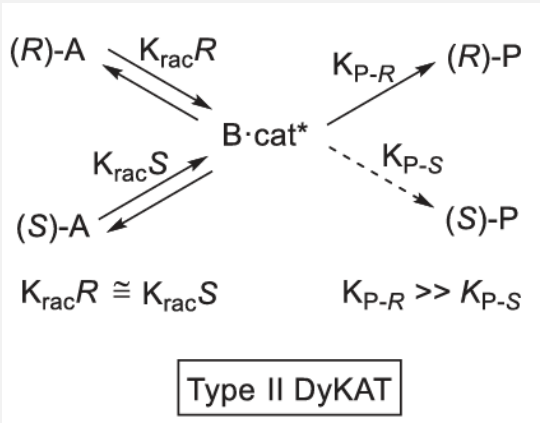
When does desymmetrization occur?

“Stereoablative”

★Loss of stereocenter

★Achiral intermediate

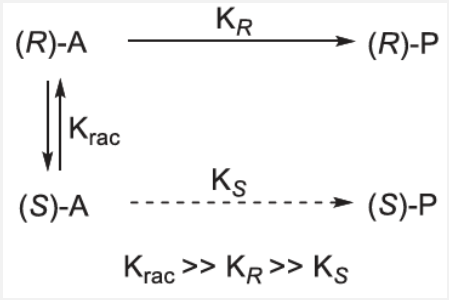




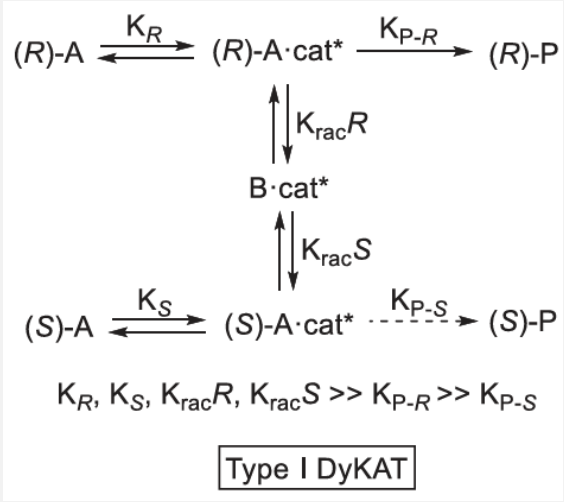
“Stereomutative”

★Racemization

▲Racemization rate is crucial for high y.



Dynamic kinetic resolution (DKR)



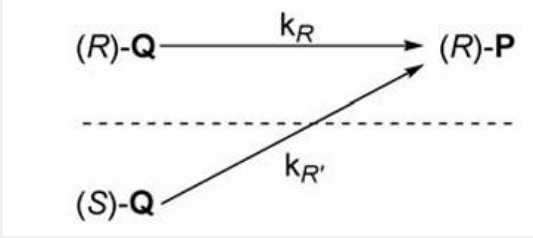
Dynamic kinetic asymmetric transformation (DyKAT)

Sansano, J.M. *et al., Chem.Rev*. **2023,** *123*,11817−11893

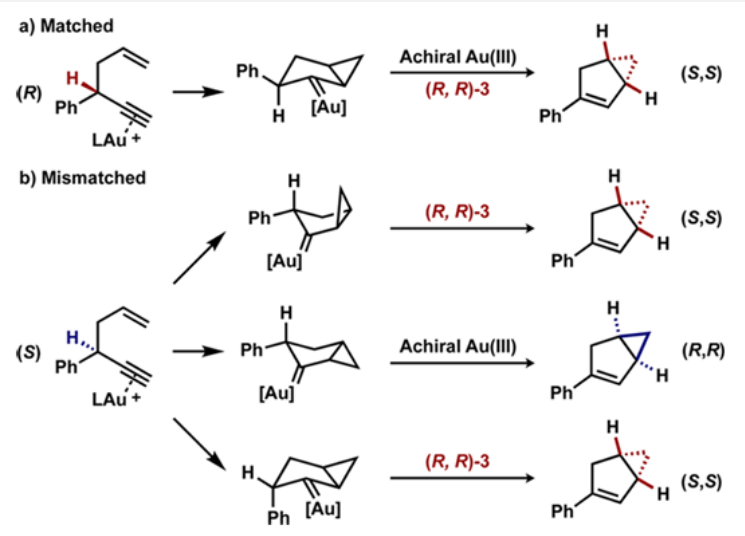
“Stereodiscordant”

★Different reactionpathway

▲Few examples



Direct enantioconvergent transformation (DET)



Zhu, Y., You, H., Chen, F.E. *et al. Chem. Sci.* **2024**,*15*, 8280

Toste, F.D. *et al., J. Am. Chem. Soc*. **2017**, *139*, 11016−11019

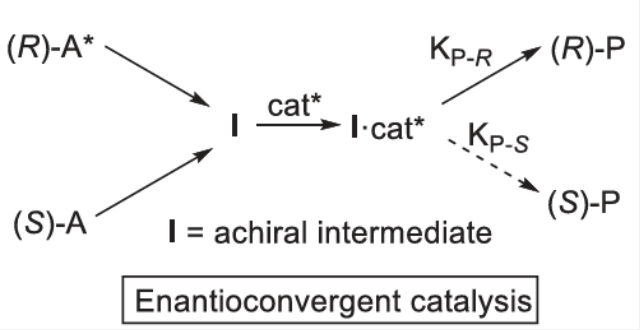
Introduction -Enantioconvergent reactions

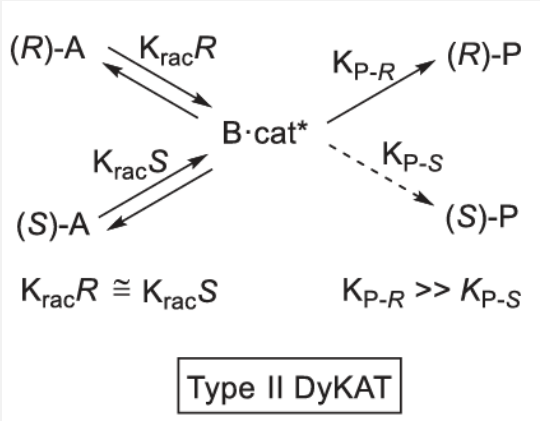
When does desymmetrization occur?

"Stereoablative"

★Loss of stereocenter

★Achiral intermediate





- Chiral catalyst captures achiral intermediate
- Applicable to unactivated C(sp^3)-H, robust bonds
- Forcible reset of stereochemical information

★Integration with radical chemistry:

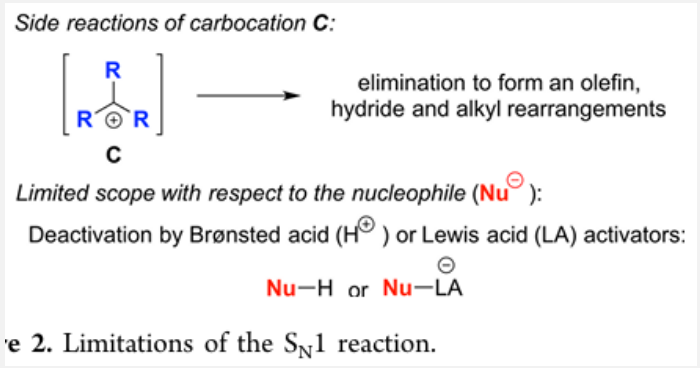
Alkyl radicals inherently function as achiral intermediates!

Zhu, Y., You, H., Chen, F.E. *et al. Chem. Sci.* **2024**,*15*, 8280
Sansano, J.M. *et al., Chem.Rev*. **2023,** *123*,11817−11893

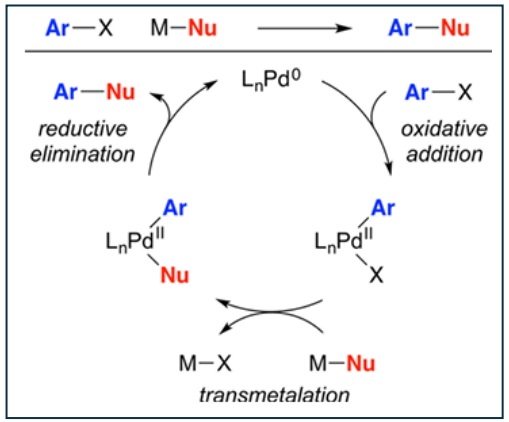
Steric hindrance and substitution strategy and chirality control

Nucleophilic substitution of an alkyl halide
Straight forward, but less explored:

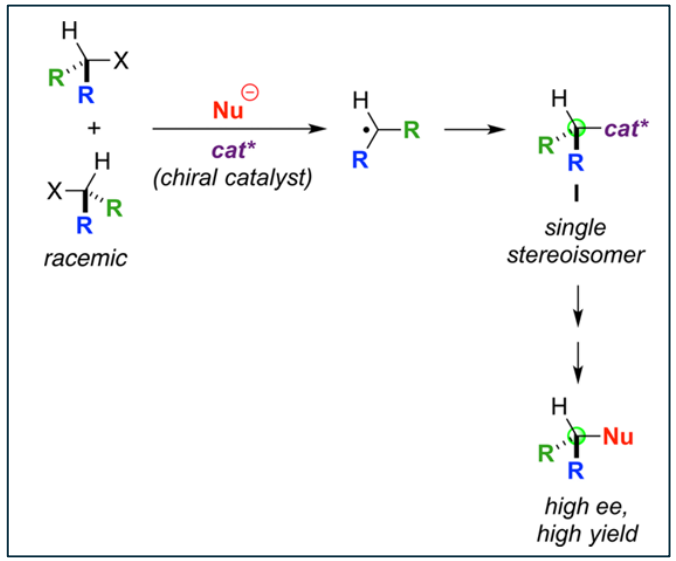
classical substitution reactions (SN1)
▲Difficulty in controlling the stereochemistry
▲Olefination as a side reaction



Due to steric considerations, direct insertion into the C–X bond of a secondary or tertiary alkyl halide is challenging ->

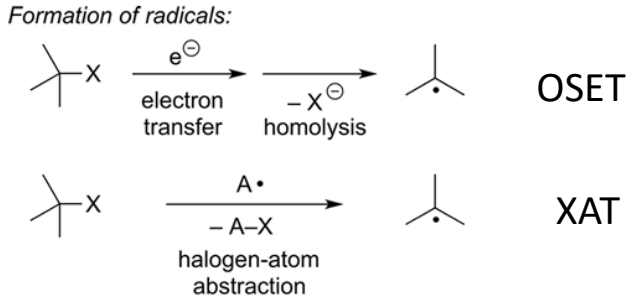


Catalytic process via prochiral radicals
-> No need of direct insertion



Enantiopure transition-metal catalyst could afford a single stereoisomer of an alkylmetal complex
➡Enantioconvergent reactions

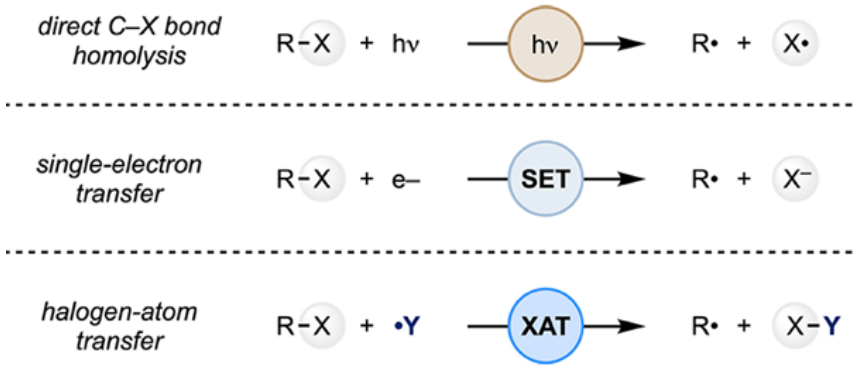
***Radical formation**



Fu, G.C. *ACS Cent. Sci.* **2017**, *3*, 692–700

Radical formation process

XAT compared to direct homolysis and SET



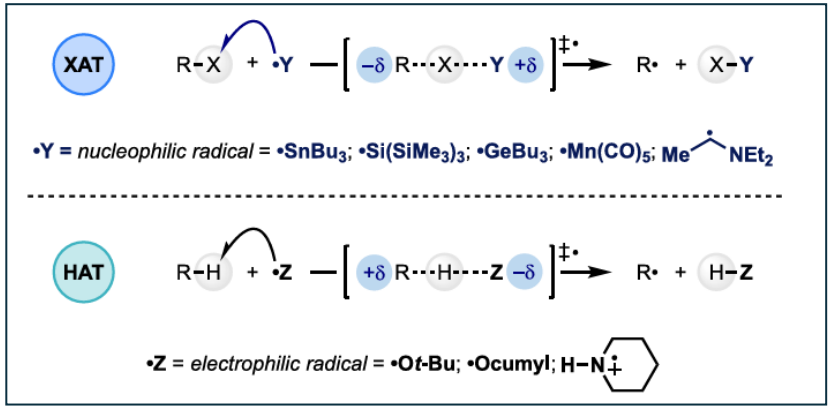
Homolytic C–halogen bond cleavage
- Require high-energy light

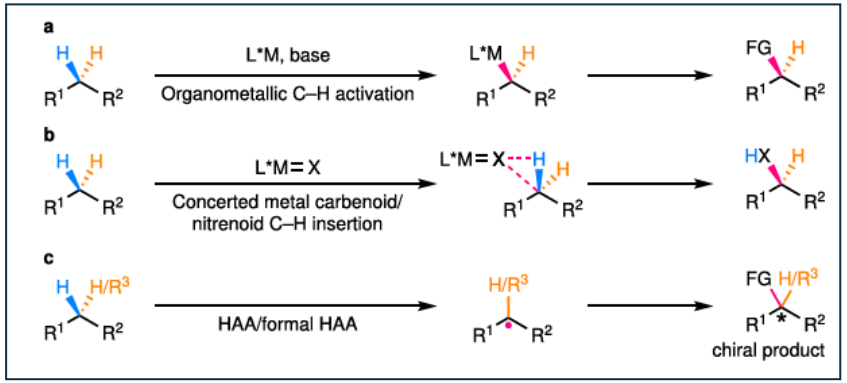
▲Low FG compatibility

SET reduction
- Strong reductants or
- EWG is necessary for reduction potential.

XAT
- Reactivity depends on BDEs and polarizability of the C–X bond.
- Strong chemoselectivity and FG tolerance

XAT or HAT?





Undesired chirality memory

H activation by transition metal, or
concerted metal carbenoid/nitrenoid C–H insertion
-> Radical rebound competing HAT process
-> Chirality retention is problematic

*Carbon radicals formed adjacent to the metal center undergo predominantly radical rebound prior to diffusion

Leonori, D. *et al., Chem.Rev*. **2022**, *122*, 2292–2352
Zhang, C., Li, ZL., Gu, QS. *et al. Nat Commun.* **2021.** *12*, 475

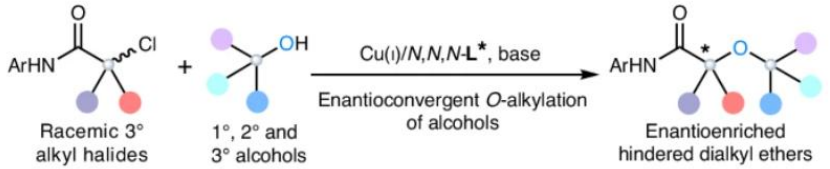
Outline

1. *O*-alkylation to form sterically-hindered dialkyl ethers

★Enantioconvergent synthesis of congested α,α'-trisubstituted ethers via direct substitution of tertiary alkyl electrophiles

- Multidentate anionic ligands
- Outer-sphere model

Liu, X.Y., *et al*., *Nat Catal,* **2025***, 8*, 919–930



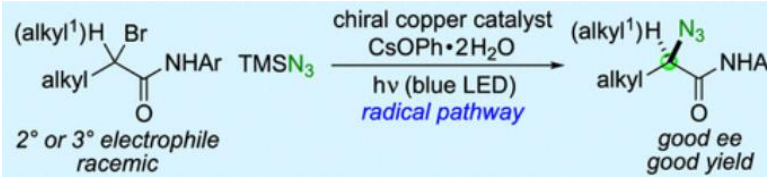
2. Azidation of alkyl Halides

★New approach for enantioconvergent azidation via alkylhalyde substitution

★Quaternary stereocenter

- Photoinduced chiral catalyst

Fu, G.C., *et al., J. Am. Chem. Soc*. **2025***, 147*, 32963–32970

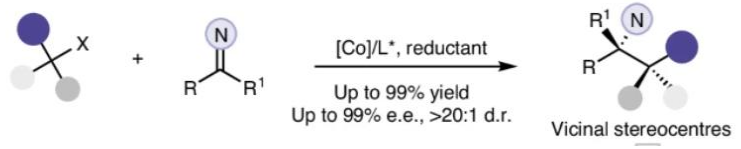


3. Synthesis of congested vicinal stereocentres

★Enantioconvergent stereocenter formation from alkyl halide racemic mixture

- Facile synthesis of valuable motifs including C-glycosylation

Wu, X., Xia, T., Bai, J. *et al., Nat. Chem*., **2025**



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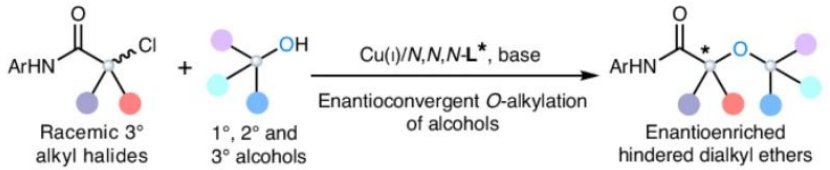

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- Facile synthesis of valuable motifs including C-glycosylation

Wu, X., Xia, T., Bai, J. *et al., Nat. Chem*., **2025**

Background: Williamson-type ether synthesis

Traditional Williamson ether synthesis
★High practicality and scalability
×Tertiary alcohol, enantioconvergent synthesis

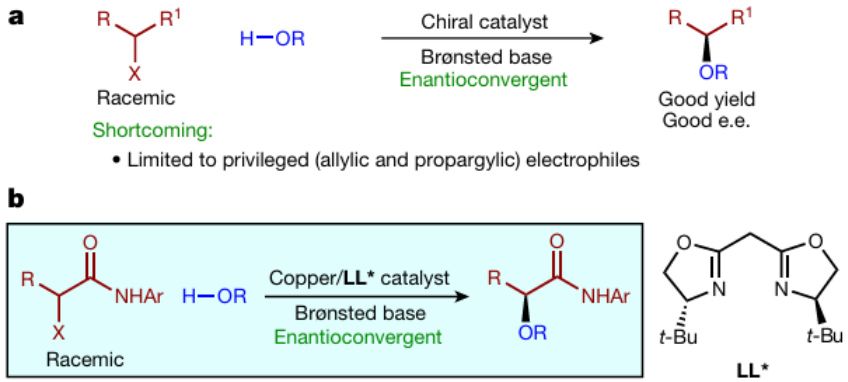
Challenges:
①Steric hindrance of both reactants &
Difficulty in substituent enantiodiscrimination

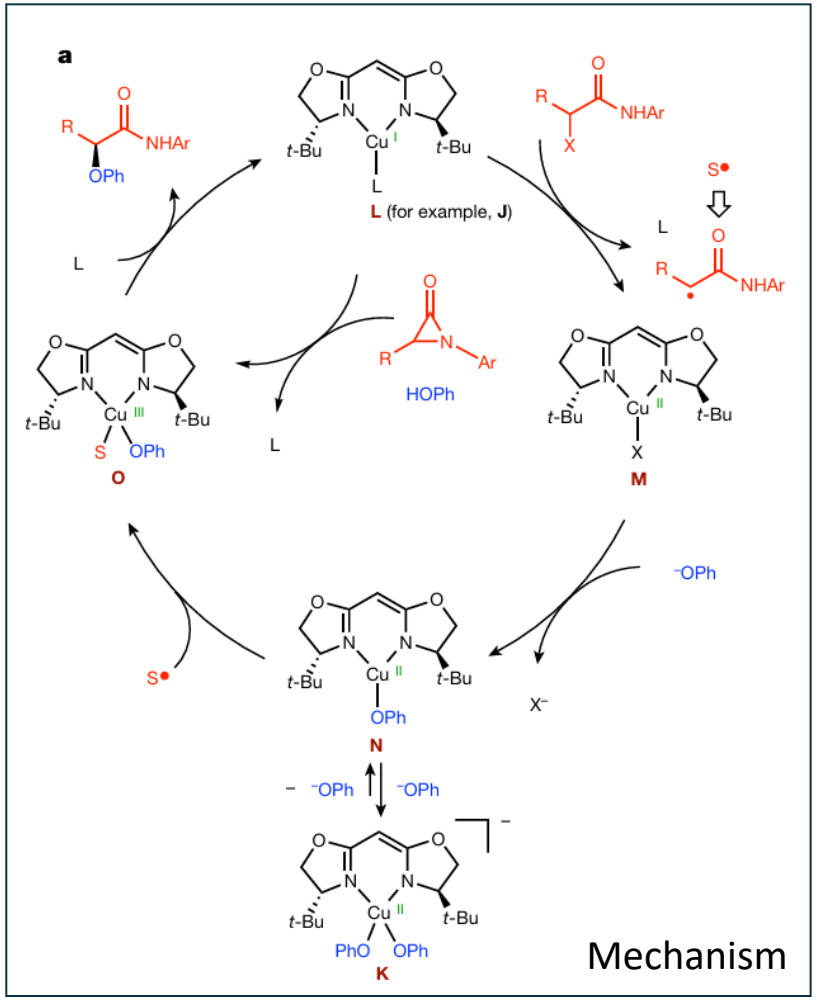
②Relatively weak nucleophilicity of tertiary alcohol

③Strong basicity of the corresponding alkoxide
->induce competing side reactions.

Williamson-type *O*-alkylation of alcohols (2023)
- Enantioconvergent
- Inner-sphere

▲Less sterically hindered alcohols





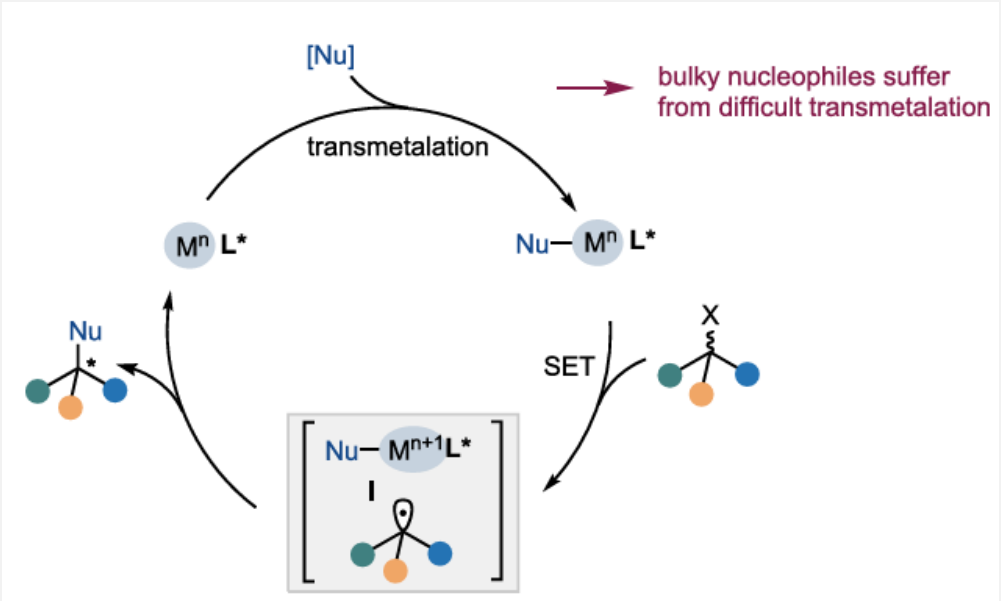
Chen, C., Fu, G.C. *Nature*. **2023**. *618*, 301–307

Background: Inner- or outer-sphere model

Inner-sphere model

・Preferred if the spin is majorly on Cu

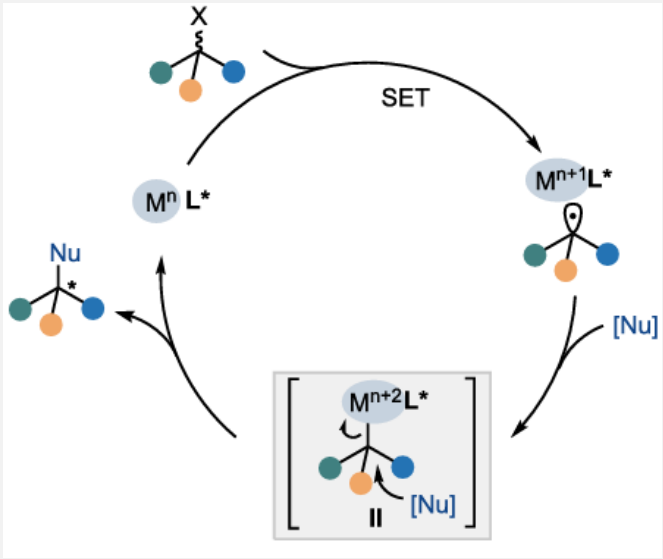
▲Transmetallation is difficult with bulky nucleophiles

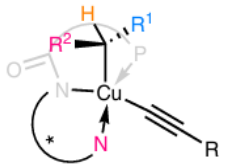


Outer-sphere model

・No need of Nu coordination to the metal center

・Reactive site of the metal complex is spatially accessible.

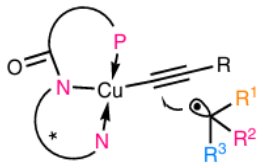




2° radical

Inner

vs



3° radical

Outer

Li, ZL., Yu, P., Liu, XY. *et al. J.Am.Chem.Soc.* **2024**,*146*,9444−9454

Liu, X.Y., *et al.*, *Nat Catal.* **2025**, *8*, 919–930

Background: Anionic ligands

Speriority of Cu against Pd or Ni

・Reductive elimination of Cu(Ⅲ) intermediate readily proceeds

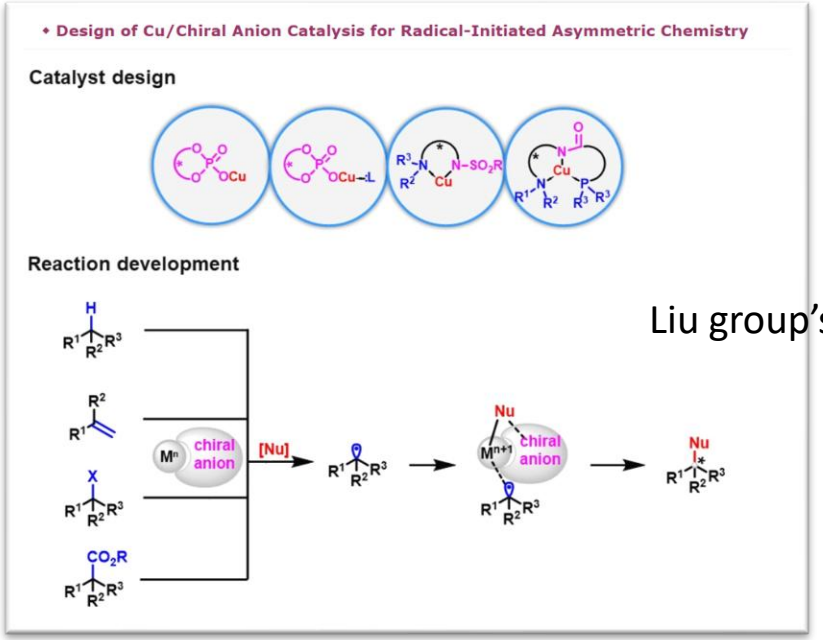
▲Weak reducing ability of Gound State-Cu

➡Inefficient oxidative addition

①Anionic tridentate ligands (topic 1.)

・Enhance the reducing ability of Cu(I)

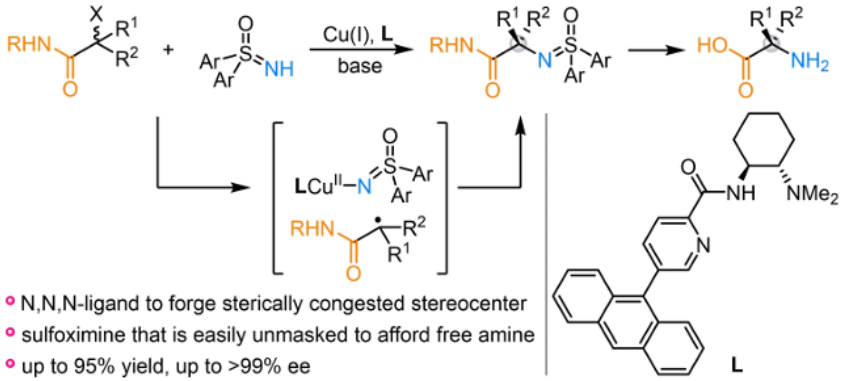
②Photo-induced strategy in mild condition (topic 2.)



Liu group's approach

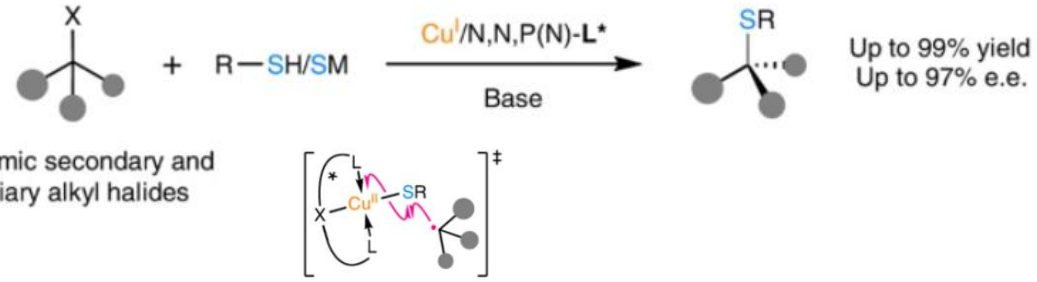
Recent enantioconvergent bond formations

・C(sp_3)-N cross coupling



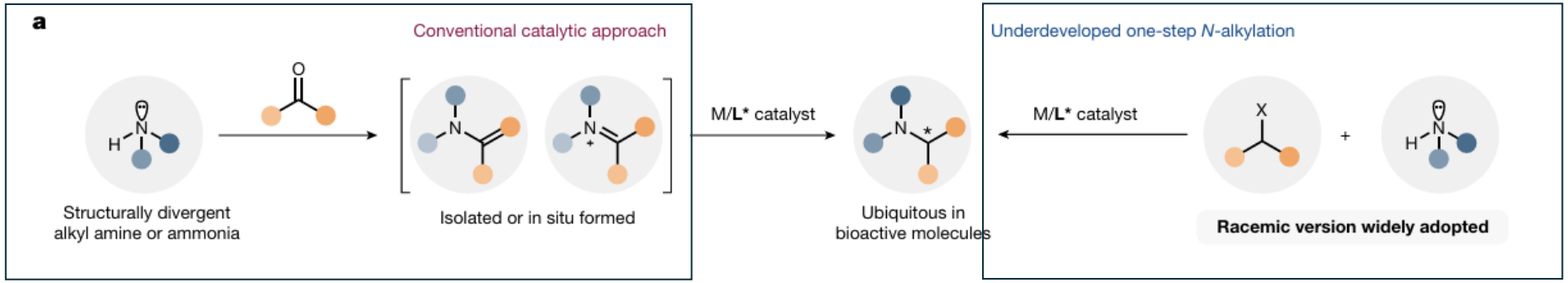
- N,N,N-ligand to forge sterically congested stereocenter
- sulfoximine that is easily unmasked to afford free amine
- up to 95% yield, up to >99% ee

・C(sp_3)-S cross coupling



Tian, Y., Li, XT., Liu, JR. *et al. Nat. Chem.,* **2024**, 16, 466–475
Zhang, YF., Wang, JH., Yang, NY. *et al. Angew. Chem. Int. Ed.* **2023**, 62

Background: Outer-sphere model and tridentate N,N,N-ligand



Challenges

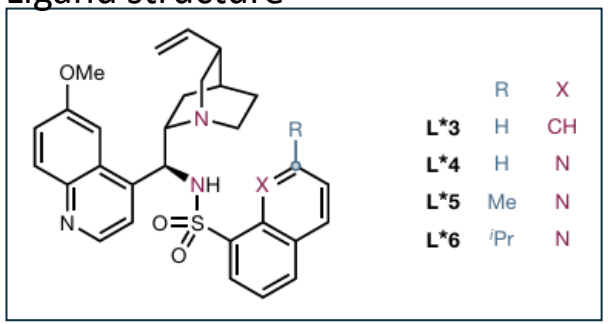
・High Lewis basicity of aliphatic amines and ammonia
->transition-metal-catalyst poisoning
・Selective deprotonation of the weakly acidic N–H bonds

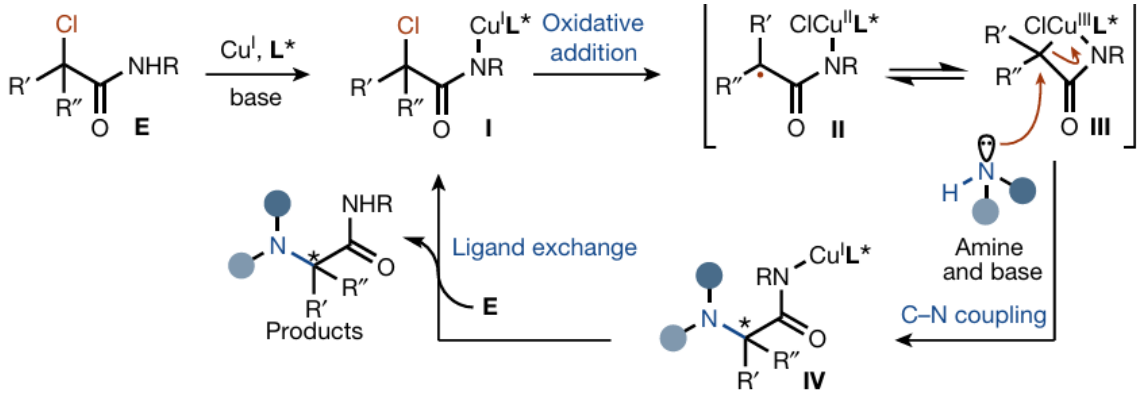
Conventional approach
▲Complicated substrates (multistep manipulation)

Enantioconvergent N-alkylation of aliphatic amines (2023)

★One-step enantioconvergent C-N bond formation
★Transition-metal-catalyst poisoning was overcome by utilizing multidentate anionic ligands. ->strong chelation
★Outer-sphere model
->with sterically bulky heteroaromatic amine

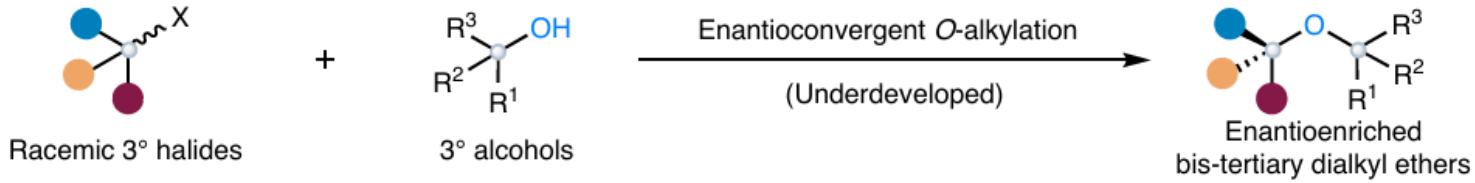
Ligand structure





Chen, JJ., Fang, JH., Du, XY. *et al*. *Nature*. **2023**. *618*, 294–300

This work: Challenges and catalyst design



Challenges

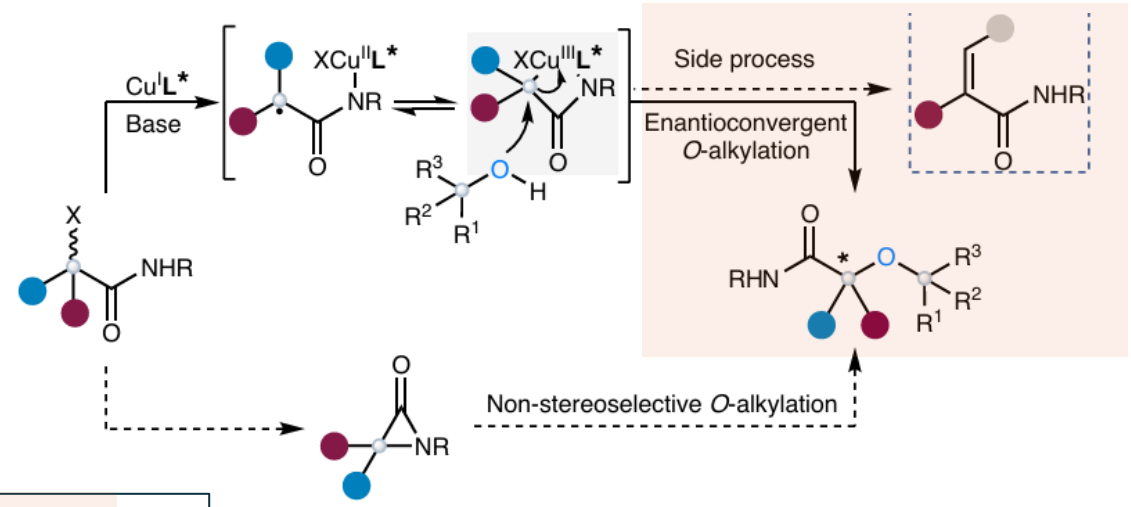
・Steric hindrance of both reactants
-> Outer-sphere model

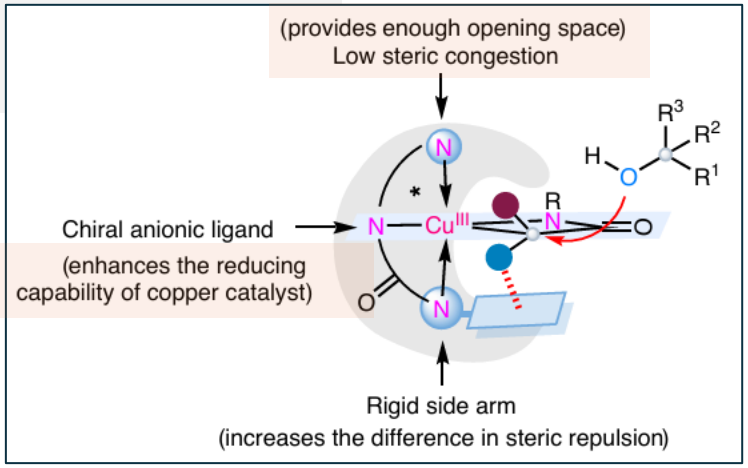
・Enantiodiscrimination of substituents
-> Bulky substituents of ligand

・Low nucleophilicity of bulky alcohols

・Strong basicity of the corresponding alkali-M alkoxides induce competing side reactions
-> Anionic ligand

Outer-sphere approach

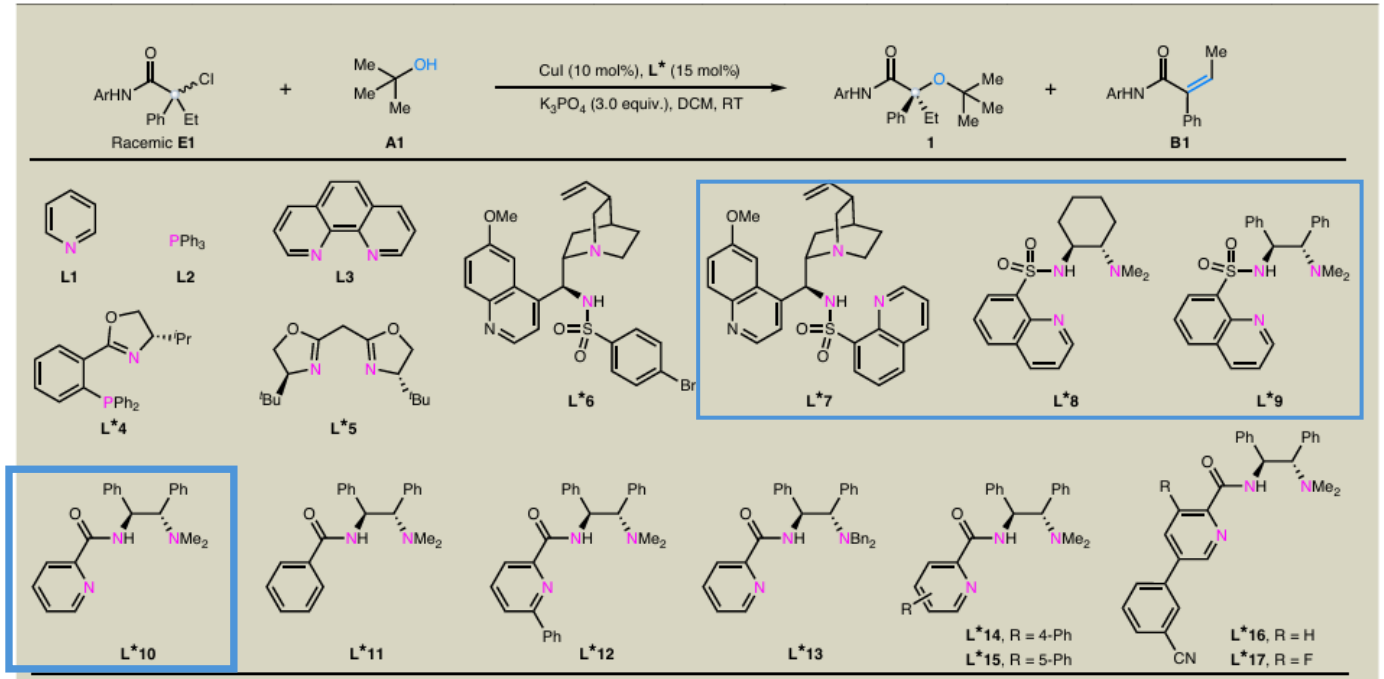




Liu, X.Y., *et al.*, *Nat Catal*, **2025**, *8*, 919–930

Reaction development and optimization

Ligand screening



Entry	L*	Conv. of E1 (%)	Yield of 1 (%)	Yield of B1 (%)	e.e. of 1 (%)	Entry	L*	Conv. of E1 (%)	Yield of 1 (%)	Yield of B1 (%)	e.e. of 1 (%)
1[a]	–	19	13	Trace	0	11	**L*9**	37	29	Trace	2
2[b]	–	88	14	70	0	12	**L*10**	99	77	Trace	59
3	**L1**	90	32	48	0	13	**L*11**	81	21	53	10
4	**L2**	97	10	83	0	14	**L*12**	100	10	84	4
5	**L3**	100	22	70	0	15	**L*13**	100	14	83	3
6	**L*4**	100	39	50	14	16	**L*14**	100	74	Trace	60
7	**L*5**	80	26	40	3	17	**L*15**	100	75	Trace	62
8	**L*6**	73	24	38	0	18	**L*16**	100	76	Trace	64
9	**L*7**	38	27	Trace	3	19	**L*17**	100	79	Trace	68
10	**L*8**	48	37	Trace	5	20[c]	**L*17**	100	91	Trace	90

Standard reaction conditions: racemic **E1** (0.05 mmol), *tert*-butanol **A1** (1.5 equiv.), CuI (10 mol%), **L*** (15 mol%) and K_3PO_4 (3.0 equiv.) in dichloromethane (0.50 ml) at room temperature for 48 h under argon. The conversion of **E1** and yields of **1** and **B1** are based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard and the e.e. values are based on chiral high-performance liquid chromatography analysis. [a]Without CuI and **L***. [b]Without **L***. [c]Cu(OTf)·tol$_{1/2}$ (10 mol%), DCE (0.50 ml) at −10 °C for 5 days. Ar, 4-cyano-2-methylphenyl; Bn, benzyl; Conv., conversion; RT, room temperature; ^{t}Bu, *tert*-butyl.

Catalyst and ligand structure–activity relationship

1: Stereospecific nucleophilic substitution

2: Mainly B1 by-product

- B1 derives from intramolecular β-elimination.

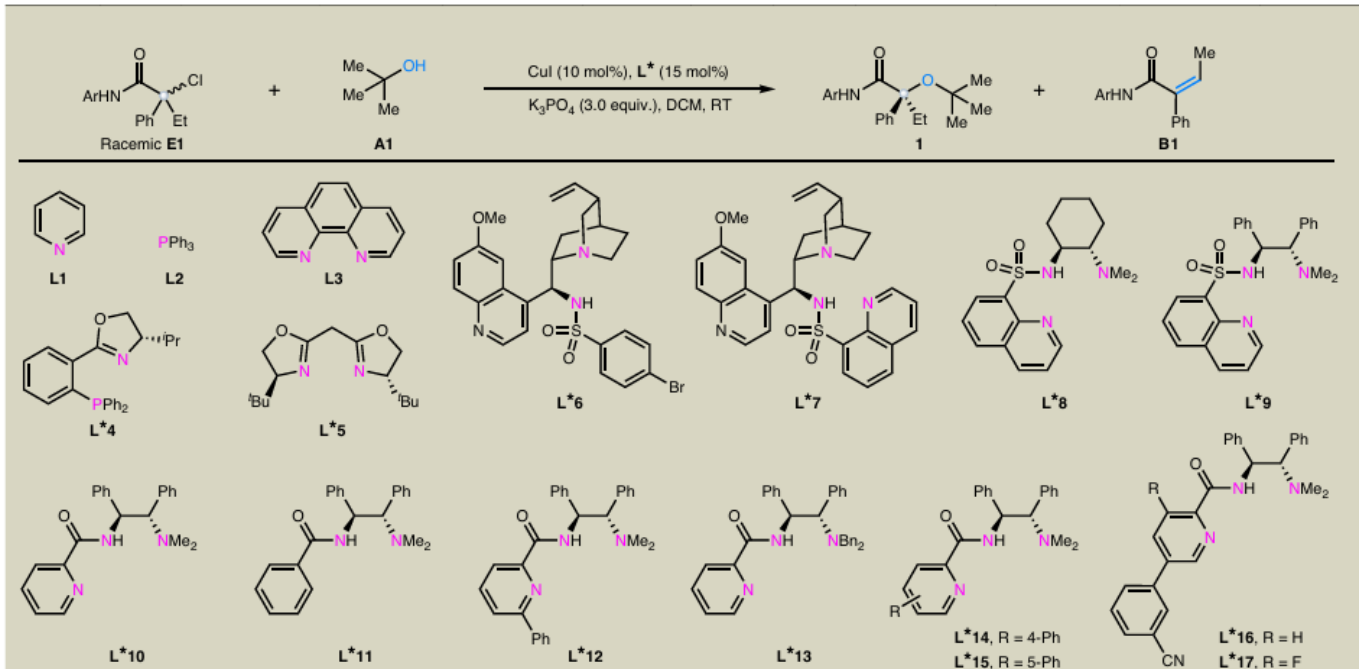
★Tridentate anionic sulfonamide ligands decreased B1.

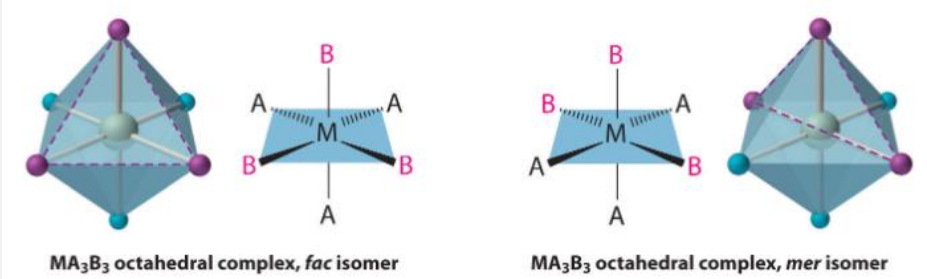
★Too much steric hindrance in side arm decreased y.

chelation pattern-> next page

Reaction development and optimization

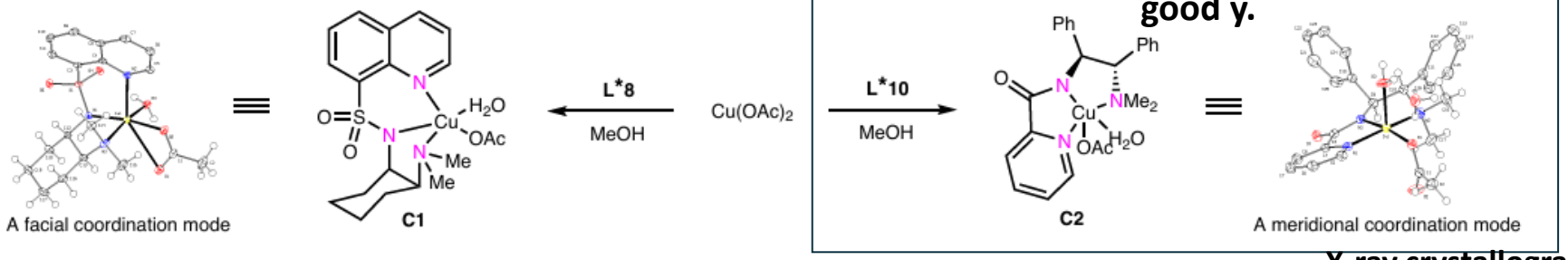
Ligand screening





not suitable

ligand can coordinate



good y.

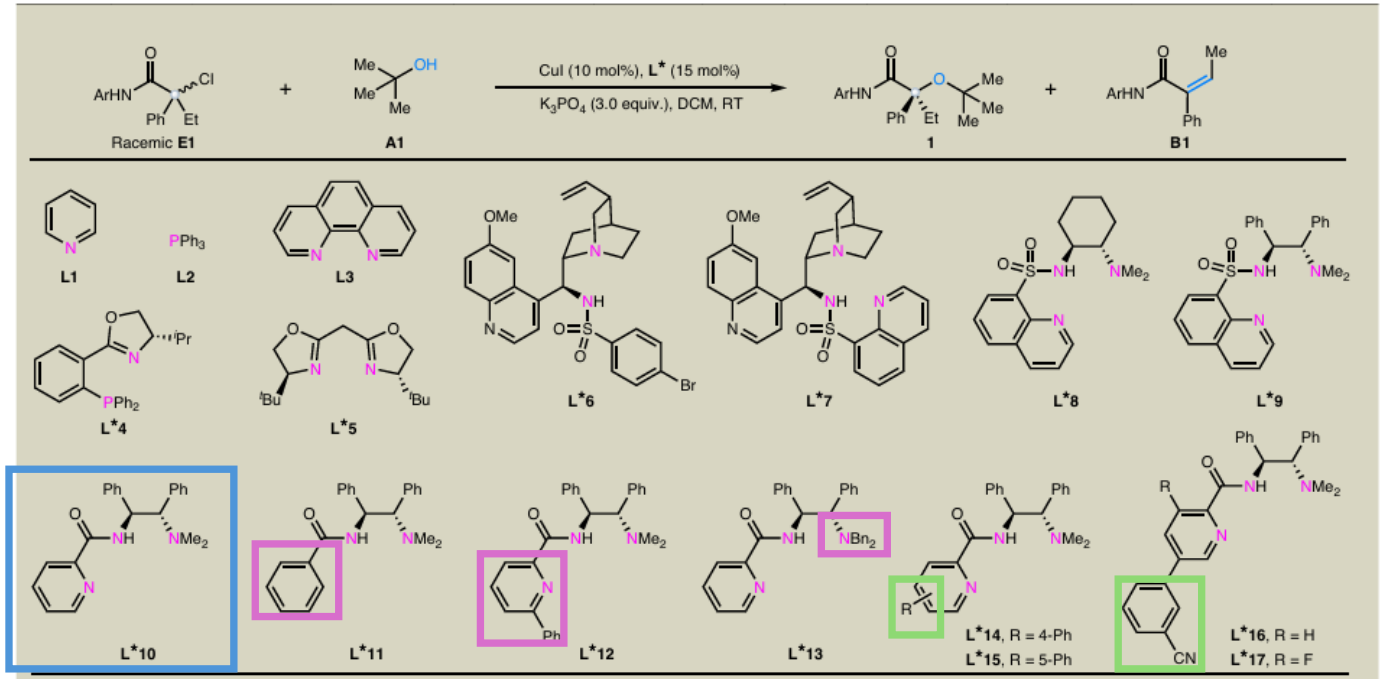
X-ray crystallography

Not facial, but meridional chelation is suitable for Nu coordination.

https://users.highland.edu/~jsullivan/principles-of-general-chemistry-v1.0/s27-04-coordination-compounds.html

Reaction development and optimization

Ligand screening



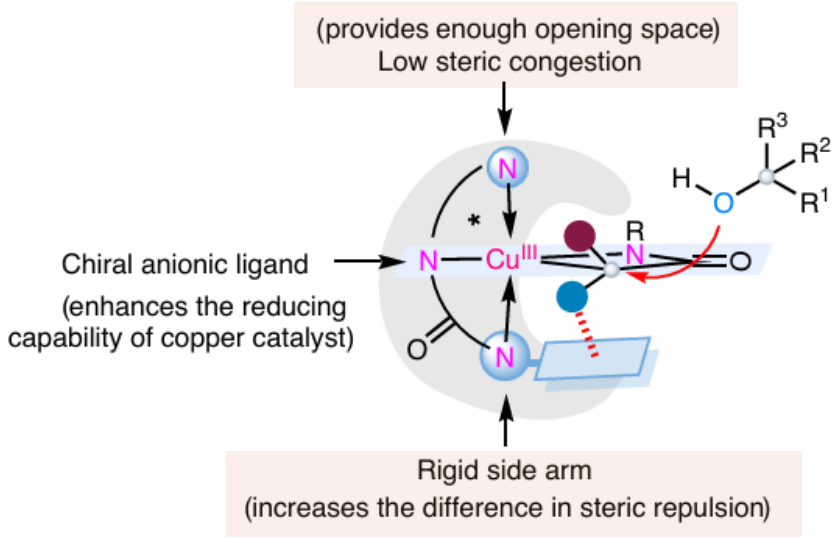
Entry	L*	Conv. of E1 (%)	Yield of 1 (%)	Yield of B1 (%)	e.e. of 1 (%)	Entry	L*	Conv. of E1 (%)	Yield of 1 (%)	Yield of B1 (%)	e.e. of 1 (%)
1[a]	–	19	13	Trace	0	11	**L*9**	37	29	Trace	2
2[b]	–	88	14	70	0	12	**L*10**	99	77	Trace	59
3	**L1**	90	32	48	0	13	**L*11**	81	21	53	10
4	**L2**	97	10	83	0	14	**L*12**	100	10	84	4
5	**L3**	100	22	70	0	15	**L*13**	100	14	83	3
6	**L*4**	100	39	50	14	16	**L*14**	100	74	Trace	60
7	**L*5**	80	26	40	3	17	**L*15**	100	75	Trace	62
8	**L*6**	73	24	38	0	18	**L*16**	100	76	Trace	64
9	**L*7**	38	27	Trace	3	19	**L*17**	100	79	Trace	68
10	**L*8**	48	37	Trace	5	20[c]	**L*17**	100	91	Trace	90

Best

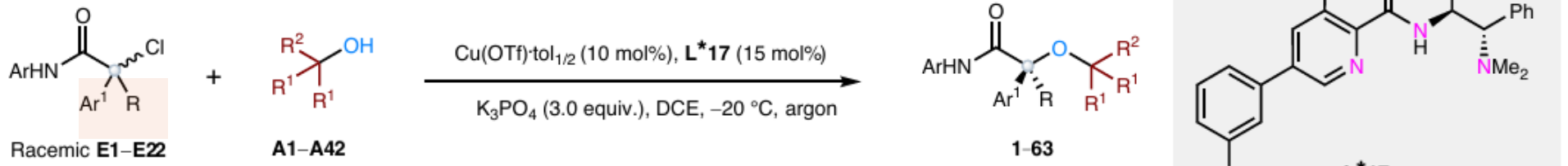
Standard reaction conditions: racemic **E1** (0.05 mmol), *tert*-butanol **A1** (1.5 equiv.), CuI (10 mol%), **L*** (15 mol%) and K_3PO_4 (3.0 equiv.) in dichloromethane (0.50 ml) at room temperature for 48 h under argon. The conversion of **E1** and yields of **1** and **B1** are based on ^{1}H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard and the e.e. values are based on chiral high-performance liquid chromatography analysis. [a]Without CuI and **L***. [b]Without **L***. [c]Cu(OTf)·tol$_{1/2}$ (10 mol%), DCE (0.50 ml) at −10 °C for 5 days. Ar, 4-cyano-2-methylphenyl; Bn, benzyl; Conv., conversion; RT, room temperature; ^{t}Bu, *tert*-butyl.

■Steric hindrance <u>in coordinating center</u> decreased e.e.
-> <u>Low congestion around Cu(Ⅲ)</u> is important.

■PhCN side arm increased e.e.
-> <u>Stereodiscriminating interactions far from the Cu center</u> are necessary.



Substrate scope

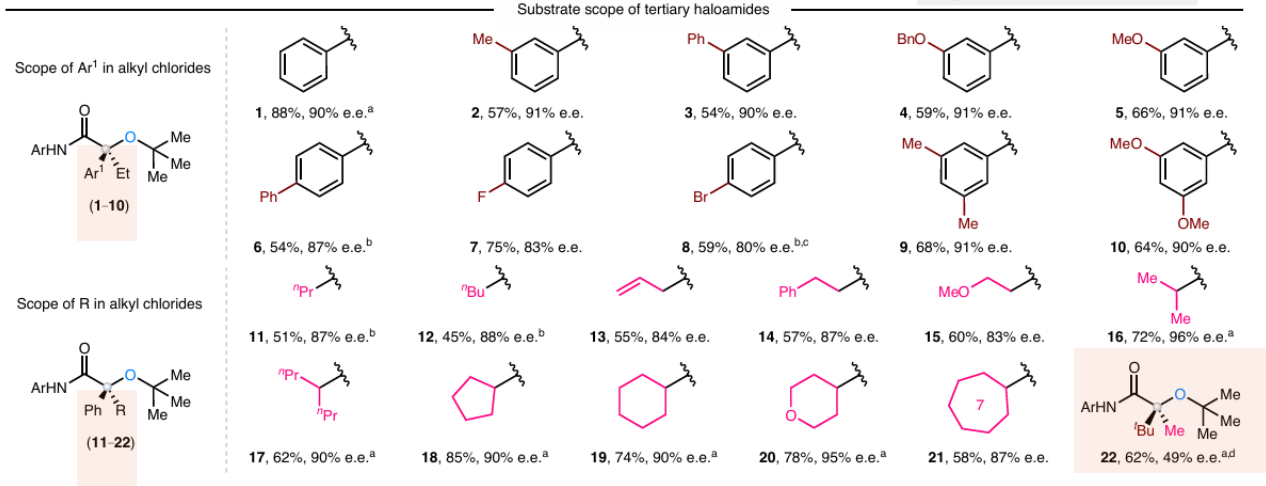


Tertiary haloamides

Substrate scope of tertiary haloamides

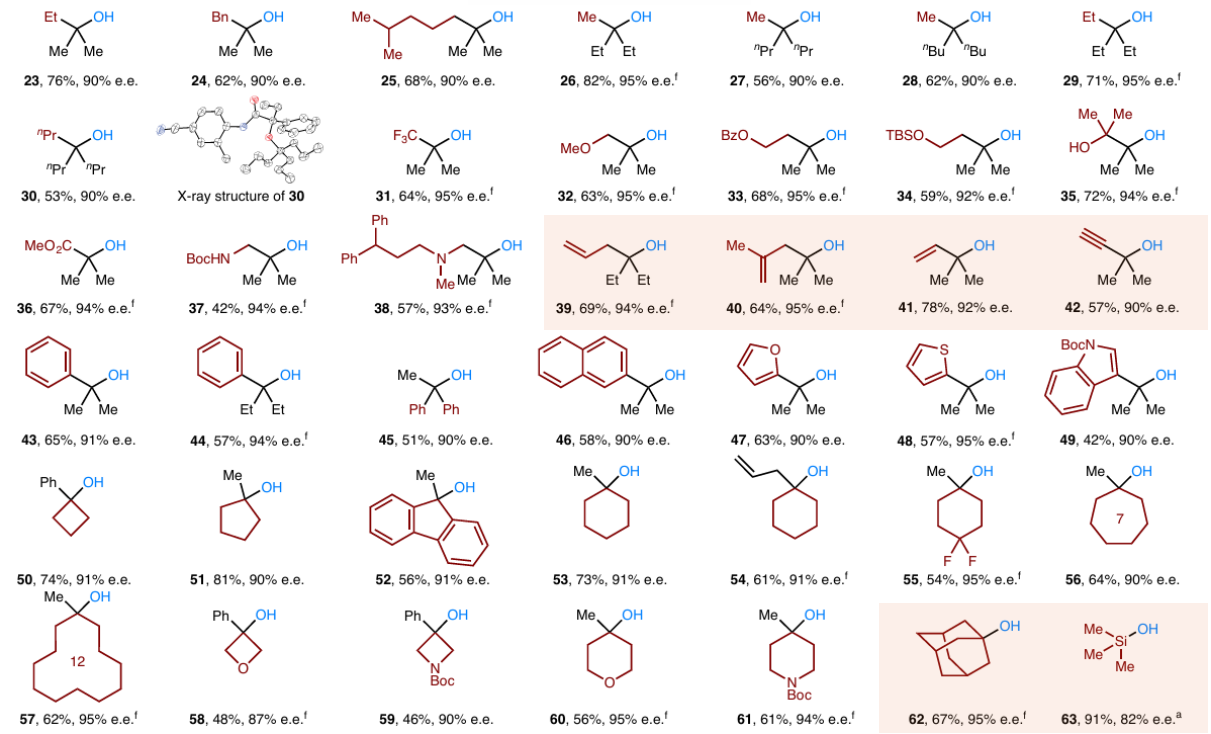
Scope of Ar[1] in alkyl chlorides (1–10)

Scope of R in alkyl chlorides (11–22)



Tertiary alcohols

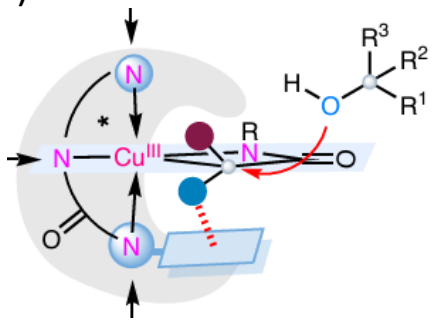
Substrate scope of tertiary alcohols[e]



Steric disparity for enantiodifferentiation

✓α,α-dialkyl-substituted electrophile *Under optimization

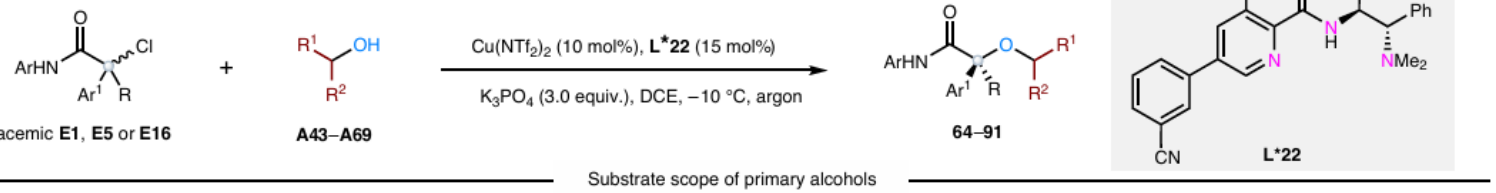
(➡Interacting moiety with ligand is Ar-amide?)

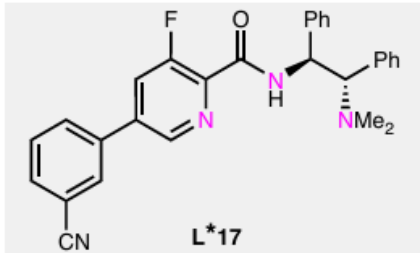


- Radical-sensitive moiety
- Bulky alcohol

Substrate scope

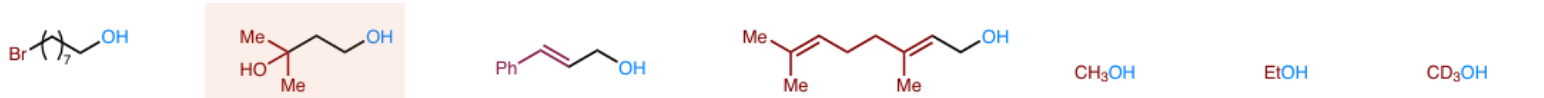
(Secondaly alcohols)





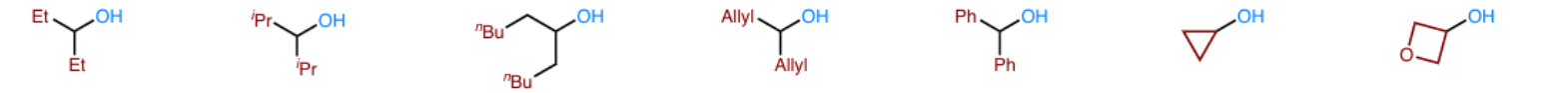
Substrate scope of primary alcohols

64, 94%, 91% e.e.[a] **65**, 93%, 94% e.e.[b] **66**, 68%, 90% e.e. **67**, 62%, 95% e.e.[b] **68**, 71%, 92% e.e.[b] **69**, 64%, 91% e.e.[b]

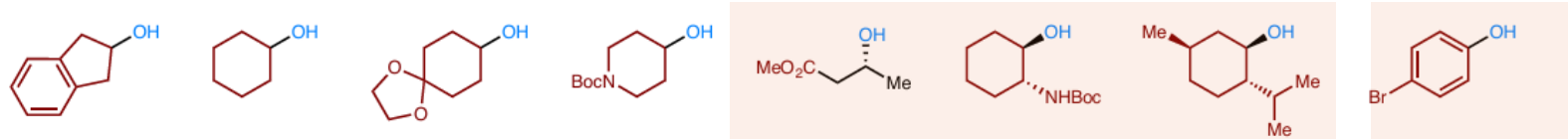


70, 69%, 91% e.e. **71**, 87%, 90% e.e. **72**, 73%, 91% e.e. **73**, 87%, 94% e.e.[b] **74**, 97%, 95% e.e.[b] **75**, 84%, 90% e.e. **76**, 94%, 91% e.e.

Substrate scope of secondary alcohols and phenol



77, 87%, 91% e.e. **78**, 87%, 93% e.e.[b] **79**, 82%, 91% e.e. **80**, 78%, 91% e.e. **81**, 75%, 92% e.e. **82**, 74%, 90% e.e.[b] **83**, 76%, 92% e.e.[b]



84, 69%, 92% e.e. **85**, 82%, 90% e.e. **86**, 78%, 91% e.e. **87**, 71%, 91% e.e. **88**, 68%, >20:1 d.r.[b] **89**, 74%, >20:1 d.r. **90**, 67%, 19:1 d.r. **91**, 57%, 32% e.e.[c,d]

Substrate scope of secondary haloamide

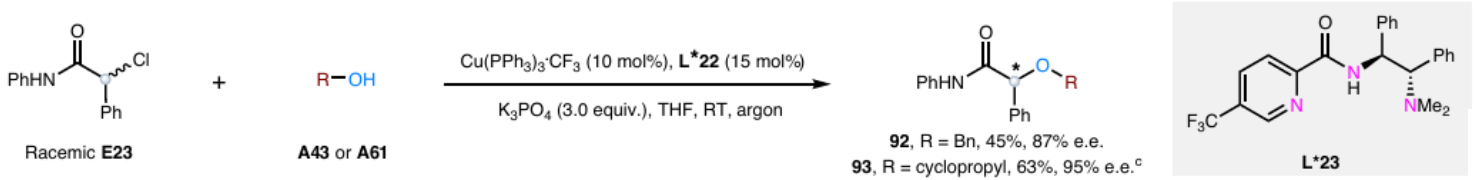
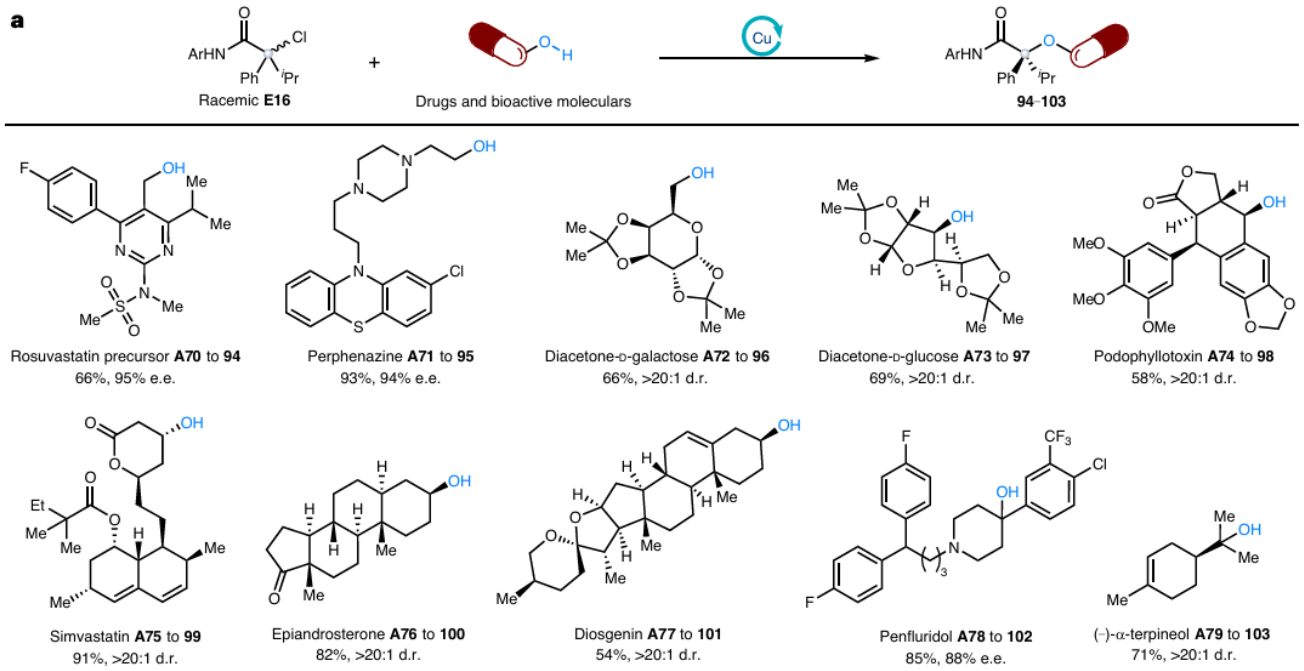


Fig. 3 | Substrate scope for primary and secondary alcohols or α-secondary haloamides. Standard reaction conditions: racemic **E5** (Ar^1 = 3-$MeOC_6H_4$; R = Et; 0.20 mmol), primary or secondary alcohol (1.5 equiv.), $Cu(NTf_2)_2$ (10 mol%), **L*22** (15 mol%) and K_3PO_4 (3.0 equiv.) in DCE (2.0 ml) at −10 °C for 5 days under argon. Isolated yields are shown, followed by e.e. values based on chiral high-performance liquid chromatography analysis or d.r. values based on crude ^{1}H NMR analysis. [a]**E1** was used. [b]**E16** was used. [c]**L*23** was used. [d]**E1** (0.20 mmol) and 4-bromophenol (1.2 equiv.) in *p*-xylene (2.0 ml) at room temperature for 3 days. Ar, 4-cyano-2-methylphenyl; d.r., diastereomeric ratio; THF, tetrahydrofuran; RT, room temperature.

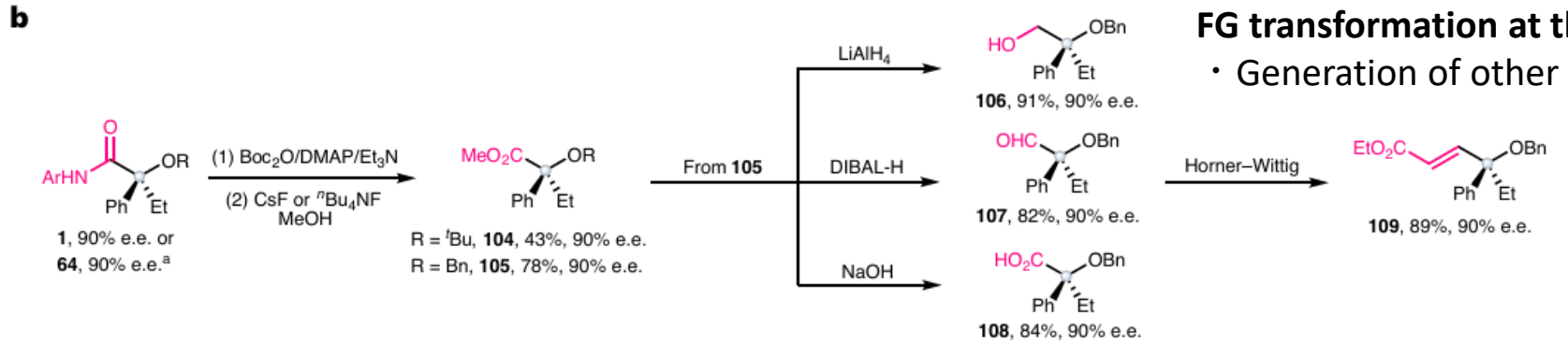
- Selectivity among other heteroatoms by utilizing bulkiness difference
- Tolerable for metal-ligand substrate
- ligand fine-tuning

Synthetic utility and Application for late-stage functionalization



FG tolerance

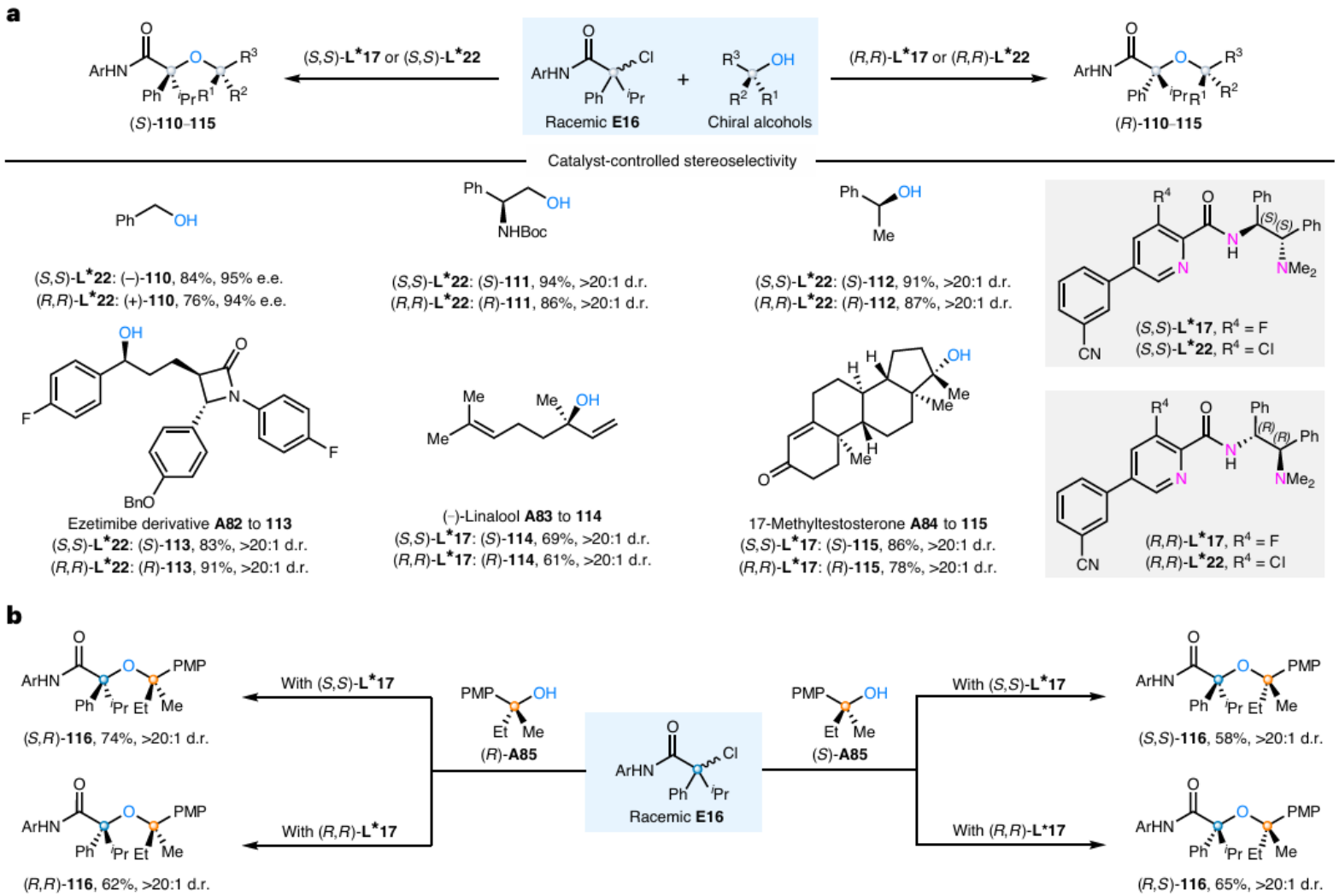
- Chiral centre introduction with other FG untouched
- Gram-scale
- Valuable in the initial phase of drug development



FG transformation at the carboxamide moiety

- Generation of other valuable enantioenriched building blocks

Catalyst control

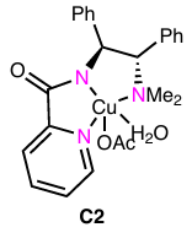


Stereocontrolled synthesis

- Ligand chirality
- Alcohol enantiomer

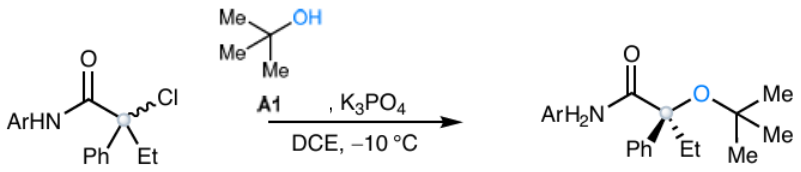
Mechanistic studies

・Coordination to a chiral <u>tridentate</u> N,N,N-ligand is necessary (chelation affects y.)



C2

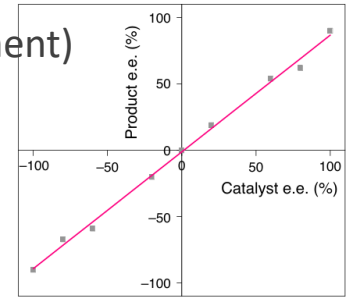
b



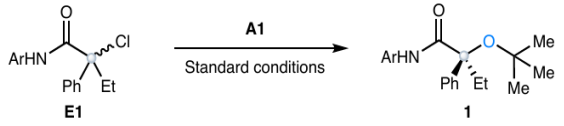
Ar = 4-cyano-2-methylphenyl
Racemic **E1**

With **C2**: **1**, 72%, 74% e.e.
With $Cu(OAc)_2$/**L*10**: **1**, 51%, 74% e.e.

・Mononuclear copper species (nonlinear experiment)

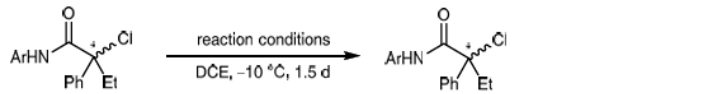


・Uniform mechanism for both enantiomers
・Subtle racemization (supported by DFT calc.)



E1 **1**

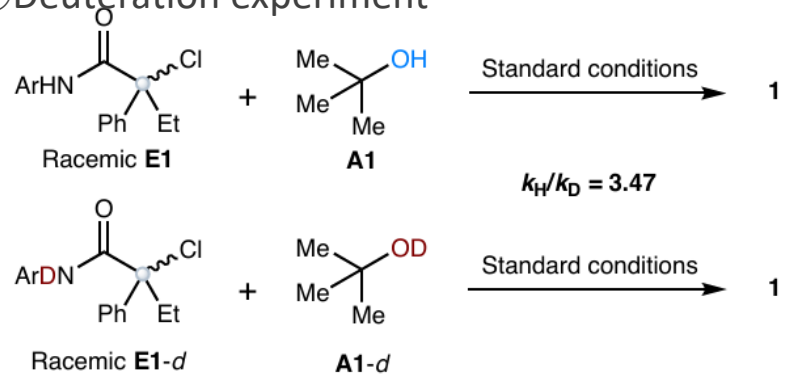
Entry	Substrate	Time (d)	Recovered **E1**	**1**
1	**E1** (0% e.e.)	1	69%, 1% e.e. (**E1'**)	30%, 90% e.e.
2	**E1** (0% e.e.)	2	35%, 7% e.e. (**E1'**)	63%, 90% e.e.
3	**E1'** (>99% e.e.)	1	58%, 91% e.e. (**E1'**)	40%, 90% e.e.
4	**E1'** (>99% e.e.)	2	26%, 84% e.e. (**E1'**)	71%, 90% e.e.
5	**E1"** (>99% e.e.)	1	65%, 96% e.e. (**E1"**)	31%, 90% e.e.
6	**E1"** (>99% e.e.)	2	39%, 92% e.e. (**E1"**)	55%, 90% e.e.



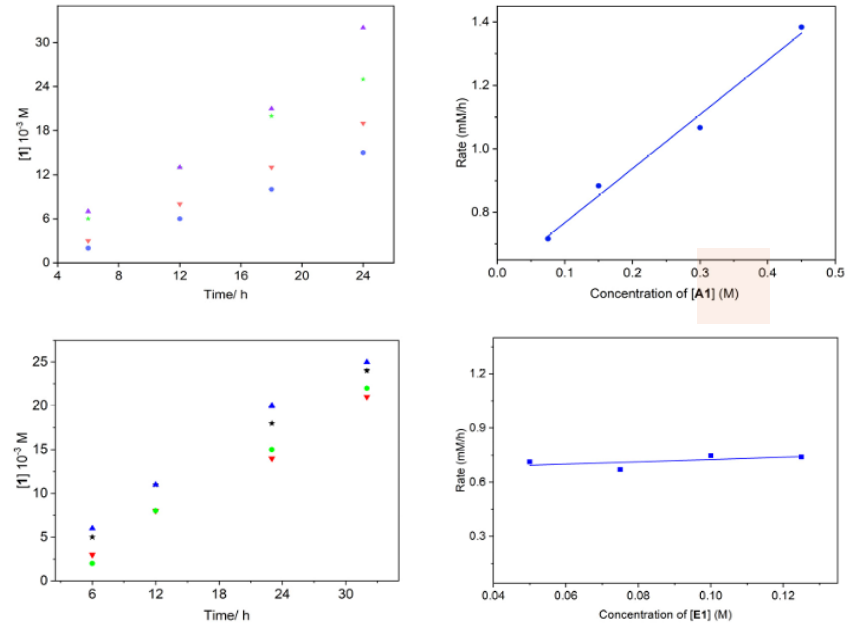
Chiral **E1**
(>99% e.e.)
Ar = 4-cyano-2-methylphenyl

e.e. of recovered **E1**
(1) without Cu(OTf)-$tol_{1/2}$: >99% e.e.
(2) without **L*17**: >99% e.e.
(3) Cu(OTf)-$tol_{1/2}$, **L*17** and K_3PO_4: 85% e.e.

①Deuteration experiment



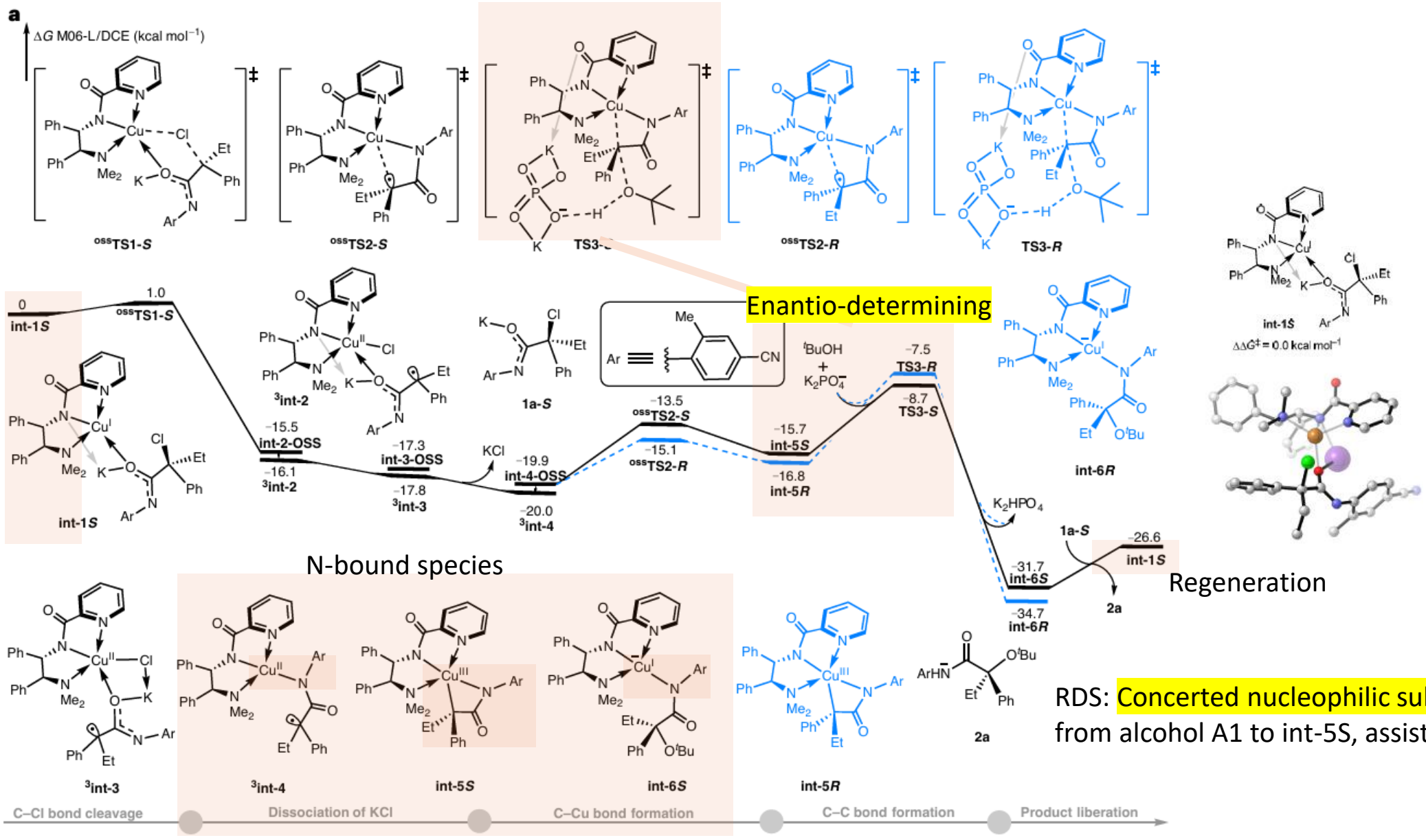
②Kinetic experiments



RDS involves concerted <u>nucleophilic attack and deprotonation.</u>

Mechanistic studies

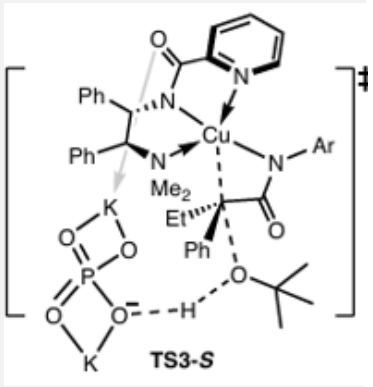
DFT calculations

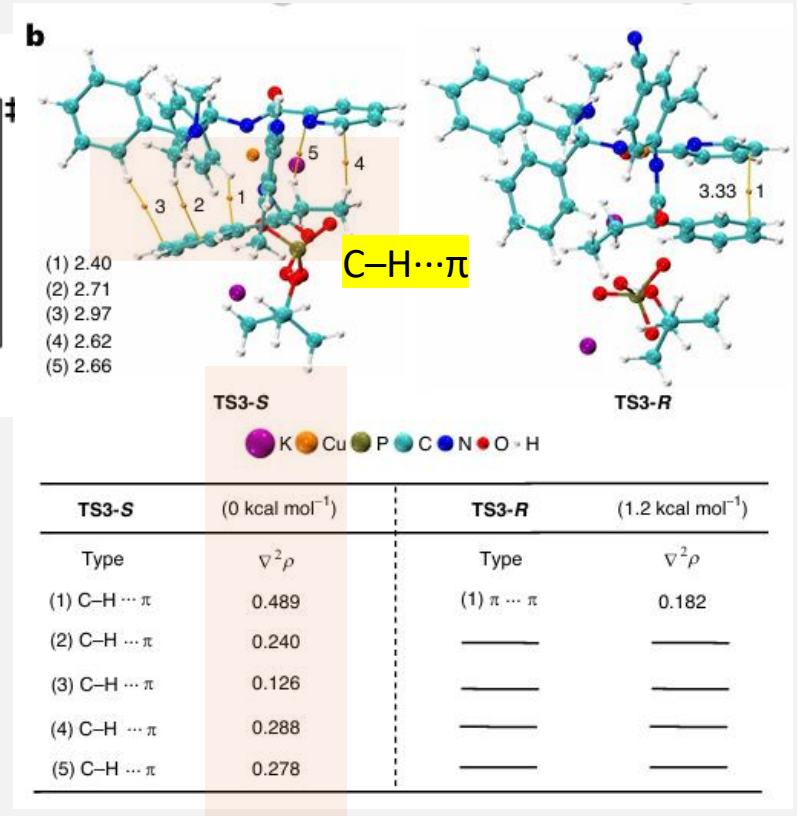


RDS: Concerted nucleophilic substitution step leading from alcohol A1 to int-5S, assisted by the $K_2PO_4^-$ anion

Mechanistic studies

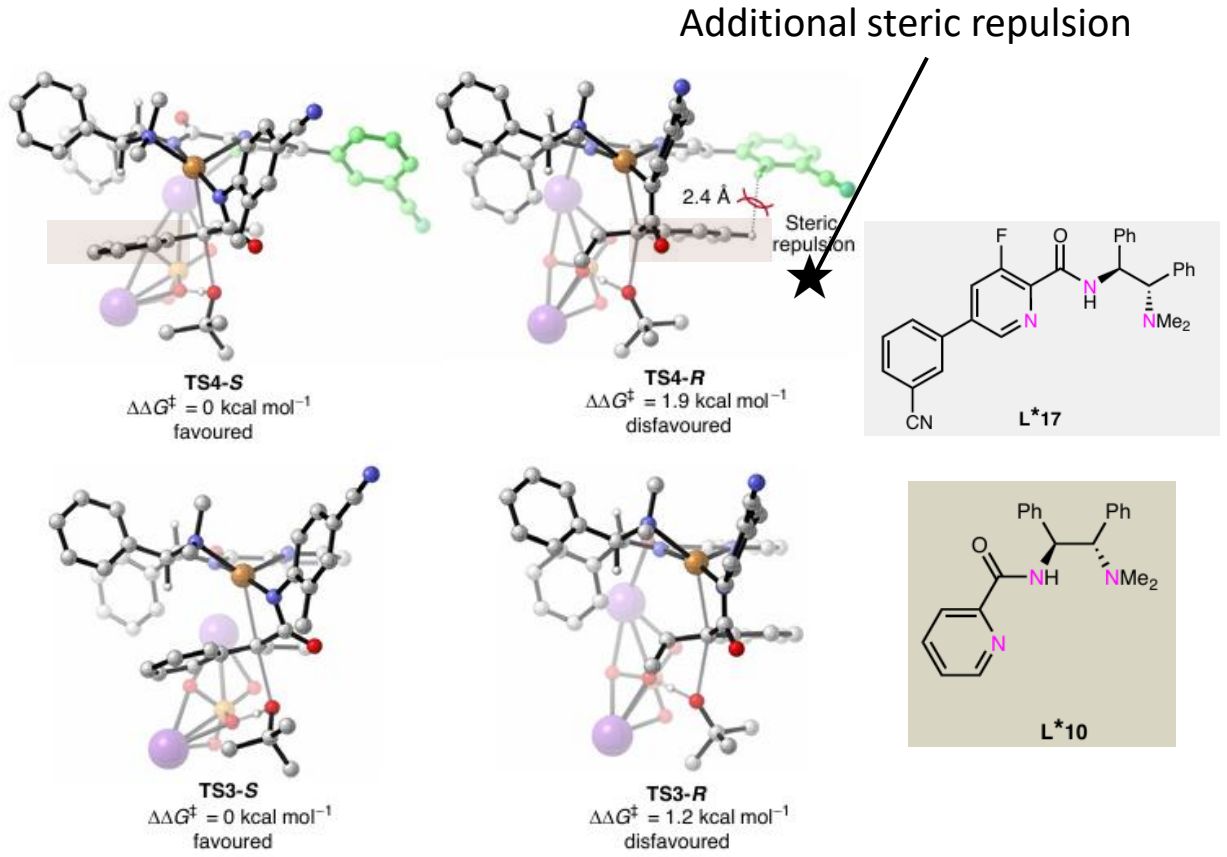
ORigins of enantioselectivity
Quantitative Bader's atoms-in-molecules analyses
Non-covalent interactions contributed TS3-S stabilization.





TS3-*S*	(0 kcal mol^{-1})	TS3-*R*	(1.2 kcal mol^{-1})
Type	$\nabla^2\rho$	Type	$\nabla^2\rho$
(1) C–H ··· π	0.489	(1) π ··· π	0.182
(2) C–H ··· π	0.240	———	———
(3) C–H ··· π	0.126	———	———
(4) C–H ··· π	0.288	———	———
(5) C–H ··· π	0.278	———	———

Installing a side chain at the meta-position of the pyridyl unit in ligand L10 resulted in improved enantioselectivity.



Short summary

Achievements:
★Enantioconvergent synthesis of congested α,α’-trisubstituted ethers via direct substitution of tertiary alkyl electrophiles (first example)

・Multidentate anionic ligands enabled strong chelation
➡Transition-metal-catalyst poisoning was overcome.

・Meridional chelation
➡Enouguh space for Nu chelation

・Outer-sphere model
➡Sterically congested O-alkylation

Outline

1. *O*-alkylation to form sterically-hindered dialkyl ethers

★Enantioconvergent synthesis of congested α,α'-trisubstituted ethers via direct substitution of tertiary alkyl electrophiles

- Multidentate anionic ligands
- Outer-sphere model

Liu, X.Y., *et al.*, *Nat Catal*, **2025**, *8*, 919–930

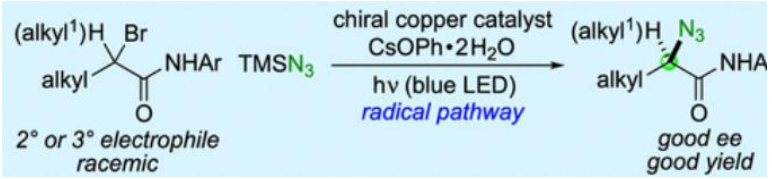
2. Azidation of alkyl Halides

★New approach for enantioconvergent azidation via alkylhalyde substitution

★Quaternary stereocenter

- Photoinduced chiral catalyst

Fu, G.C., *et al., J. Am. Chem. Soc*. **2025**, *147*, 32963–32970



3. Synthesis of congested vicinal stereocentres

★Enantioconvergent stereocenter formation from alkyl halide racemic mixture

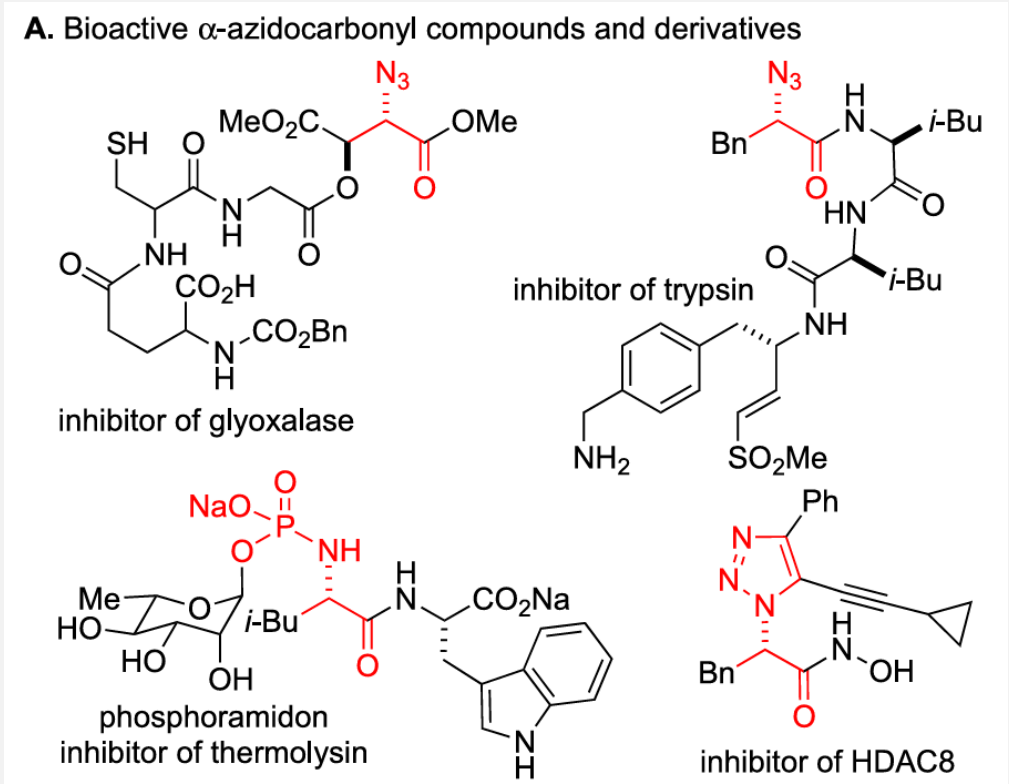
- Facile synthesis of valuable motifs including C-glycosylation

Wu, X., Xia, T., Bai, J. *et al., Nat. Chem.*, **2025**

Background: Conventional catalytic asymmetric synthesis of alkyl azides

Synthetic utility of azide compounds

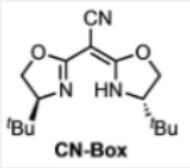
- Click chemistry
- Staudinger ligation



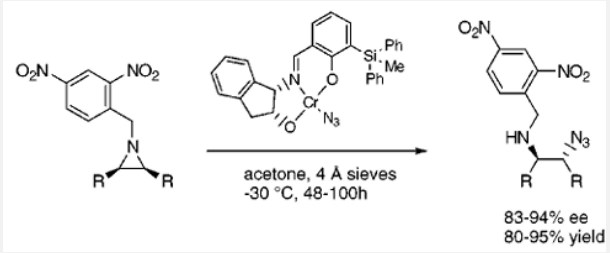
Lin, Z., Liu, G. *et al. Angew. Chem. Int. Ed.* **2021**, *60*, 6997 – 7001
Nugent, W.A. *J.Am. Chem. Soc.* **1992**, *114*, 2768-2769
Jacobsen, E.N. *et al. Org. Lett.* **1999**, *1*, 1611–1613
Fu, G.C., *et al., J. Am. Chem. Soc.* **2025**, *147*, 32963–32970

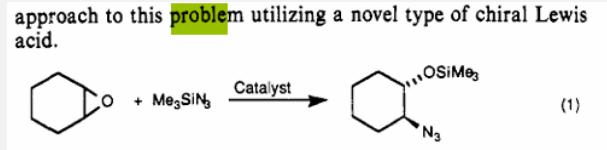
Various ways, but not enantioconvergent

- Azidations of olefins



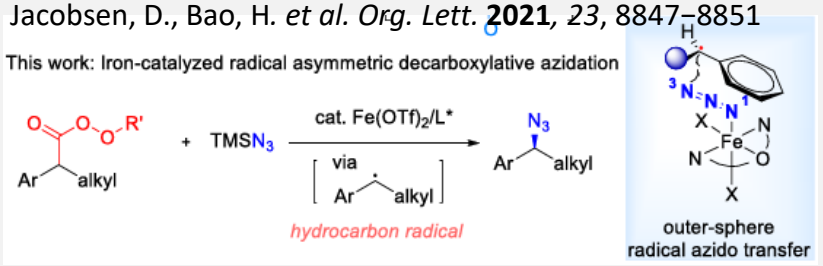
- Ring openings of epoxides and aziridines by nucleophilic azide reagents





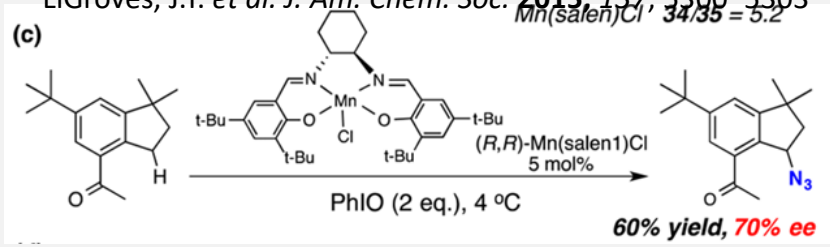
- Azidative function decarboxylative azidations

Jacobsen, D., Bao, H. *et al. Org. Lett.* **2021**, *23*, 8847–8851



- Azidations of C–H bonds

LiGroves, J.T. *et al. J. Am. Chem. Soc.* **2015**, *137*, 5300–5303



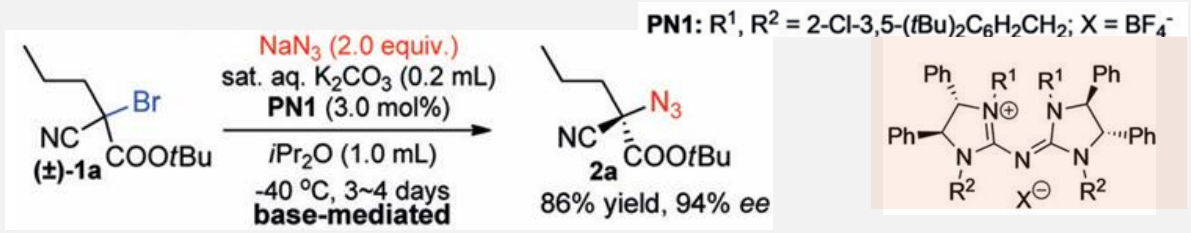
Background: Recent studies for enantioconvergent azidation

Halogenophilic SN2X strategy (DKR) (2020)

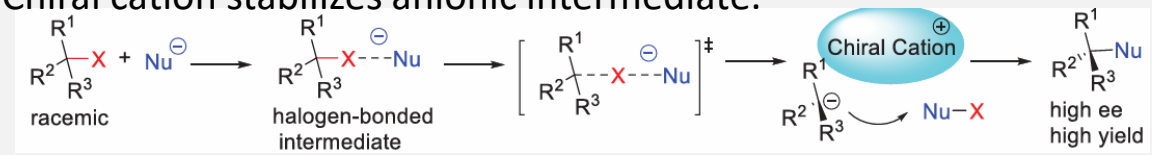
★Only example of alkylhalide substitution

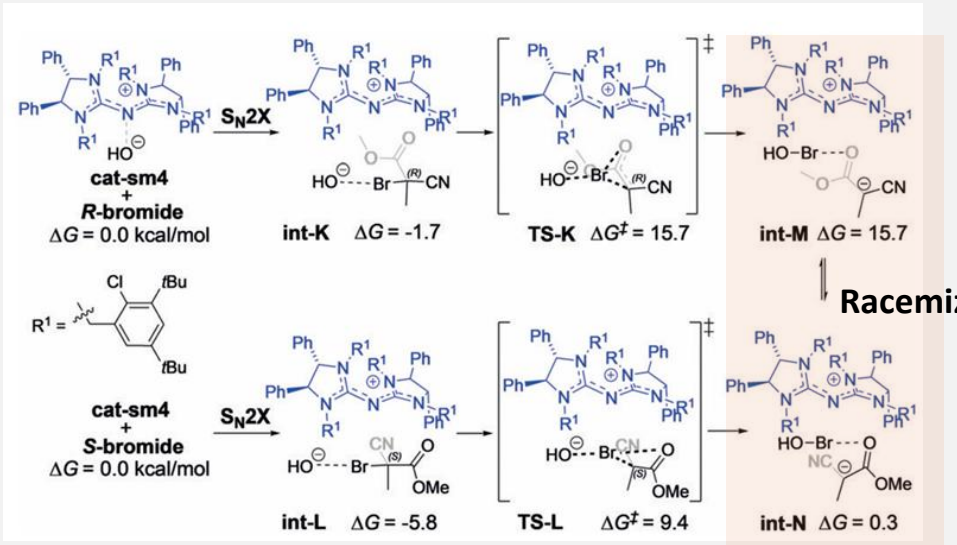
★New SN_2X mechanism

▲Use of less general α-cyanoacetates



Chiral cation stabilizes anionic intermediate.





Lee, R., Tan, CH. *et al. Angew.Chem. Int. Ed.* **2020**, *59*, 9055–9058

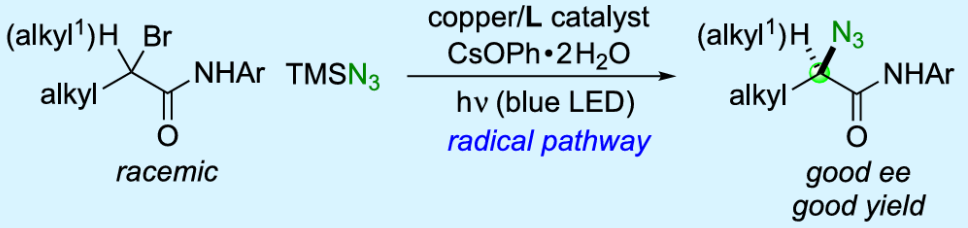
This work

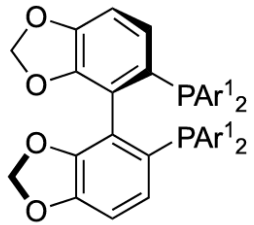
★Quaternary stereocenter

★Use of general α-halocarbonyl

・Photoinduced chiral catalyst

C. Catalytic enantioconvergent azidation of secondary and tertiary α-halocarbonyl compounds: *This study*





(*R*)-**L** (DTBM-SEGPHOS)

- *Secondary and tertiary electrophiles (cyano group not required)*
- *Commercially available chiral ligand*
- *Useful derivatizations*
- *Mechanistic studies*

Photo-induced strategy

Speriority of Cu against Pd or Ni

・Reductive elimination of Cu(Ⅲ) intermediate

▲Weak reducing ability of GS-Cu

➡Inefficient oxidative addition

①**Anionic tridentate ligands (topic 1.)**

・Enhance the reducing ability of Cu(I)

②**Photo-induced strategy in mild condition (topic 2.)**

・Overcome high-reduction potential of alkyl elecrophiles

・Elimination of side reactions

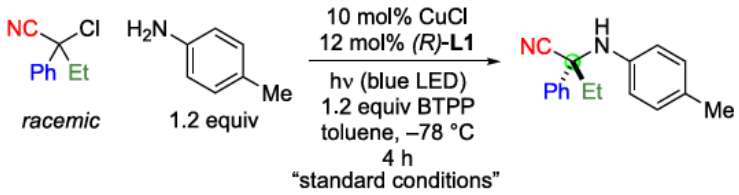
・Enantiomeric control

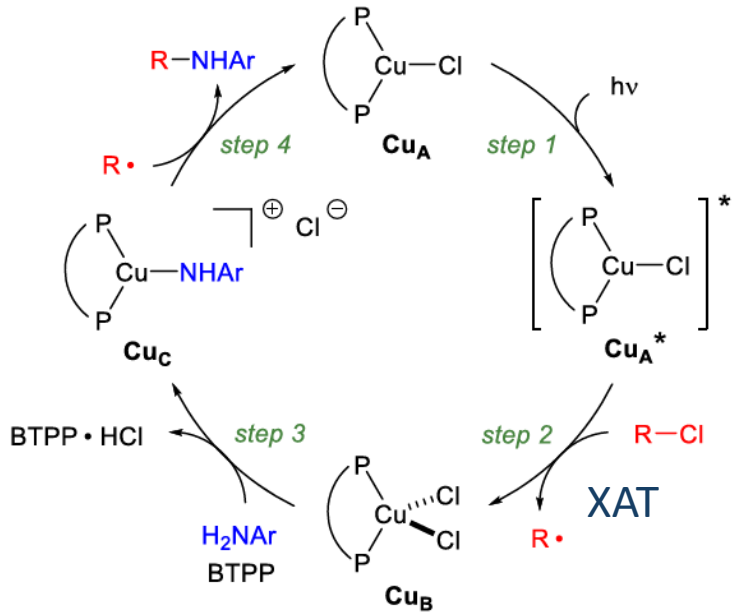
Previous work:

Alkylations of Anilines (2022)

・Photo-induced Cu catalysis

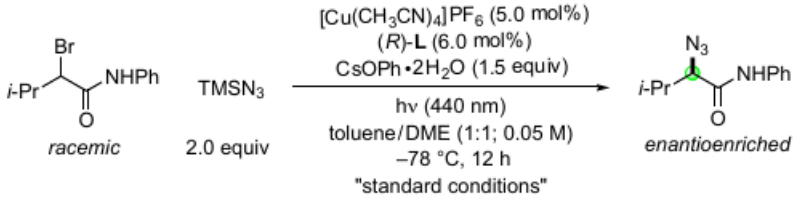
・Enantioconvergent





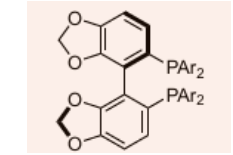
Peters, JC., Fu, GC. *et al., J. Am. Chem. Soc*. **2022**, *144*, 4550–4558

Reaction and ligand optimization

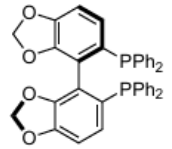


Entry	Change from the "standard conditions"	Yield (%)	ee (%)
1	**none**	**>99**	**94**
2	no $[Cu(CH_3CN)_4]PF_6$	<1 (<1[a])	–
3	no (*R*)-**L**	<1 (<1[a])	–
4	no $[Cu(CH_3CN)_4]PF_6$ and no (*R*)-**L**	<1	–
5	no $CsOPh•2H_2O$	<1	–
6	no hν	<1 (<1[a])	–
7	**L1**, instead of (*R*)-**L**	8	<5
8	**L2**, instead of (*R*)-**L**	38	<5
9	**L3**, instead of (*R*)-**L**	65	79
10	**L4**, instead of (*R*)-**L**	<1	–
11	$CsOPh•H_2O$, instead of $CsOPh•2H_2O$	96	94
12	CsOPh, instead of $CsOPh•2H_2O$	38	81
13	$LiOPh•2H_2O$, instead of $CsOPh•2H_2O$	80	80
14	TMG, instead of $CsOPh•2H_2O$	>99	83
15	NEt_3, instead of $CsOPh•2H_2O$	<5	–
16	CuBr, instead of $[Cu(CH_3CN)_4]PF_6$	99	94
17	$CuCl_2$, instead of $[Cu(CH_3CN)_4]PF_6$	74	93
18	toluene/DME (1:1, 0.1 M)	97	93
19	toluene/DME (1:2, 0.05 M)	96	93
20	toluene/DME (2:1, 0.05 M)	88	94
21	toluene (0.05 M)	<5	–
22	DME (0.05 M)	98	88
23	−60 °C, instead of −78 °C	>99	91
24	room temperature, instead of −78 °C	48	–33
25	no hν, room temperature, instead of −78 °C	<5	–
26	1.2 equiv of $CsOPh•2H_2O$ and 1.3 equiv of $TMSN_3$	98	94
27	$[Cu(CH_3CN)_4]PF_6$ (1.25 mol%), (*R*)-**L** (1.5 mol%)	86 (83[a])	94 (94[a])
28	427 nm, instead of 440 nm	89	94
29	456 nm, instead of 440 nm	89	95
30	1.0 equiv of H_2O added	97 (96[a])	93 (93[a])
31	0.1 mL of air added to the headspace	81 (81[a])	93 (93[a])

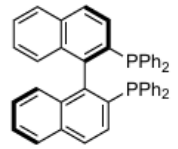
[a]1.2 equiv of $CsOPh•2H_2O$ and 1.3 equiv of $TMSN_3$ were used.



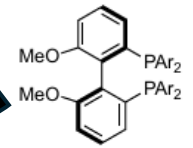
Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C$_6$H$_2$
(*R*)-DTBM-SEGPHOS ((*R*)-**L**)



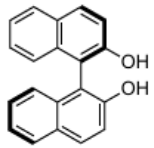
(*R*)-SEGPHOS (**L1**)



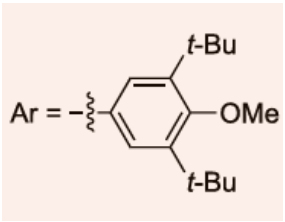
(*R*)-BINAP (**L2**)



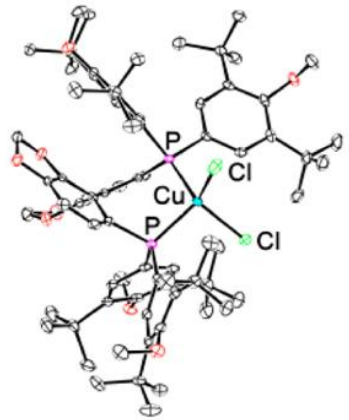
Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C$_6$H$_2$
(*R*)-DTBM-MeO-BIPHEP (**L3**)



(*R*)-BINOL (**L4**)



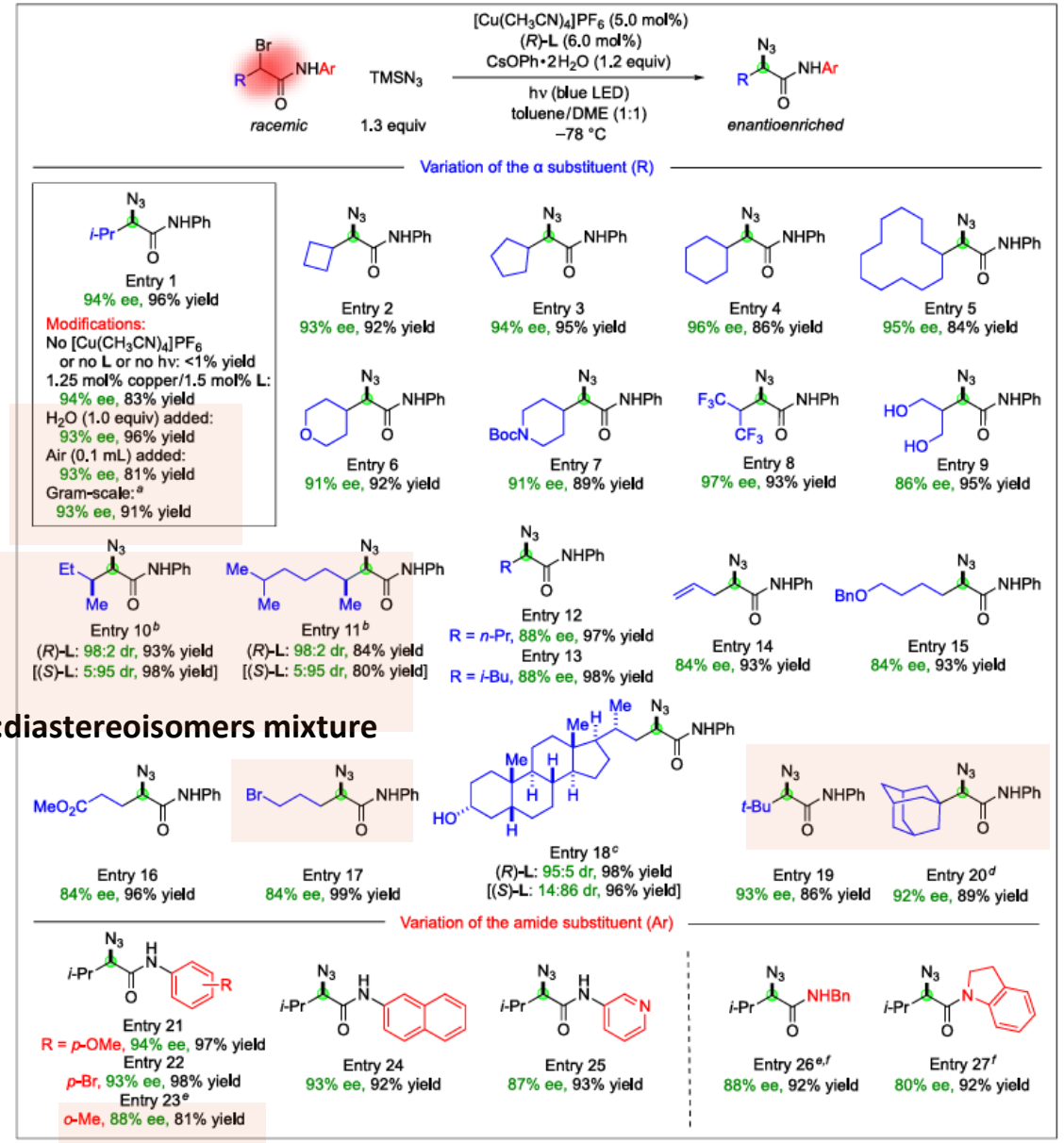
- Bulky substituent is necessary for high ee.
- EDGs increase the reducing power of Cu.



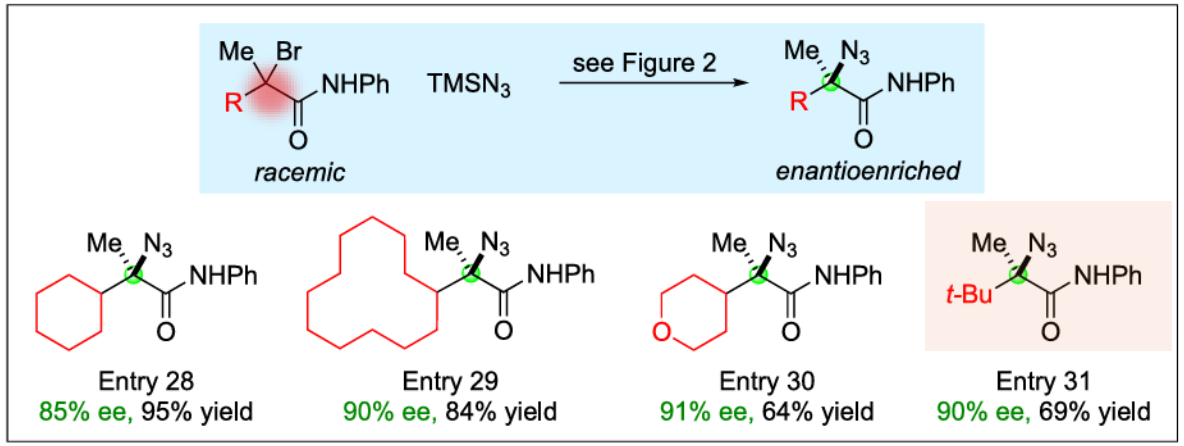
Origin of selectivity

Fu, G.C., Peters J.C. *et al. J.Am.Chem.Soc.* **2022**, *144*,4550−4558

Reaction development and scope



Quaternary azidation was accomplished.



- Acyclic substituent (31)
- 3-membered ring-> poor differentiation?

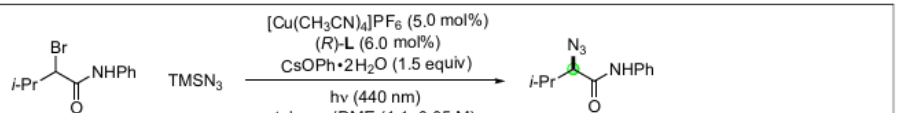
- **Air, moisture tolerable** (1)
- Diastereomer substrates (10-11)
- α-bromoketone (17)
- Bulky substrate (19-20)
- FG tolerance

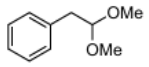
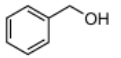
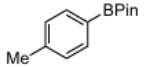
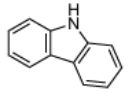
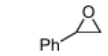
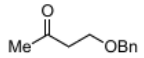
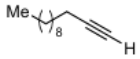
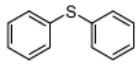
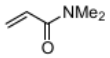
▲α-chloroamide is much less reactive
▲α-substituted ketones and esters* (poor e.e.)
*structure not reported

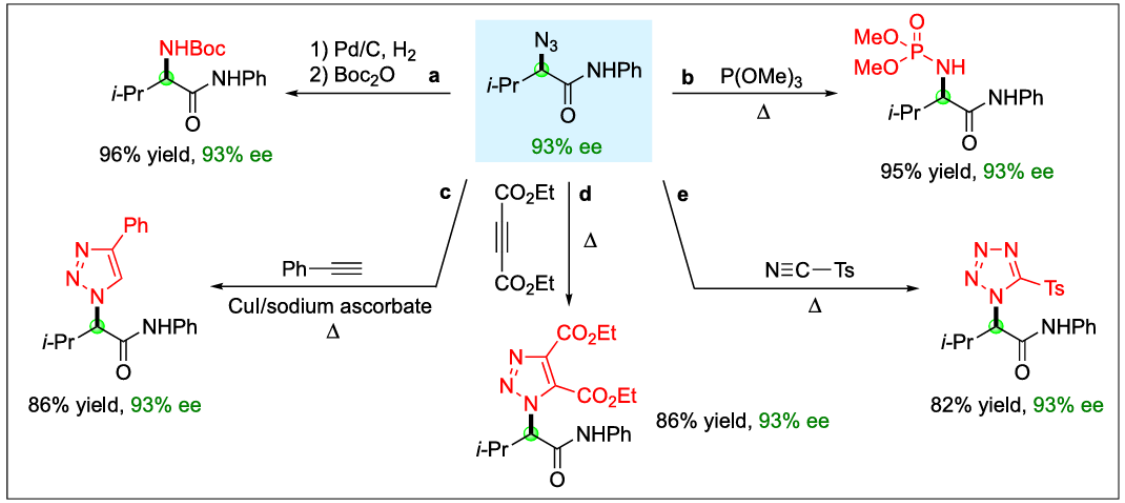
Fu, G.C., *et al., J. Am. Chem. Soc.* **2025**, *147*, 32963–32970

Synthetic applications

Compatibility check



Entry	Additive	Recovery of additive	Yield (%)	ee (%)
1	none	–	>99	94
2		>95	94	93
3		>95	>99	94
4		>95	98	94
5		>95	>99	94
6		>95	98	93
7		>95	>99	93
8		>95	96	93
9		>95	98	94
10		>95	98	94
11		>95	>99	94
12		>95	96	94
13		>95	96	92
14		>95	98	92
15		>95	95	92
16		>95	96	93
17		>95	>99	93
18		>95	96	91



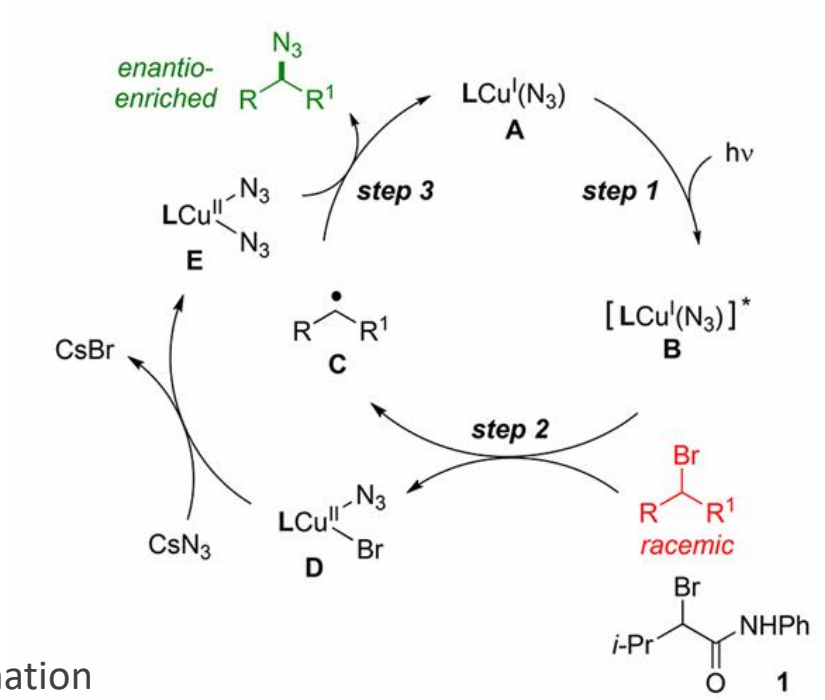
★Synthetically useful building block

- Boc-protected amine (Reduction)
- Phosphoramidate (Staudinger-type reaction)
- Triazole, tetrazole (Click chemistry)

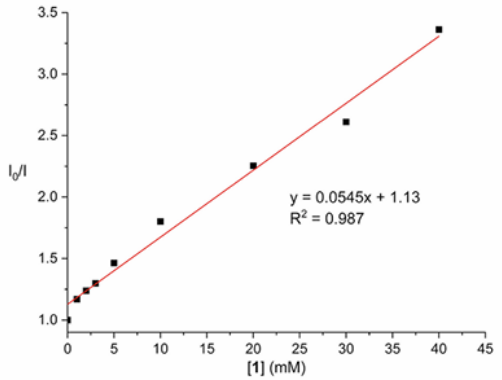
Fu, G.C., *et al.*, *J. Am. Chem. Soc.* **2025**, *147*, 32963–32970

Mechanistic studies①

Supposed catalytic cycle



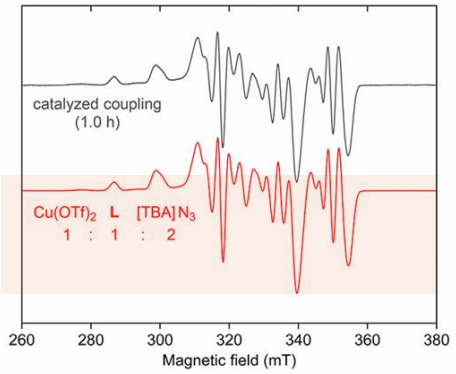
C. [LCuI(N3)]* (B): Stern–Volmer quenching by electrophile 1



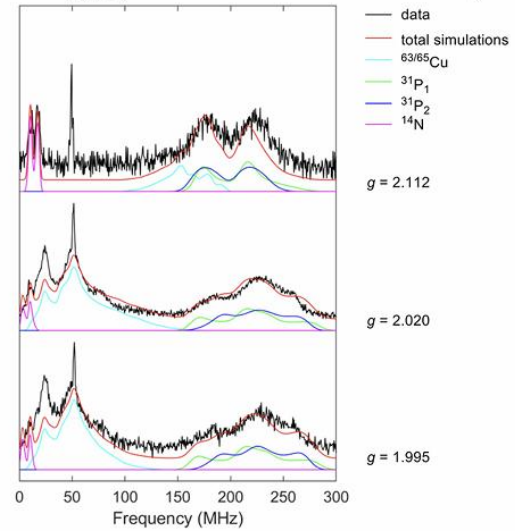
Oxidative quenching by α-bromoketone

LCuII(N3)2 was identified as active species.

D. LCuII(N3)2 (E): X-band CW–EPR spectra



E: LCuII(N3)2 (E): Q-band Davies ENDOR data and DFT analysis

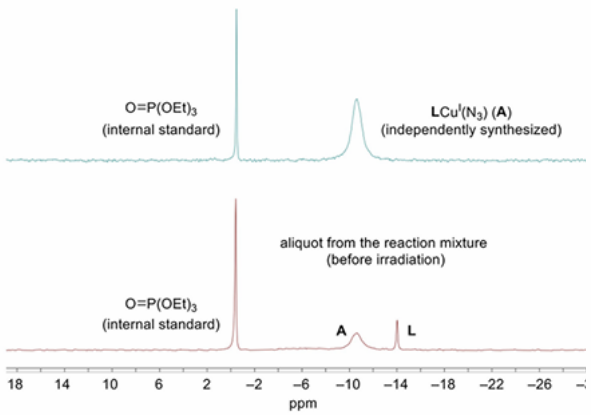


Nucleus	Experiment	DFT calculations	
		$LCu(N_3)_2$	$[LCu(N_3)]^+$
$^{63/65}Cu$	154	185	50
$^{31}P_1$	428	403	188
$^{31}P_2$	434	386	512
$^{14}N_\alpha$	16.5	11.0, 11.6	0.3
$^{14}N_\beta$	N.D.	1.6, 2.0	3.3
$^{14}N_\gamma$	N.D.	1.3, 1.2	1.6

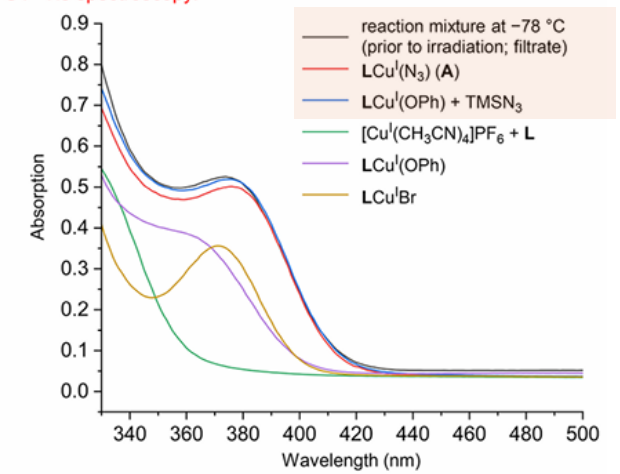
CsN_3 formation

B. LCuI(N3) (A): Presence at the start of the reaction

^{31}P NMR spectroscopy:



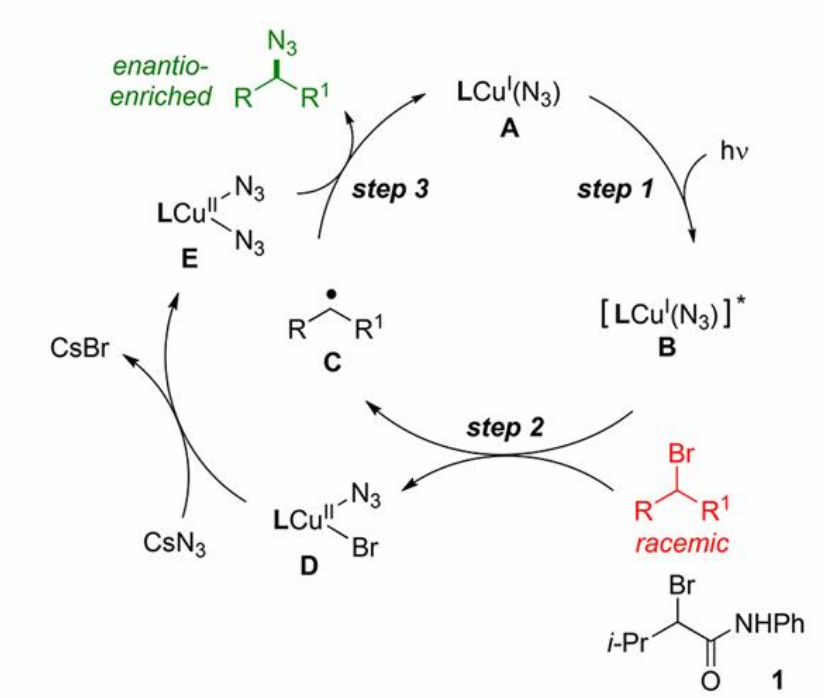
UV–Vis spectroscopy:



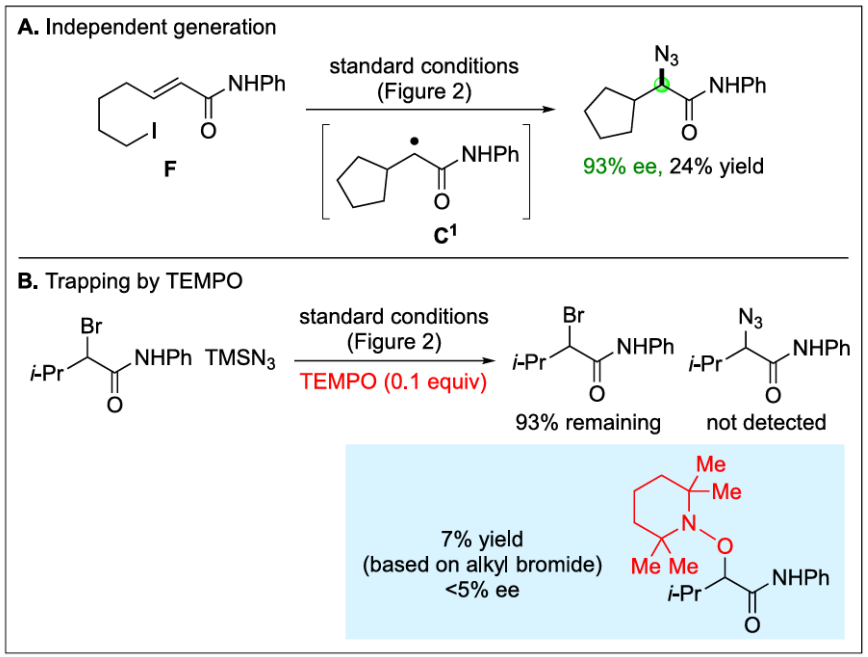
Fu, G.C., *et al., J. Am. Chem. Soc*. **2025**, *147*, 32963–32970

Mechanistic studies②

Supposed catalytic cycle



・Alkyl radical existence



・Radical trapping and catalytic cycle inhibition

Fu, G.C., *et al., J. Am. Chem. Soc*. **2025**, *147*, 32963–32970

Short summary

Achievements:

★New approach for enantioconvergent azidation via alkylhalyde substitution

★Quaternary stereocenter (first example)

★Use of general α-halocarbonyl

★commercially available chiral ligand (SEGPHOS)

・Photoinduced chiral catalyst

Limitation:

▲α-chloroamide is much less reactive

▲α-substituted ketones and esters (poor e.e.)

▲Necessitate α-carbonyl

Fu, G.C., *et al., J. Am. Chem. Soc*. **2025**, *147*, 32963–32970

Outline

1. *O*-alkylation to form sterically-hindered dialkyl ethers

★Enantioconvergent synthesis of congested α,α'-trisubstituted ethers via direct substitution of tertiary alkyl electrophiles

- Multidentate anionic ligands
- Outer-sphere model

Liu, X.Y., *et al*., *Nat Catal*, **2025**, *8*, 919–930

2. Azidation of alkyl Halides

★New approach for enantioconvergent azidation via alkylhalyde substitution

★Quaternary stereocenter (first example)

- Photoinduced chiral catalyst

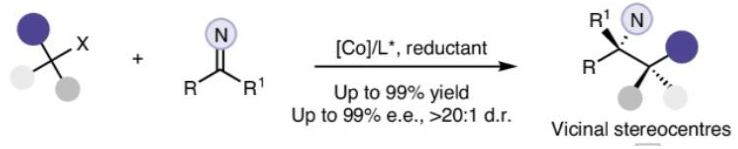
Fu, G.C., *et al., J. Am. Chem. Soc*. **2025**, *147*, 32963–32970

3. Synthesis of congested vicinal stereocentres

★Enantioconvergent stereocenter formation from alkyl halide racemic mixture

- Facile synthesis of valuable motifs including C-glycosylation

Wu, X., Xia, T., Bai, J. *et al., Nat. Chem*., **2025**



Backgrounds: Conventional approaches for enantioselective vicinal stereocenter formation

Not enantioconvergent synthesis (chiral substrate)

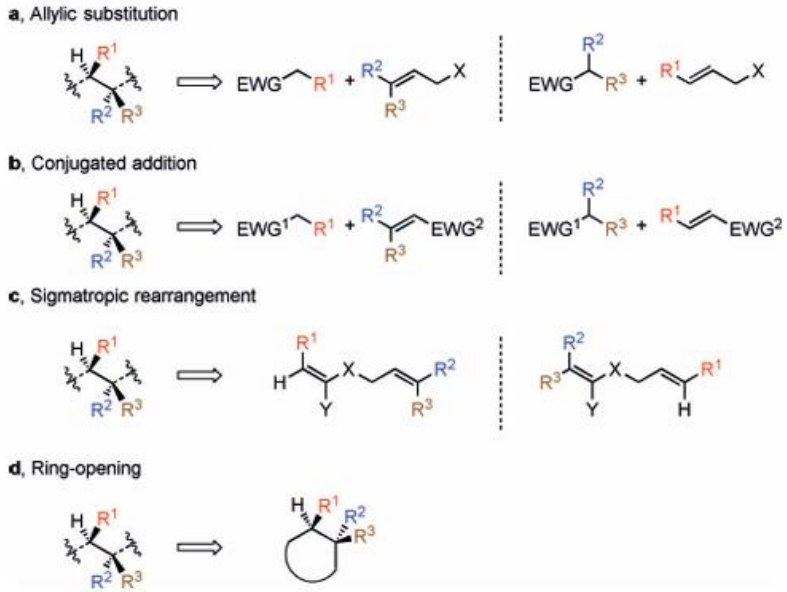
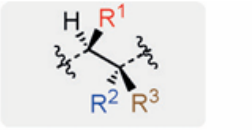


Figure 1. Main strategies for the enantioselective preparation of vicinal tertiary and quaternary stereocenters in acyclic systems.



Complete stereocontrol ?

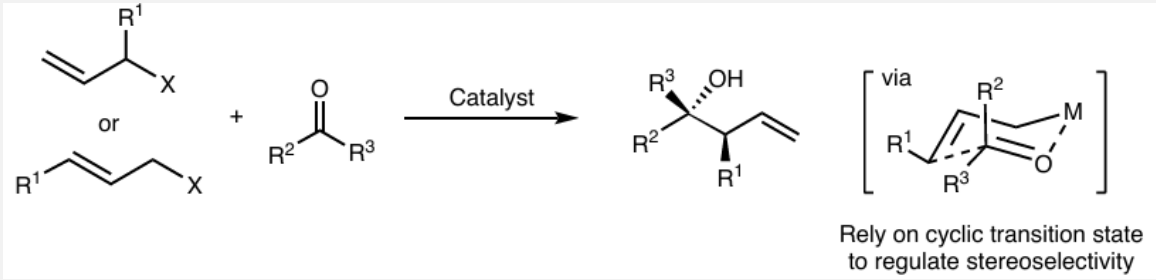
Cu catalysis
- Oxidative radical addition

Ni/Co catalysis
- Reductive addition
- Reducing agent: In, Mn, Zn etc.

Stereoselective NHK reaction
- Addition of organoelectrophiles to carbonyl compounds(Ni,Cr)

★No need for organometallic reagents

Vinyl halides and activated allylic electrophiles
- Generate catalytic organometallics intermediates
- Zimmerman–Traxler transition states



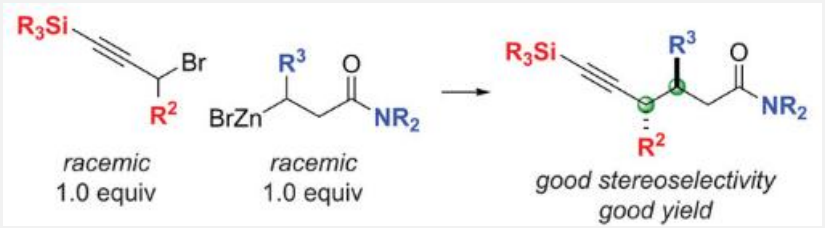
Asymmetric reductive addition
➡application to alkyl halides (recent work)

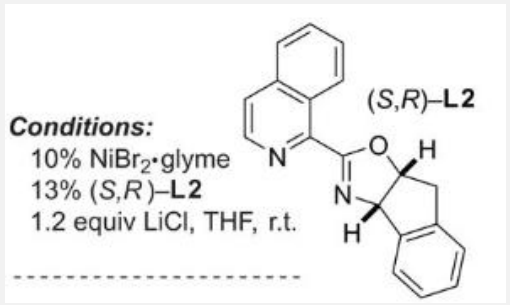
Marek, I. & Pierrot, D., *Angew.Chem. Int. Ed.* **2020**, *59,*36–49

Background: Recent work of doubly enantioconvergent stereocenter formation

Radical-radical coupling (2020)

★Secondary E & secondary nucleophiles





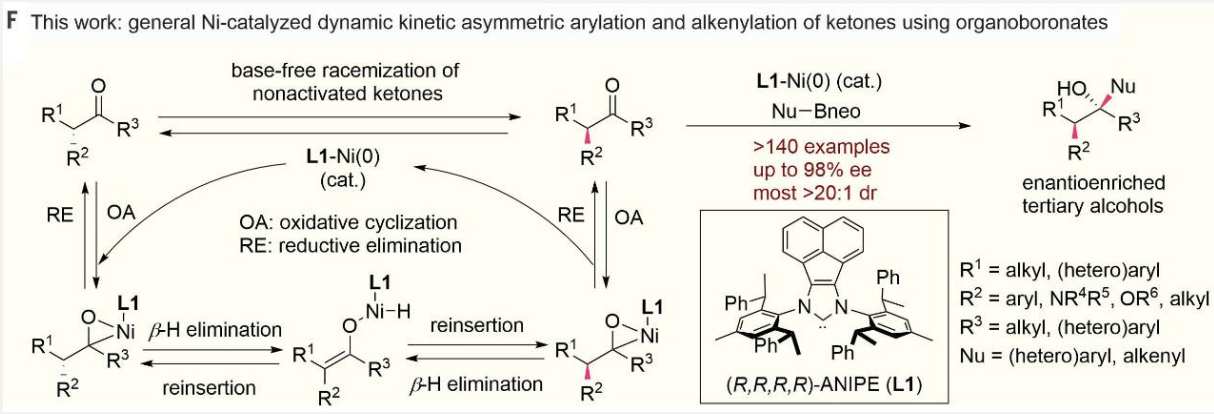
・Bidentate rather than a tridentate ligand is effective

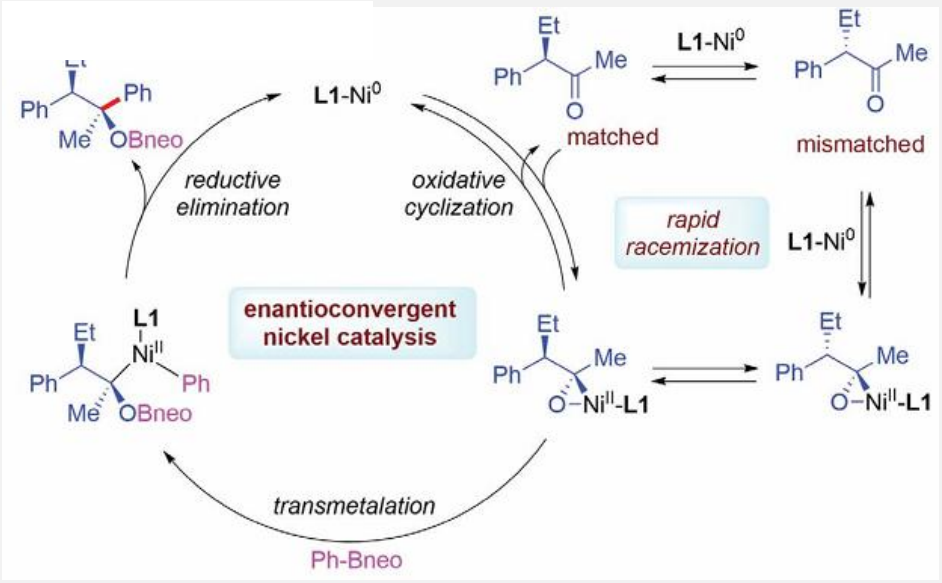
<- Low congestion around Ni helps amide-O complexation in the stereochemistry-determining step.

Fu, G.C. *et al., Science*. **2020**, *367*, 559–564

DyKAT approach (2023)

・Contiguous stereocentres (not both quaternary)





Shi, SL. *et al., Science.* **2023**. *379*, 662–670

This work: New approach for enantioconvergent stereocenter formation

Enantio aza-Barbier reaction (2024)

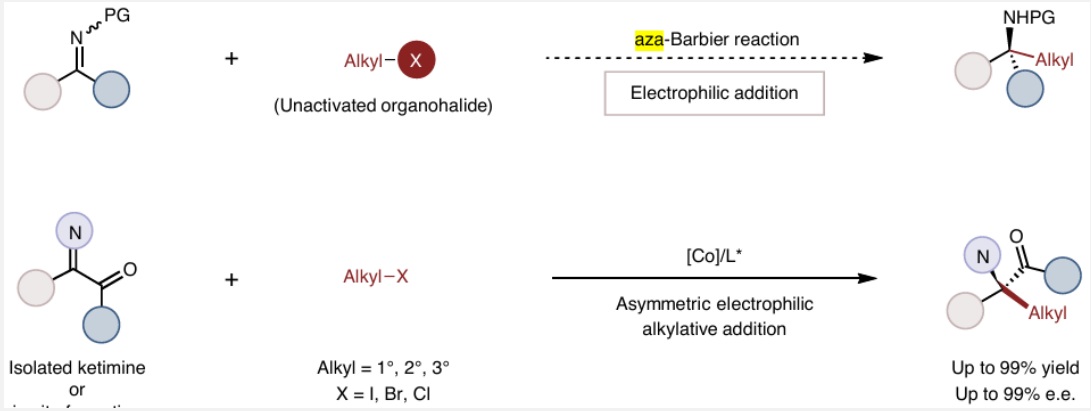
★chiral α-tertiary amino esters

★complementary method without *moisture- and air-sensitive organometallic reagents

・Easily accessible alkyl halides

・Reductive addition approach

▲Chiral alkyl substrates not tested



Chen, Y. *et al*. *Nat. Chem.* **2024**, *16*, 398–407

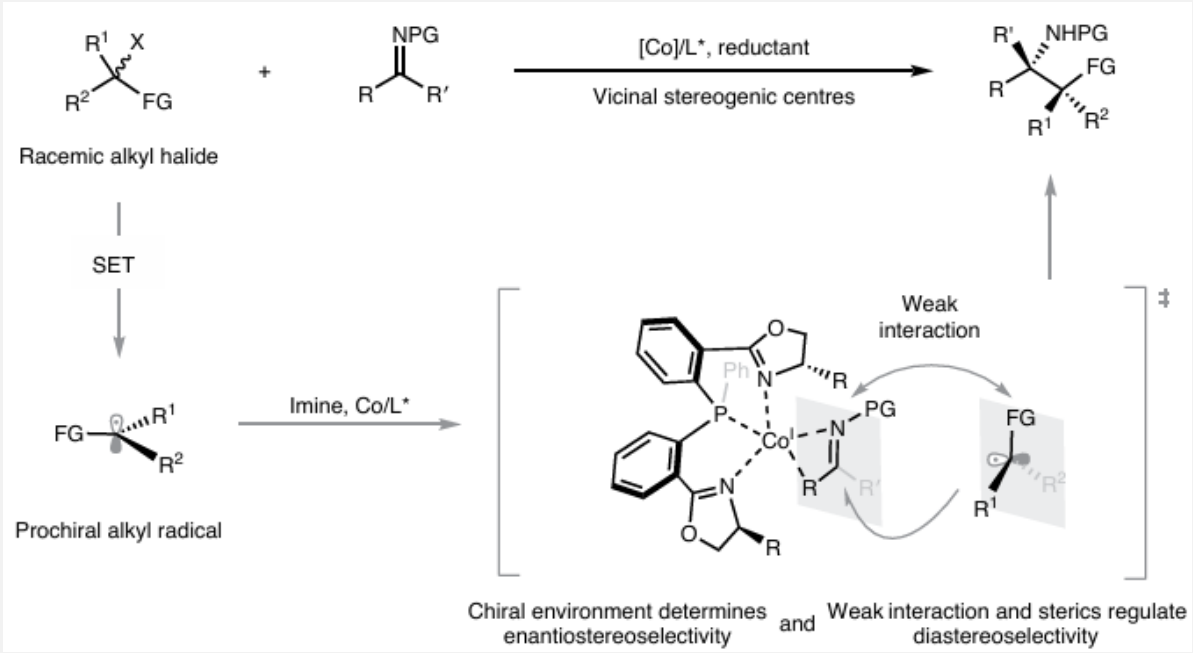
This report (following work):

★Enantioconvergent stereocenter formation from alkyl halide racemic mixture (first)

★Various modes of vicinal stereocentres

・Precise mechanistic study

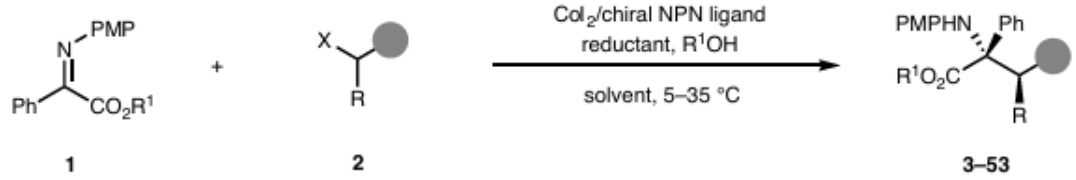
・C-glycosylation

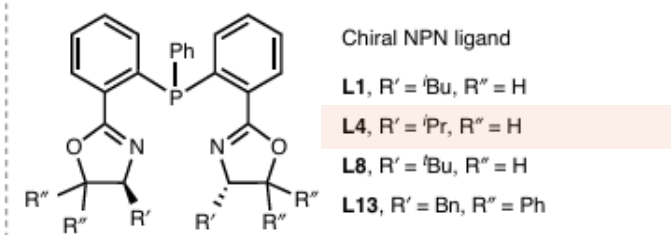


Wu, X., Xia, T., Bai, J. *et al. Nat.Chem*. **2025**

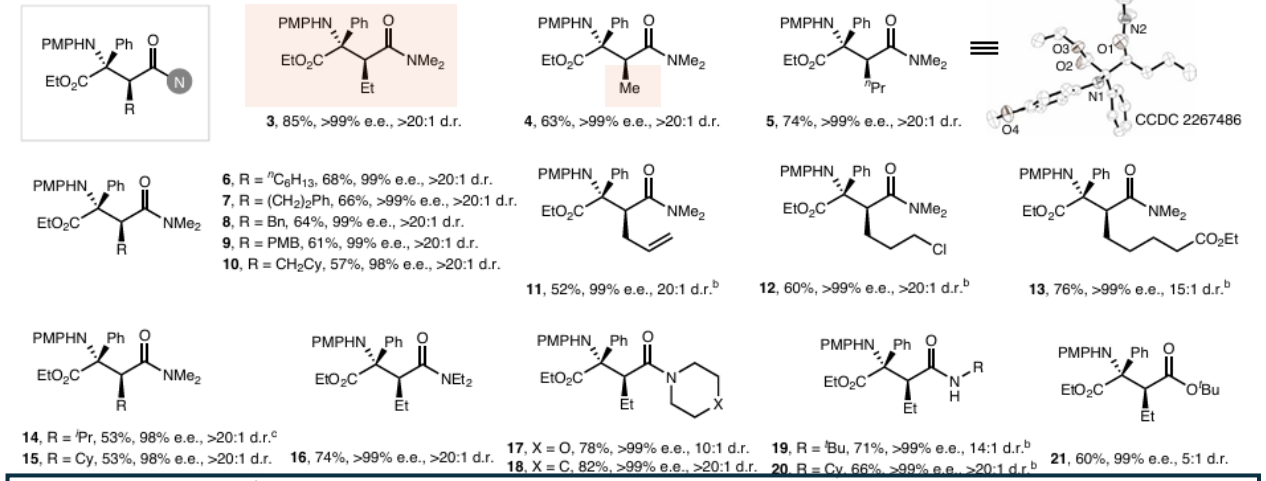
Substrate scopes

Secondary alkylhalides

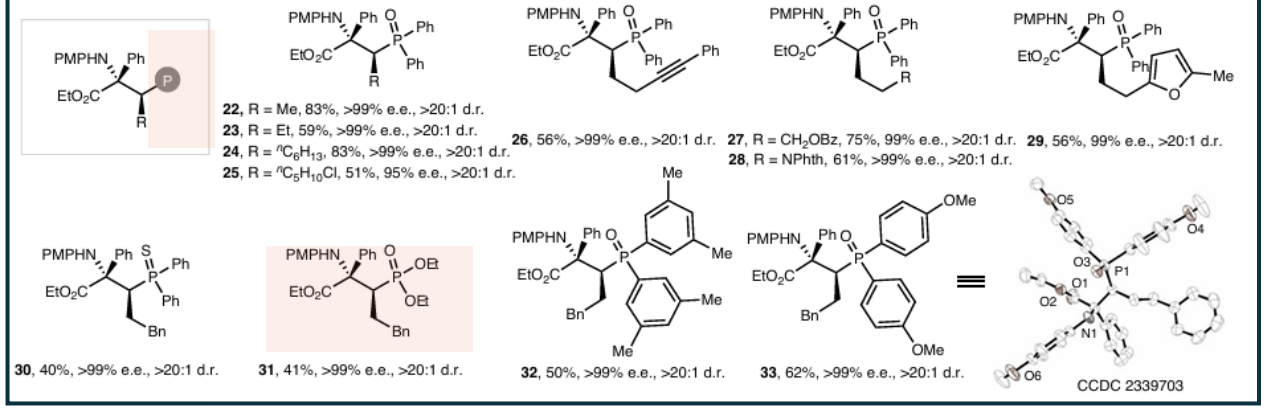




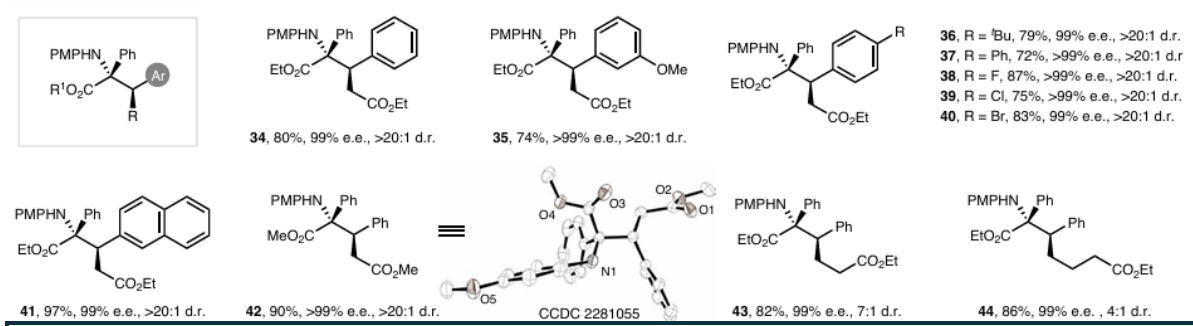
Racemic α-carbonyl chloride[a]



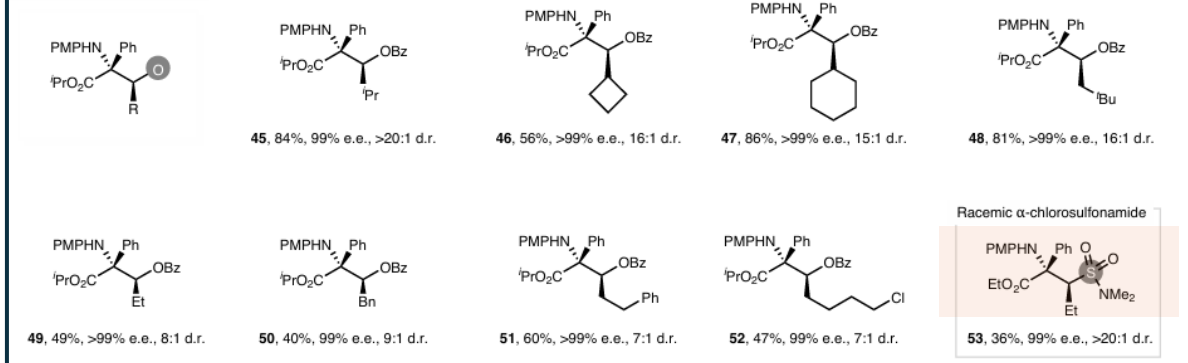
Racemic α-chlorophosphine oxide[d]



Racemic benzyl chloride[e]



Racemic α-bromobenzoate[f]



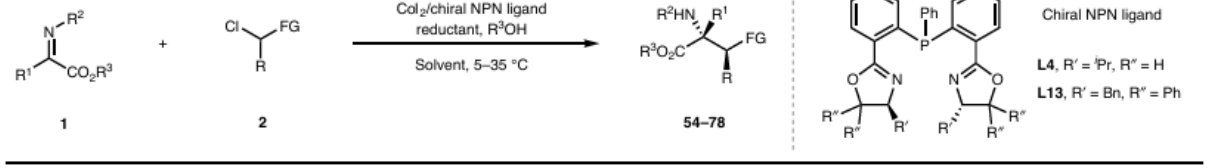
α-bromoalkyl benzoate substrates

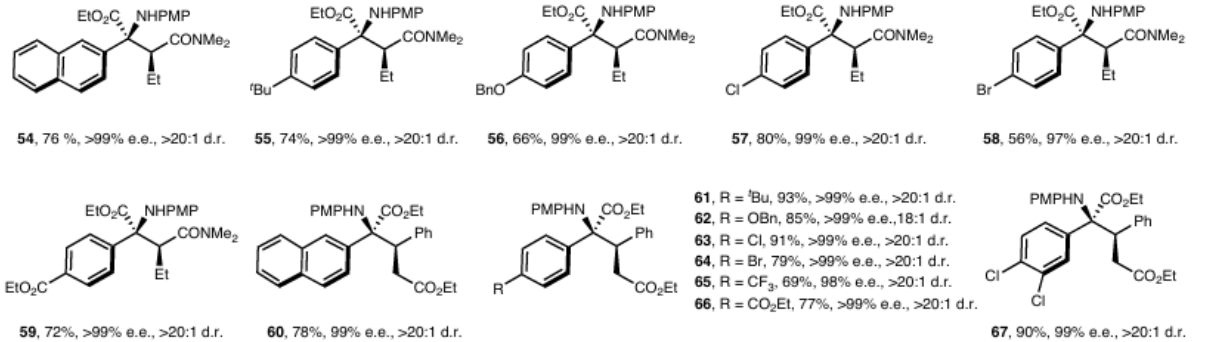
Chiral organophosphorus compounds

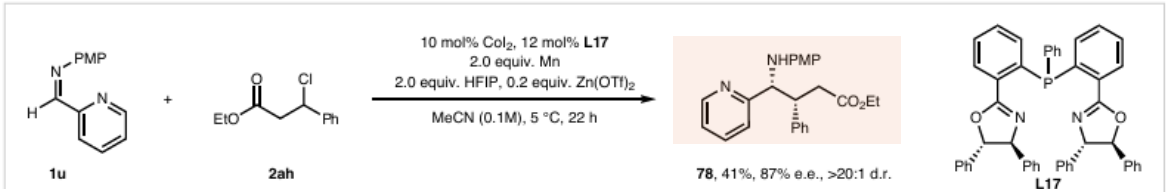
Isolated yields are reported; the e.e. was determined by chiral HPLC analysis and the d.r. was determined by crude NMR or chiral HPLC analysis. [a]**1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (5 mol%), **L4** (6 mol%), indium (2.0 equiv.), R^1OH (1.0 equiv.) in MeCN/THF (1:1 v/v, 0.2 M) under 35 °C for 24–48 h. [b]Indium (3.0 equiv.), **L8** (6 mol%) in MeCN/THF (1:4 v/v, 0.2 M), 72 h. [c]CoI_2 (10 mol%), **L4** (12 mol%). [d]**1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (10 mol%), **L1** (12 mol%), indium (2.0 equiv.), R^1OH (1.0 equiv.), NaBr (1.0 equiv.) in MeCN (0.2 M) under 35 °C for 24 h. [e]**1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (10 mol%), **L13** (12 mol%), manganese (2.0 equiv.), R^1OH (2.0 equiv.) in MeCN (0.2 M) under 5 °C for 6 h. [f]**1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (10 mol%), **L17** (12 mol%), manganese (2.0 equiv.), iPrOH (1.0 equiv.) in MeCN (0.1 M) under 15 °C for 24 h. PMP, *p*-methoxyphenyl.

Substrate scopes

Imines

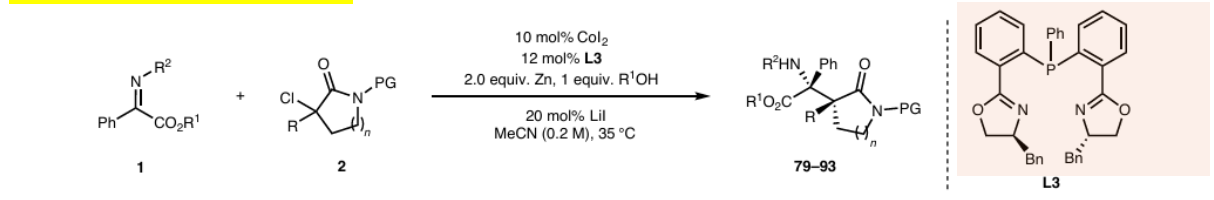


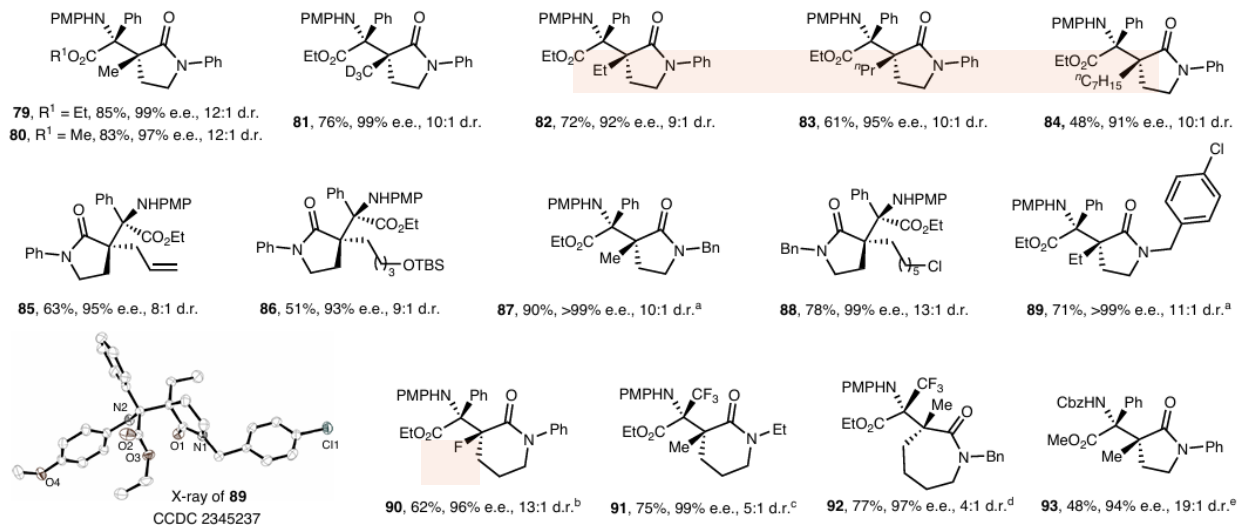




Reaction conditions: **1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (5–10 mol%), **L4** or **L13** (6–12 mol%), indium or manganese (2.0 equiv.), R^3OH (1.0 equiv.) in MeCN (0.2 M) under 35 °C. Isolated yields are reported; the e.e. was determined by chiral HPLC analysis and the d.r. was determined by crude NMR or chiral HPLC analysis. See Supplementary Information, pp. 100–125, for more details.

Tertiary alkylhalides





Reaction conditions: **1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (10 mol%), **L3** (12 mol%), zinc (2.0 equiv.), R^1OH (1.0 equiv.), LiI (20 mol%) in MeCN (0.2 M) under 35 °C for the required time. [a]MeCN/DMA (3:2 v/v, 0.2 M). [b]**L4** (12 mol%), manganese (2.0 equiv.). [c]**L1** (12 mol%), MeCN (0.1 M). [d]**L1** (12 mol%), without LiI, MeCN (0.1 M). [e]**L1** (12 mol%), without LiI, without ethanol, MeCN (0.1 M). Isolated yields are reported; the e.e. was determined by chiral HPLC analysis and the d.r. was determined by crude NMR. PG, protecting group; DMA, *N*,*N*-dimethylacetamide.

▲limited to cyclic alkyl halides. ->low d.r.?

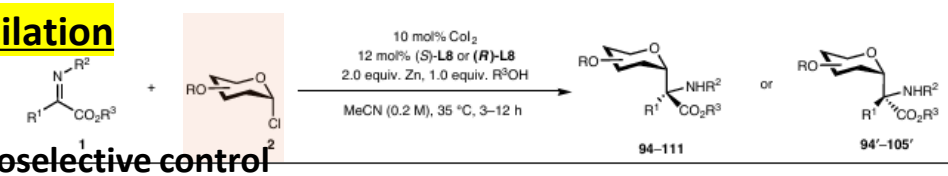
★Medicinally valuable trifluoromethyl-substituted amino acid (68)

★Aldimine substrates (78)

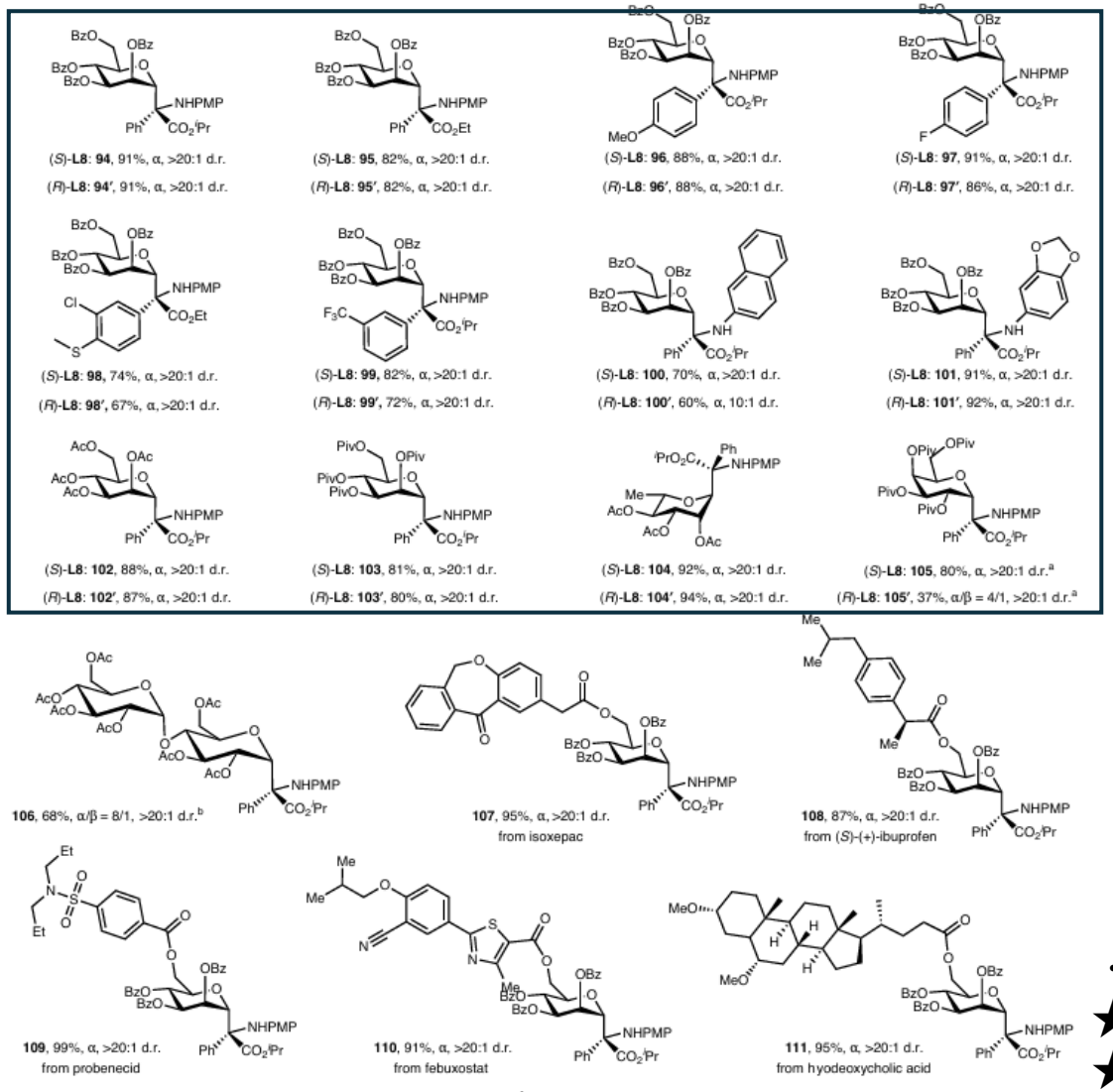
*readily act as bidentate nitrogen ligands

Substrate scopes

C-glycosilation



diastereoselective control



Reaction conditions: **1** (1.0 equiv.), **2** (1.5 equiv.), CoI_2 (10 mol%), **L8** (12 mol%), zinc (2.0 equiv.), R^3OH (1.0 equiv.) in MeCN (0.2 M) under 35 °C for the required time. Isolated yields are reported; the diastereomeric ratios were determined by crude NMR. [a]50 mol% KI as additive. [b]Indium as reductant.

Synthetic applications

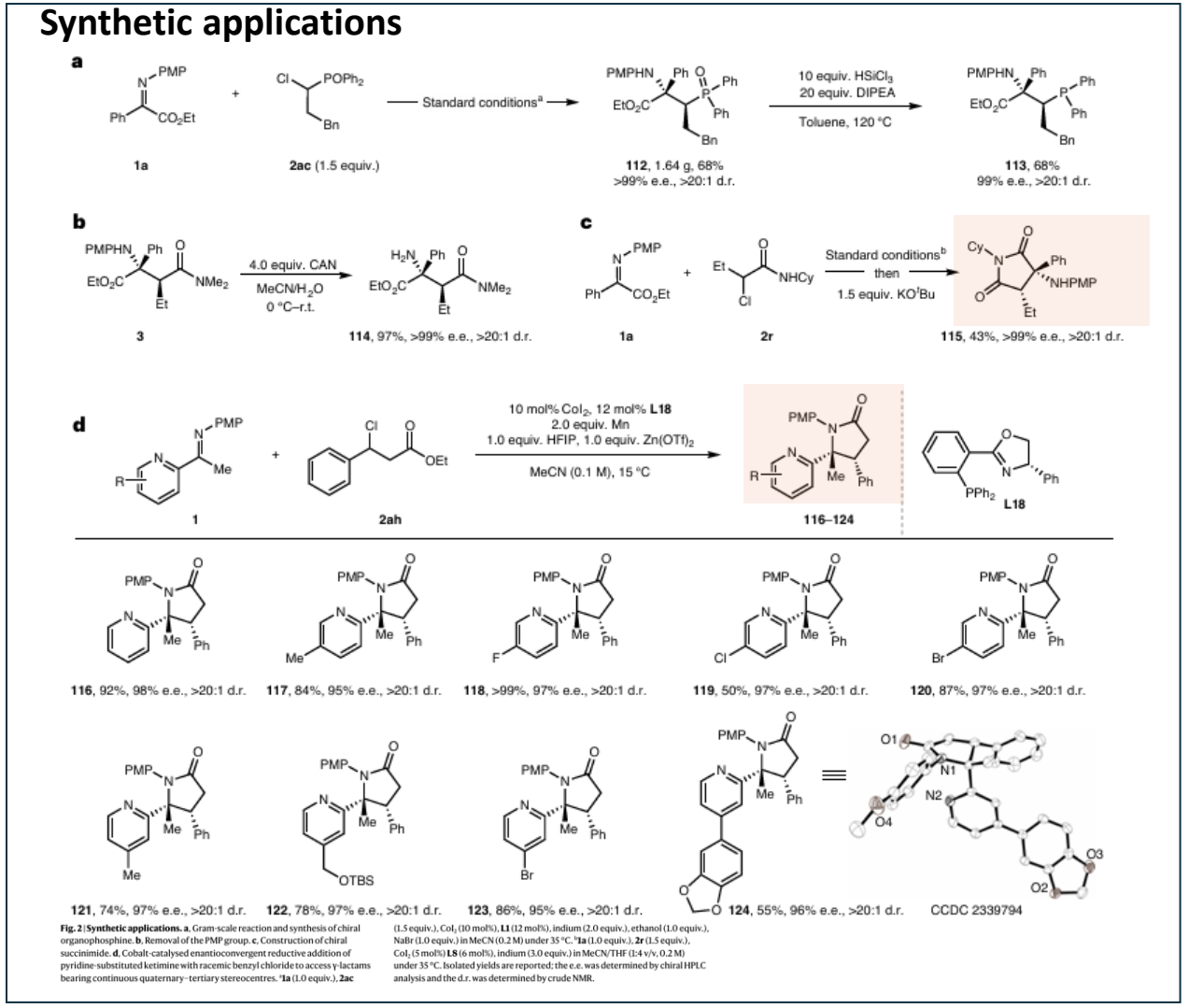


Fig. 2 | Synthetic applications. a, Gram-scale reaction and synthesis of chiral organophosphine. **b**, Removal of the PMP group. **c**, Construction of chiral succinimide. **d**, Cobalt-catalysed enantioconvergent reductive addition of pyridine-substituted ketimine with racemic benzyl chloride to access γ-lactams bearing continuous quaternary–tertiary stereocentres. [a]**1a** (1.0 equiv.), **2ac** (1.5 equiv.), CoI_2 (10 mol%), **L1** (12 mol%), indium (2.0 equiv.), ethanol (1.0 equiv.), NaBr (1.0 equiv.) in MeCN (0.2 M) under 35 °C. [b]**1a** (1.0 equiv.), **2r** (1.5 equiv.), CoI_2 (5 mol%) **L8** (6 mol%), indium (3.0 equiv.) in MeCN/THF (1:4 v/v, 0.2 M) under 35 °C. Isolated yields are reported; the e.e. was determined by chiral HPLC analysis and the d.r. was determined by crude NMR.

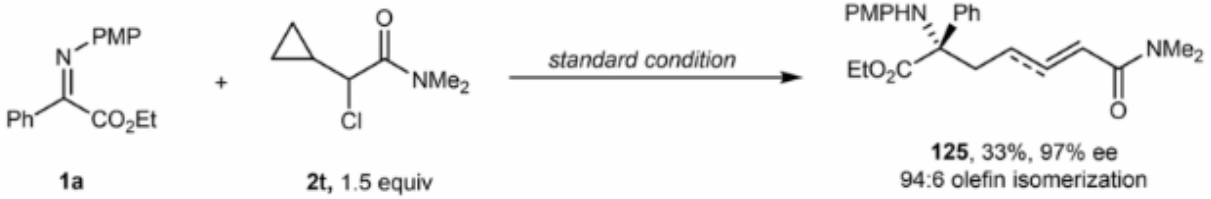
- Useful bioisosters

★Potential application to glycopeptide therapeutics

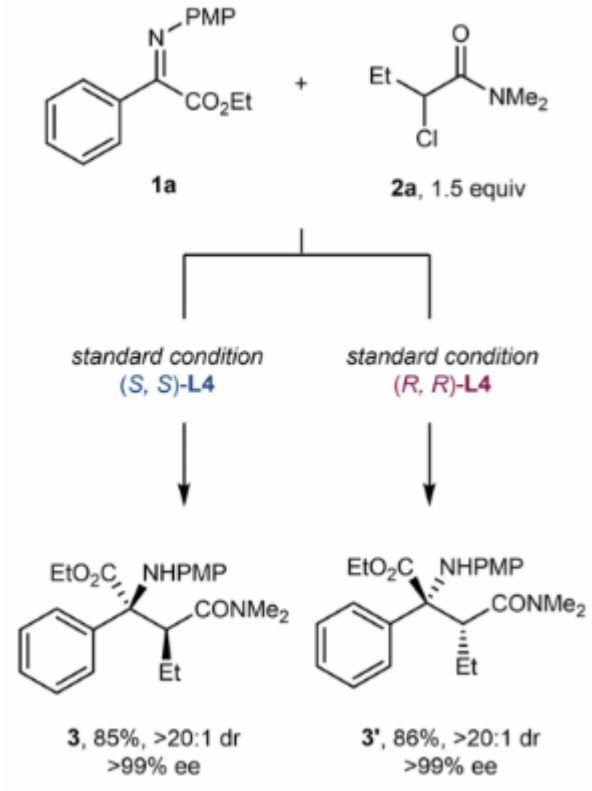
★Rare examples of glycosyl addition via cross-coupling

Mechanistic studies

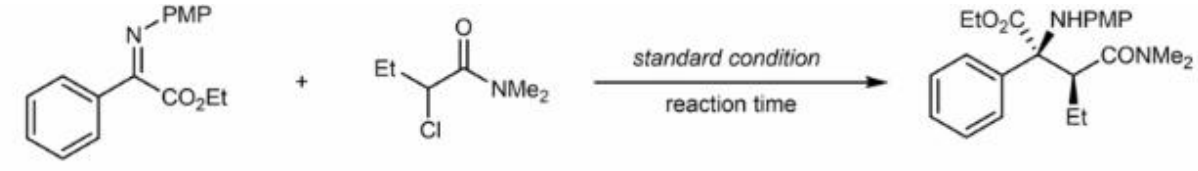
Radical clock experiment
-> Alkyl radical existence



Achieved catalytic chiral control



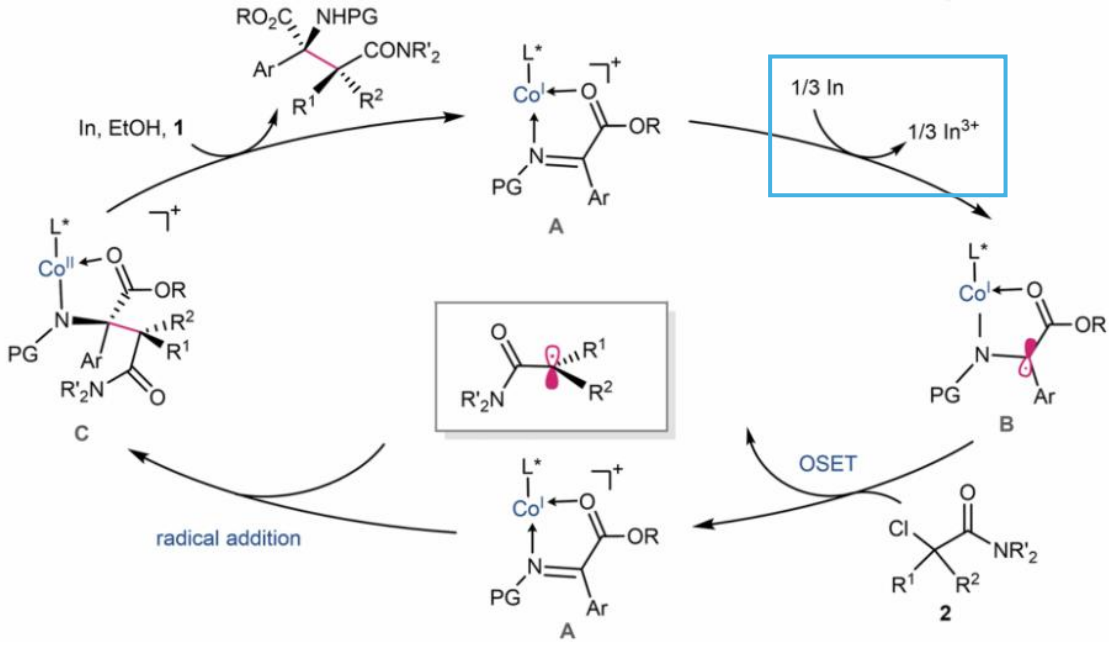
Real-time tracing experiment

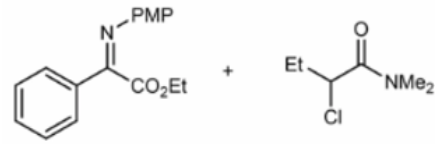


entry	original state of **2a**	reaction time	recovery of **2a**	product **3**
1	racemate	1 h	98%, 3% ee	47% yield, >99% ee, 12:1 dr
2	racemate	2 h	85%, 4% ee	54% yield, >99% ee, 12:1 dr
3	racemate	3 h	26%, 6% ee	89% yield, >99% ee, 12:1 dr
4	(*S*), 88% ee	2 h	75%, 88% ee	58% yield, >99% ee, 12:1 dr
5	(*R*), 94% ee	2 h	77%, 94% ee	53% yield, >99% ee, 12:1 dr

- Reaction rate was the same with both enantiomers.
- Nether KR nor DKR

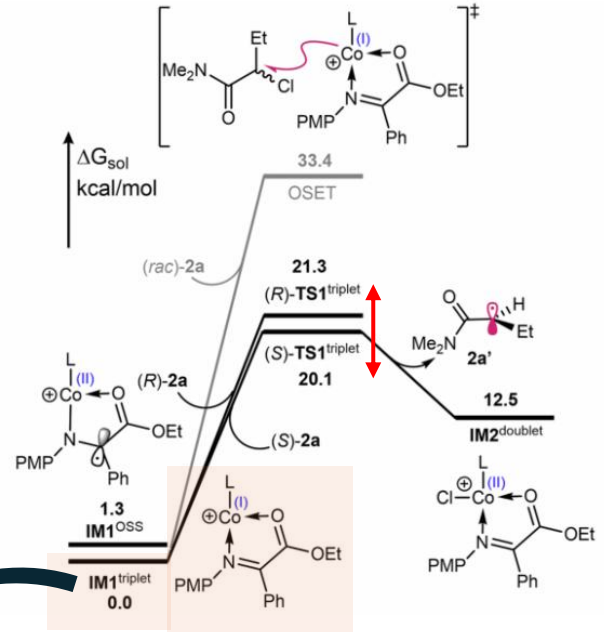
DFT calculations①

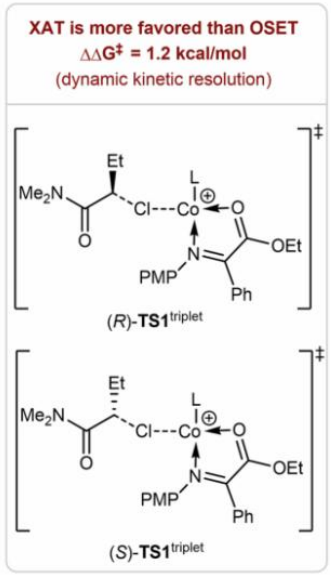




XAT is favorable

Initial state:
1e⁻ reduction

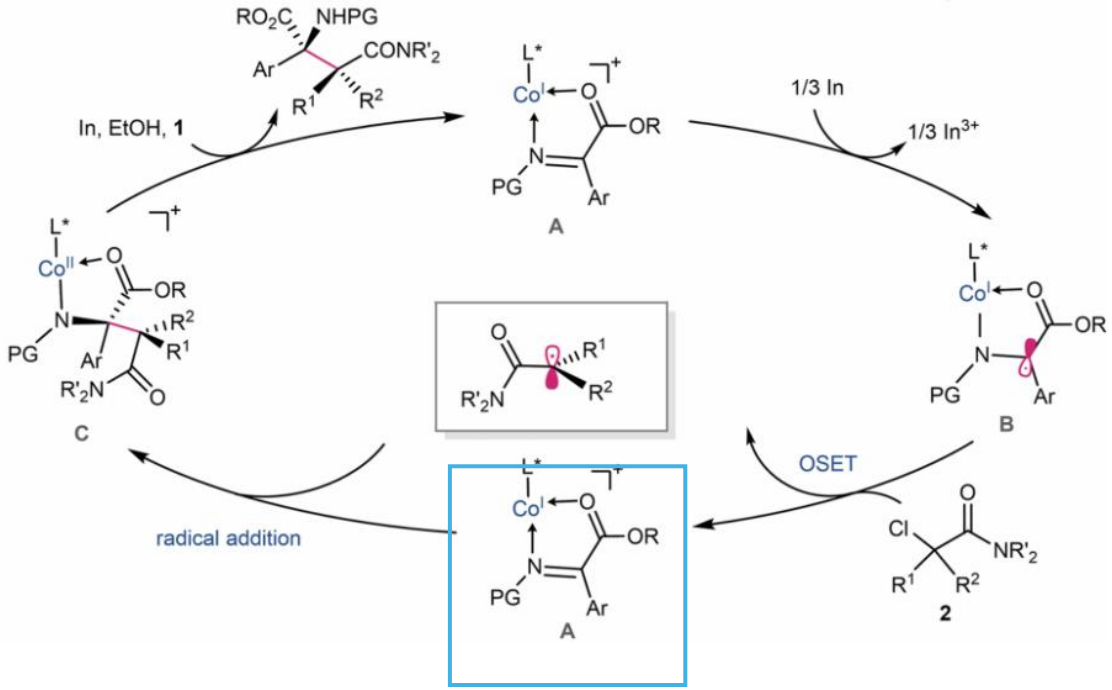




Easily racemizable, but not DKR (contradiction!)

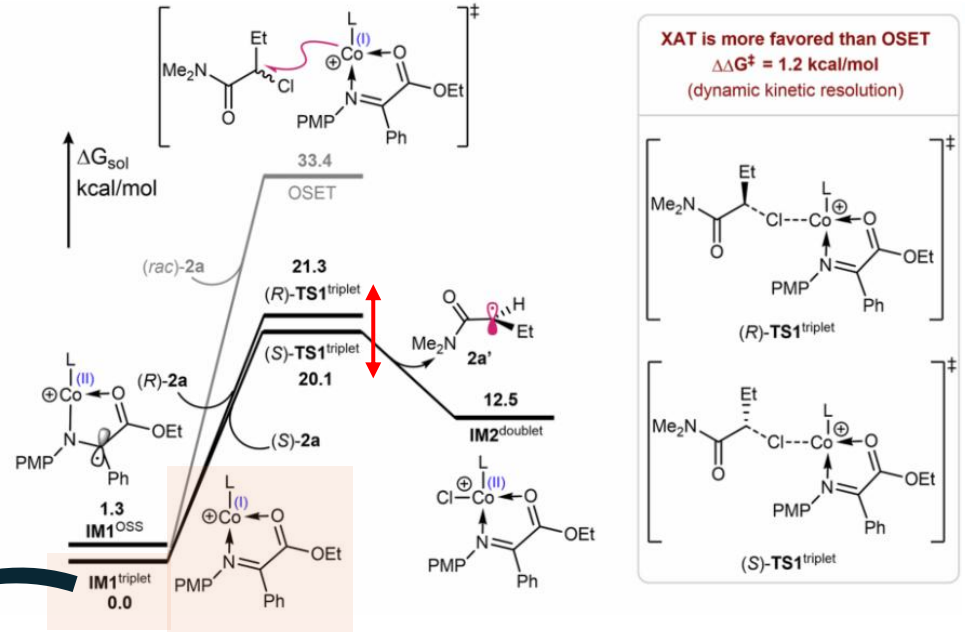
Initial state:
2e⁻ reduction

DFT calculations①

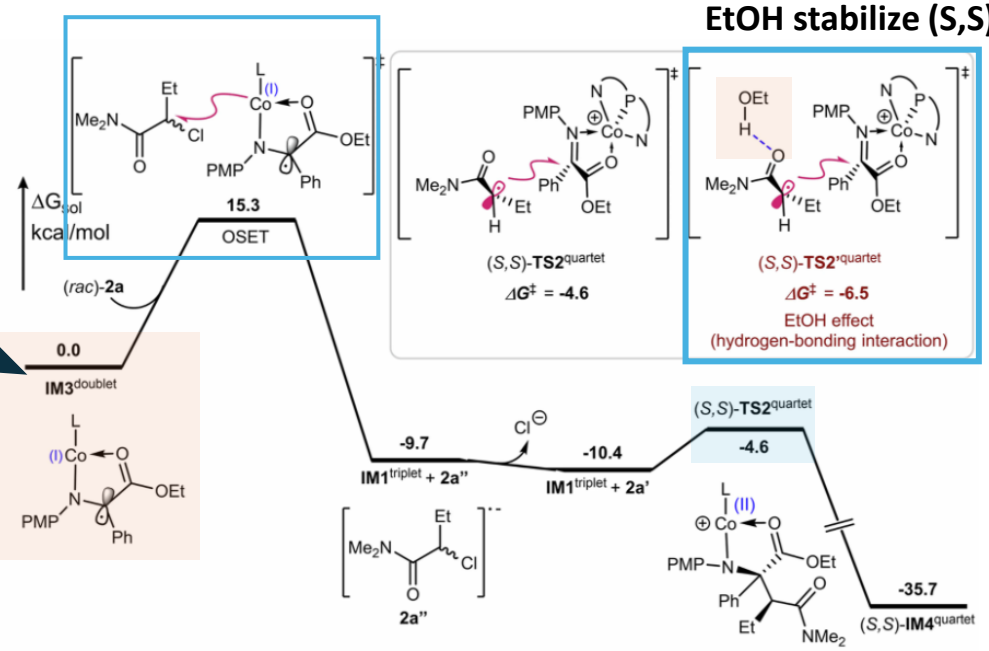


XAT is favorable

Initial state:
1e⁻ reduction



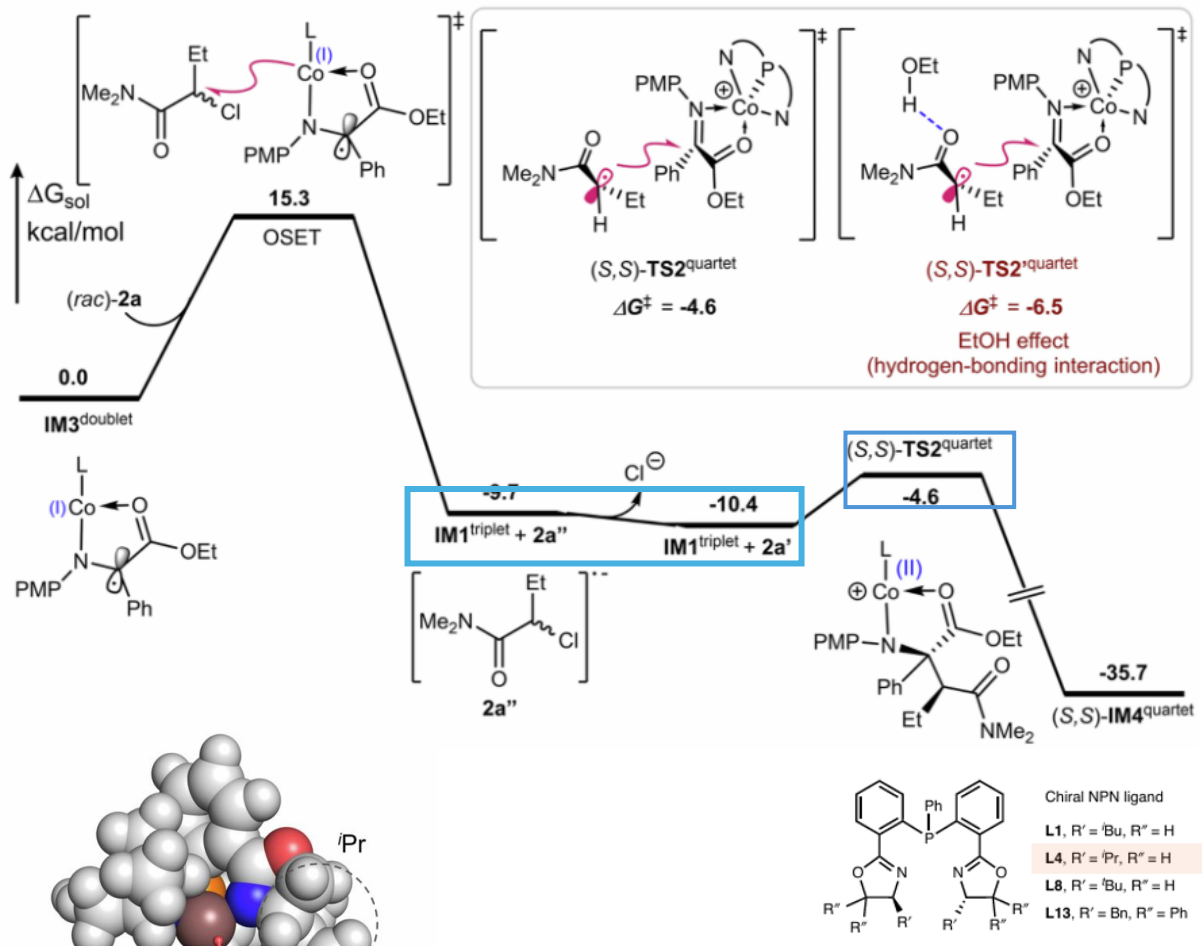
EtOH stabilize (S,S)-TS2

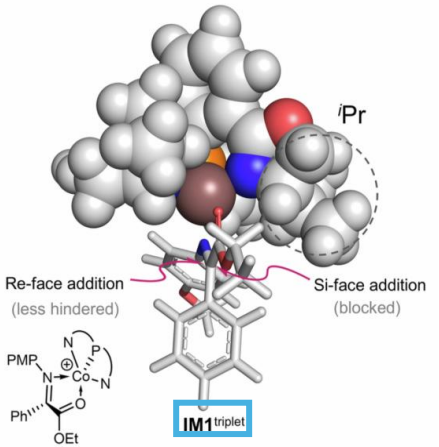


Initial state:
2e⁻ reduction

OSET is favorable

DFT calculations② Origins of stereoselectivity



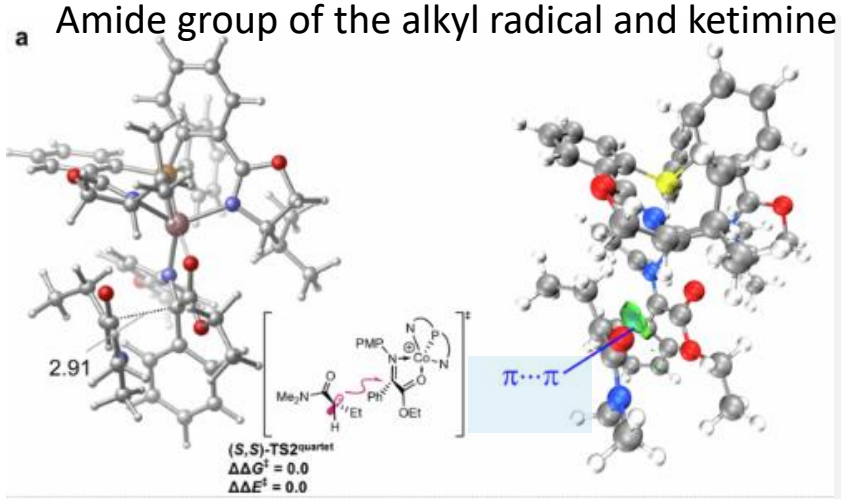


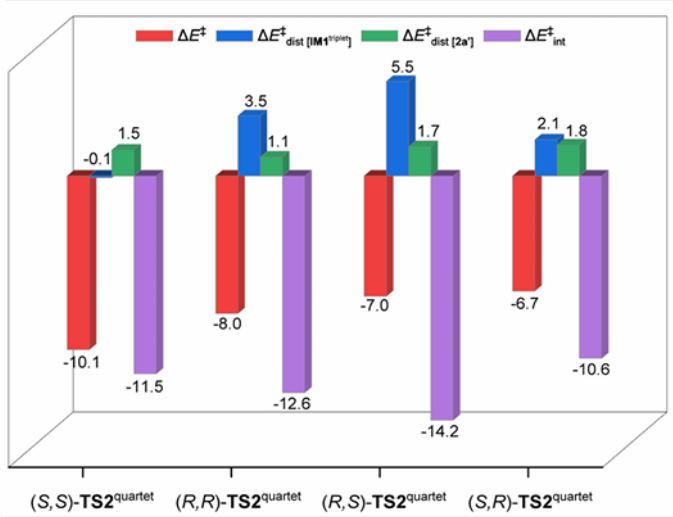
Structural analysis

Sterically blocked by iPr

➡Distortion

Amide group of the alkyl radical and ketimine moiety





Distortion/interaction analysis

less steric repulsion between the radical and chiral ligand

➡✓<u>High π-π interaction</u> & <u>low distortion energy</u>

Short summary

Achievements:

★Enantioconvergent stereocenter formation from alkyl halide racemic mixture (first)

★Various modes of vicinal stereocentres

・Precise mechanistic study

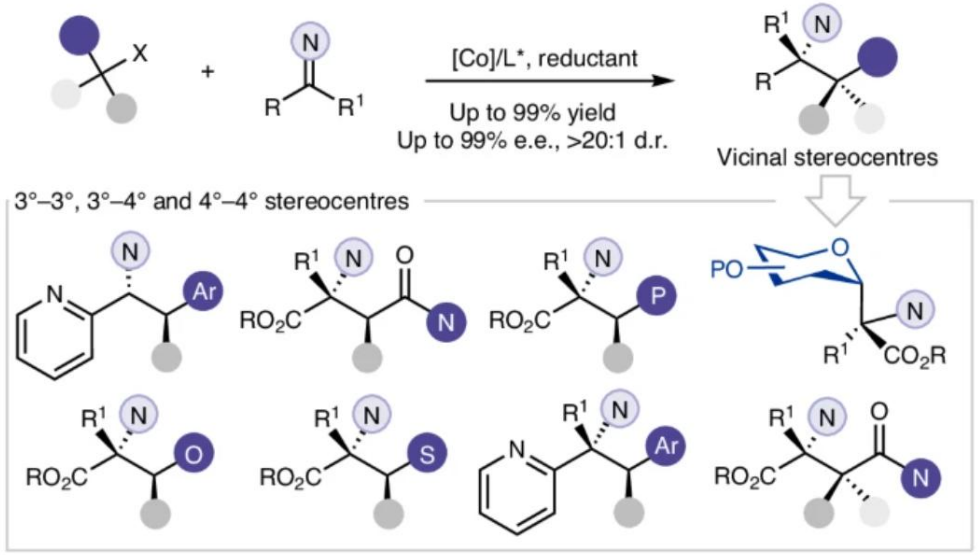
・Facile synthesis of valuable chiral amino acids, organophosphorus compounds, aminoalcohols, heterocycles and glycols

・C-glycosylation

Limitations:

▲Tertiary alkylhalides substrate: limited to cyclic alkyl halides. ->low d.r.?

▲Necessitate α-carbonyl



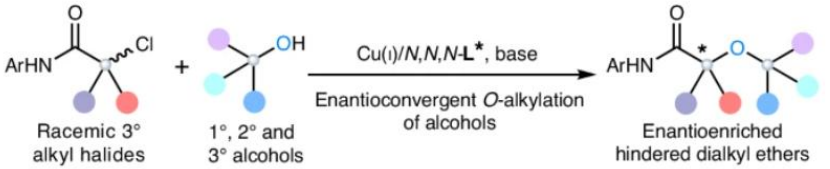
Summary

1. *O*-alkylation to form sterically-hindered dialkyl ethers

★Enantioconvergent synthesis of congested α,α′-trisubstituted ethers via direct substitution of tertiary alkyl electrophiles (first example)

- Multidentate anionic ligands enabled strong chelation
- Meridional chelation
- Outer-sphere model

Liu, X.Y., *et al*., *Nat Catal,* **2025***, 8*, 919–930



2. Azidation of alkyl Halides

★New approach for enantioconvergent azidation via alkylhalyde substitution

★Use of general α-halocarbonyl

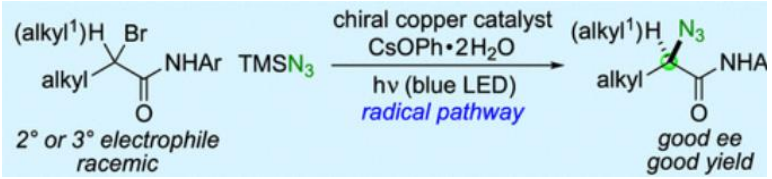
★commercially available chiral ligand (SEGPHOS)

- Photoinduced chiral catalyst

▲α-chloroamide is much less reactive

▲α-substituted ketones and esters (poor e.e.)

Fu, G.C., *et al., J. Am. Chem. Soc*. **2025***, 147*, 32963–32970



3. Synthesis of congested vicinal stereocentres

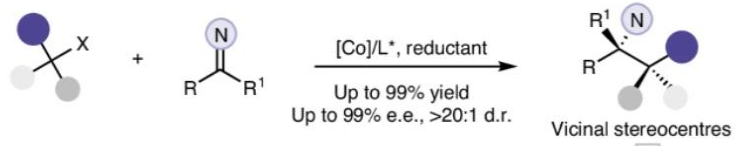
★Enantioconvergent stereocenter formation from alkyl halide racemic mixture (first)

★Various modes of vicinal stereocentres

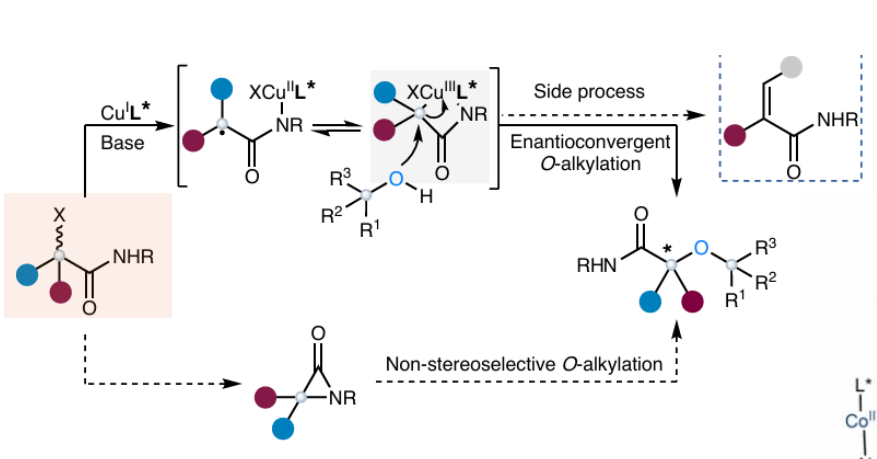
- Precise mechanistic study
- Facile synthesis of valuable chiral amino acids, organophosphorus compounds, aminoalcohols, heterocycles and glycols
- C-glycosylation

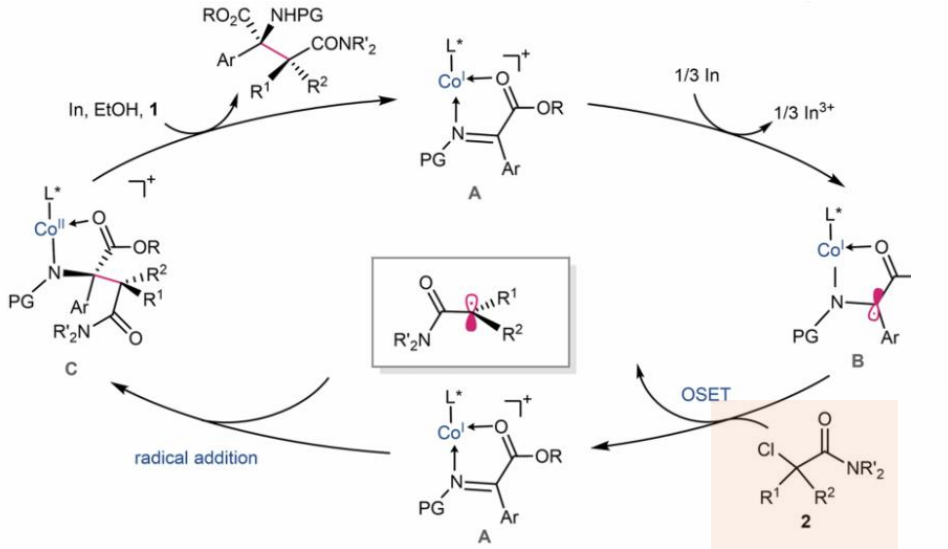
▲Tertiary alkylhalides substrate: limited to cyclic alkyl halides. ->low d.r.?

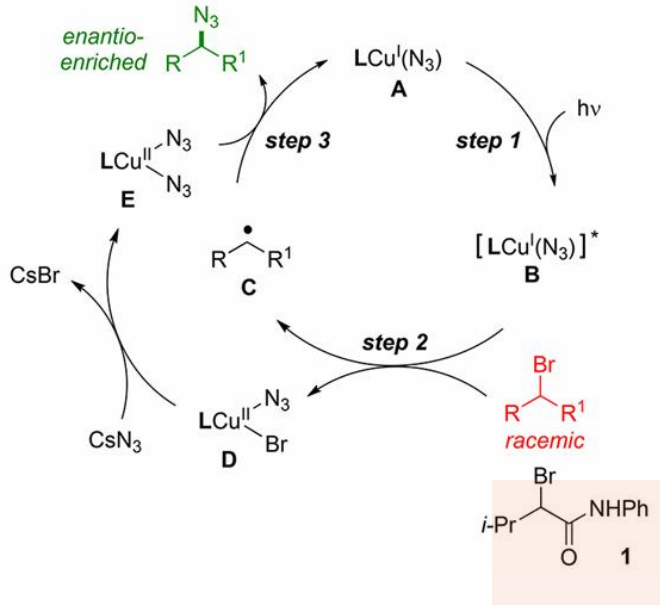
Wu, X., Xia, T., Bai, J. *et al., Nat. Chem*., **2025**



Summary -Limitations







limitations/common issues

▲Alkyl group differentiation capacity

->Catalyst and ligand development is needed. Hopefully differentiation between aliphatic substituents...

▲Electrophiles are limited to α-functionalized substrates

->Probably...

- Radical stabilization by conjugated substituents such as aryl or allyl groups, or EWGs is necessary for XAT
- Coordination of the carbonyl group to the catalyst is required for enantioselectivity

Carbonyl non-adjacent electrophiles?
-> Example: next page

Summary -limitations

HAT instead of XAT

Conventionaly: C-H was activated by organometalics

->Radical rebound occurring prior to diffusion

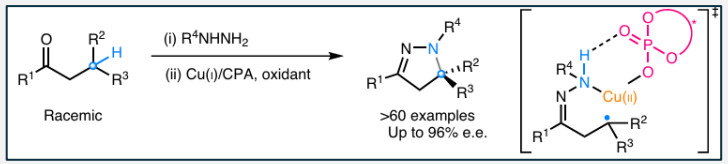
->Steric retention was problematic.

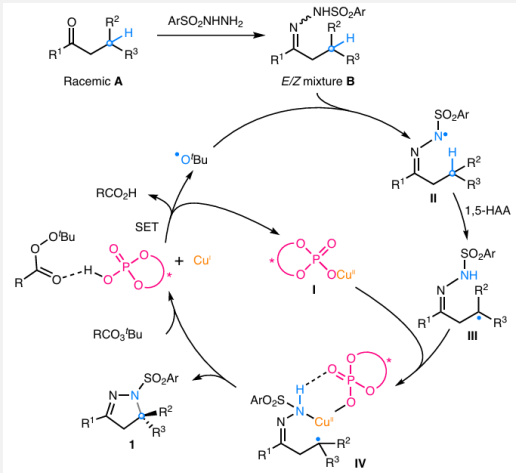
➡★Internal HAT

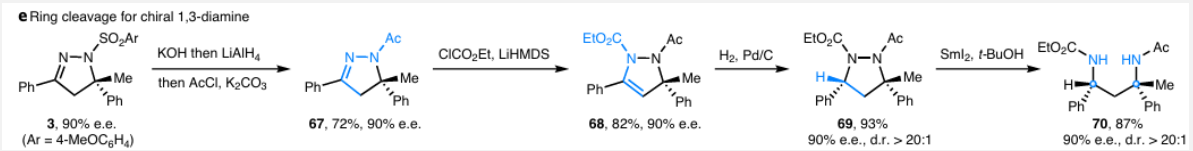
β C(sp₃)-H-functionalization (2020)

★Carbonyl non-adjacent electrophiles

▲Multistep ring cleavage



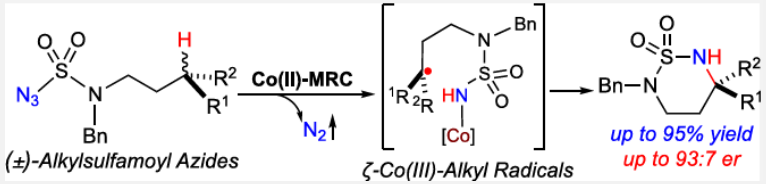


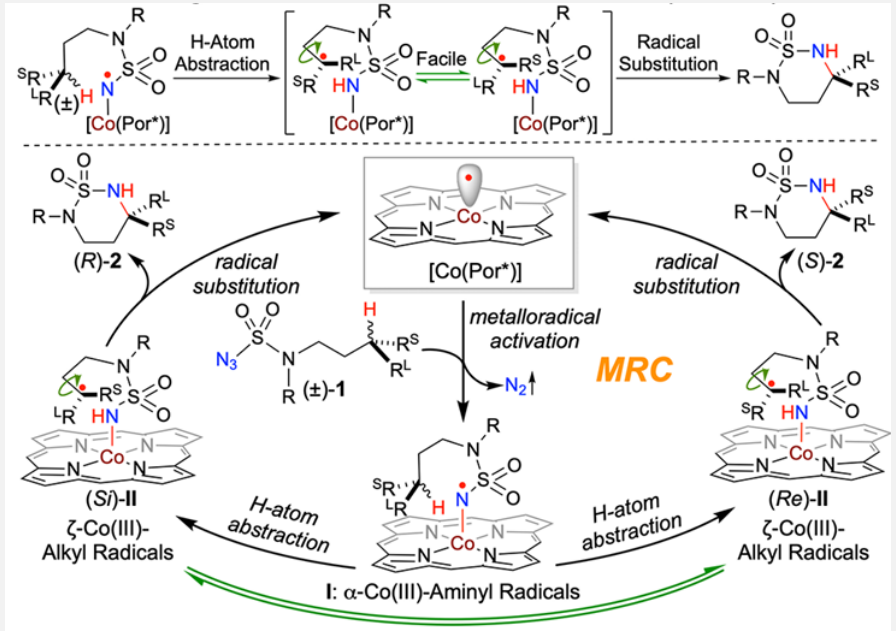


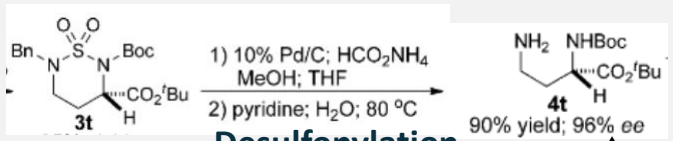
Ring cleavage

Liu, X.Y. *et al. Nat Catal.* **2020**, *3*, 539–546

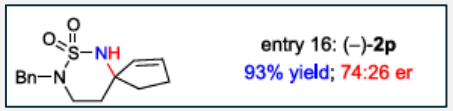
γ C(sp₃)-H-functionalization (2020)







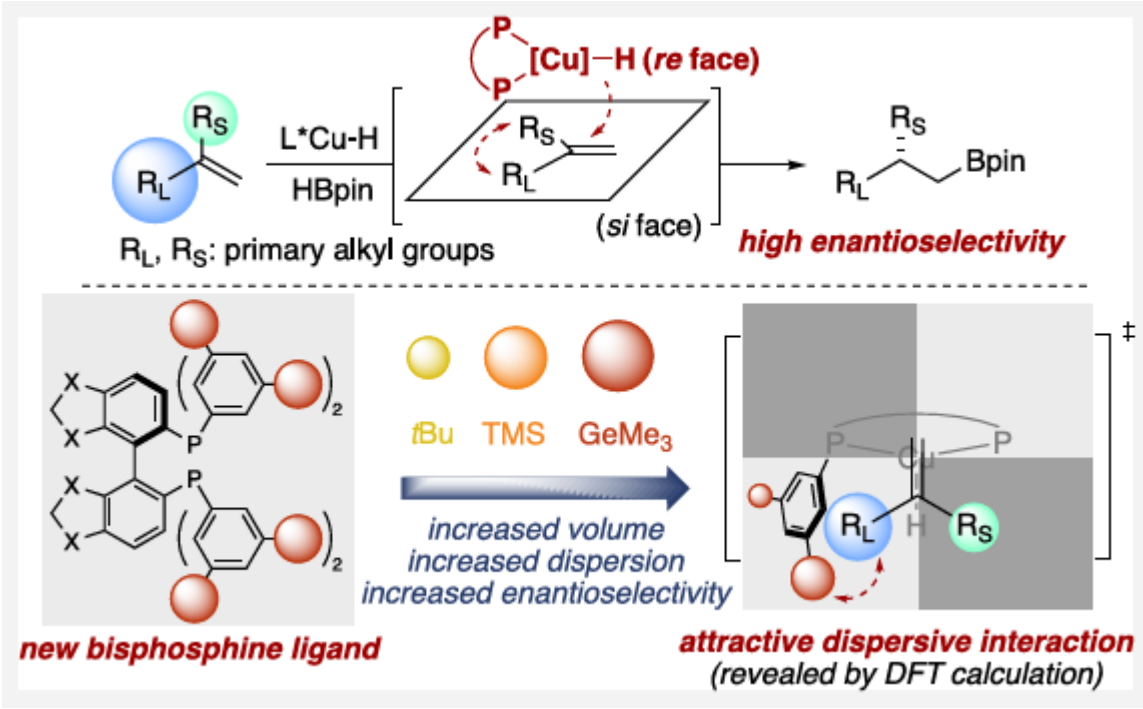
Desulfonylation

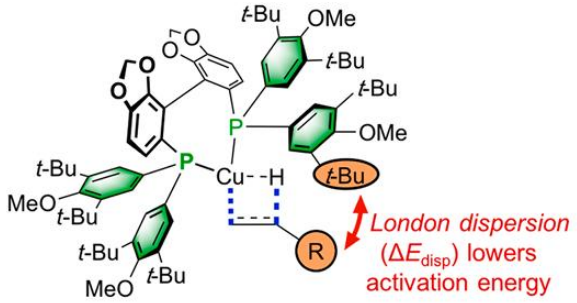


▲only 1 example
other 15 were carbonyl adjacent.

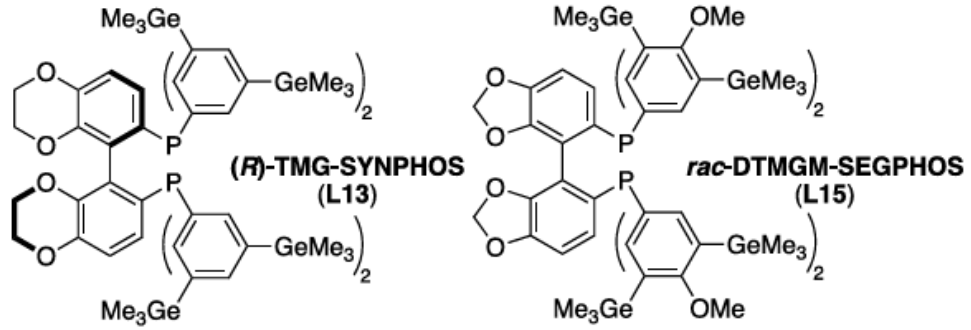
Zhang, X.P. *et al. J. Am. Chem. Soc.* **2020**, *142*, 20902−20911

Summary –insightful study





C Structures of the new ligands reported in this study



Differentiation between two substituents

・Dispersion interactions between the bulky alkyl substituent and the substrate accelerate the reaction.

-> Substitution with Si or Ge strengthened interaction.

・Two primary alkyl groups

Liu, P., Hartwig, J.F. *et al. J.Am.Chem.Soc.* **2020**,*142*,18213−18222

Appendix

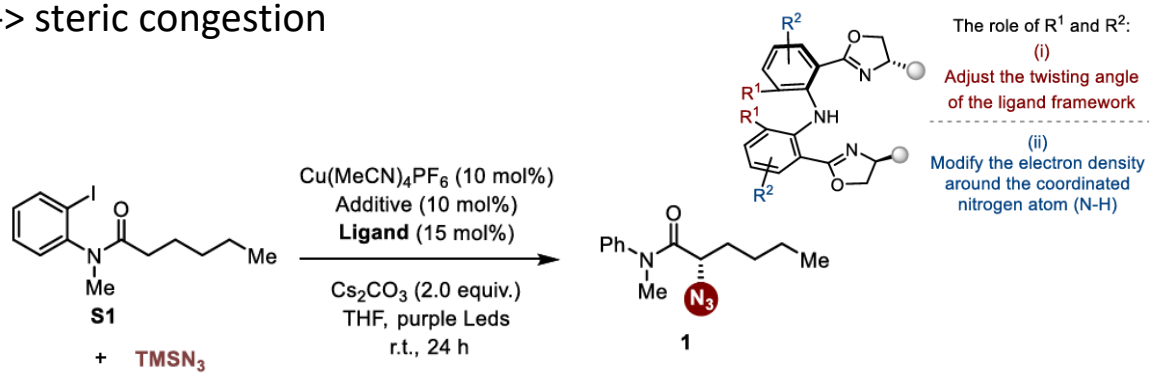
Recent studies for enantioselective azidation

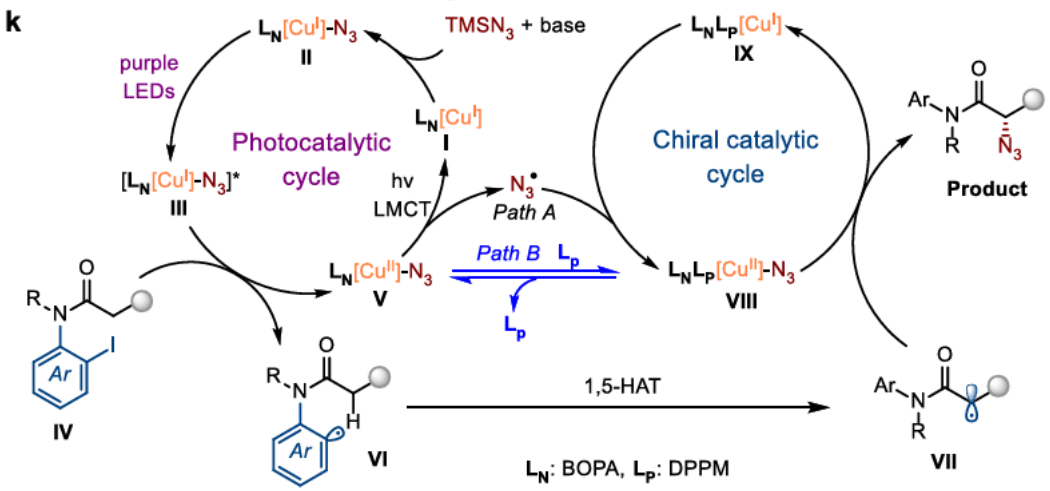
Enantiocontrol by binary-mixed ligand catalytic system (2025)

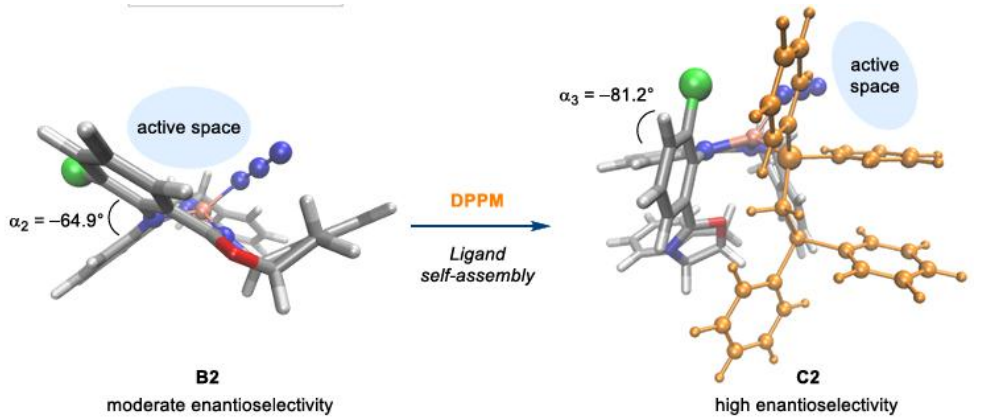
★Remote SH2 mechanism (outer)

▲compatible to only α-mono substituted amides

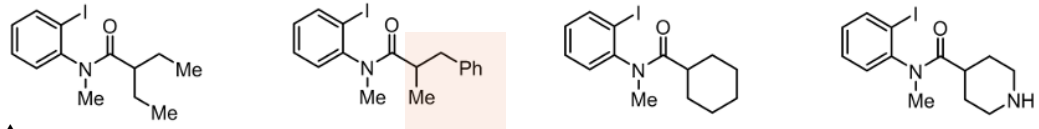
-> steric congestion







Unsuccessful substrates



▲Tertiary azidation not achieved due to steric hindrance

Qi. X., Zhang, G., Guo. R., *et al. J. Am. Chem. Soc.* **2025**, *147*, 40010–40023