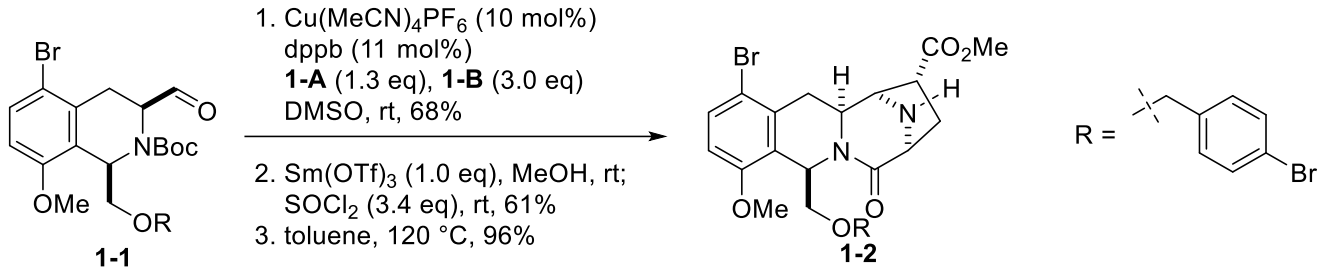
Problem Session (4)

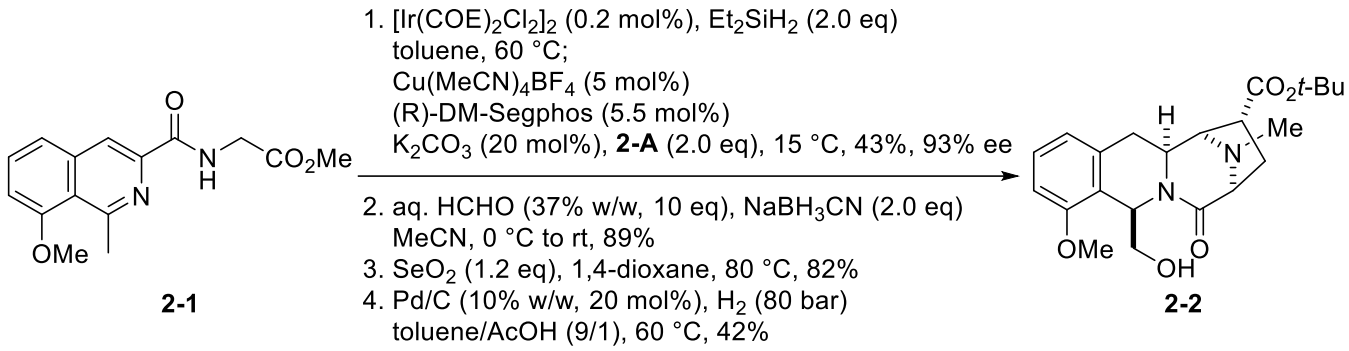
2023/6/17 Yosuke Nakata

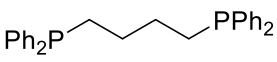
Please provide the reaction mechanisms and stereoselectivity.

1.

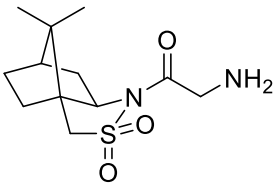


2.

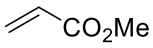




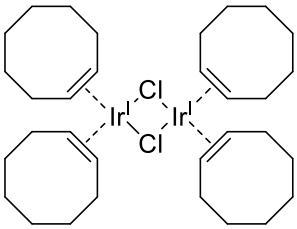
dppb



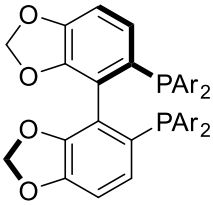
1-A



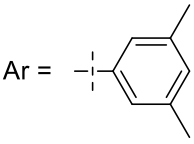
1-B

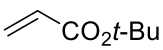


[Ir(COE)2Cl]2



(R)-DM-Segphos





2-A

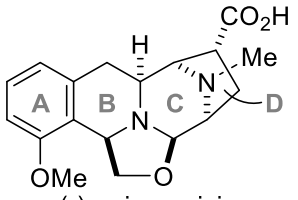
Problem Session (4) -Answer-

2023/6/17 Yosuke Nakata

Topic: Total synthesis of (-)-quinocarcin

Introduction

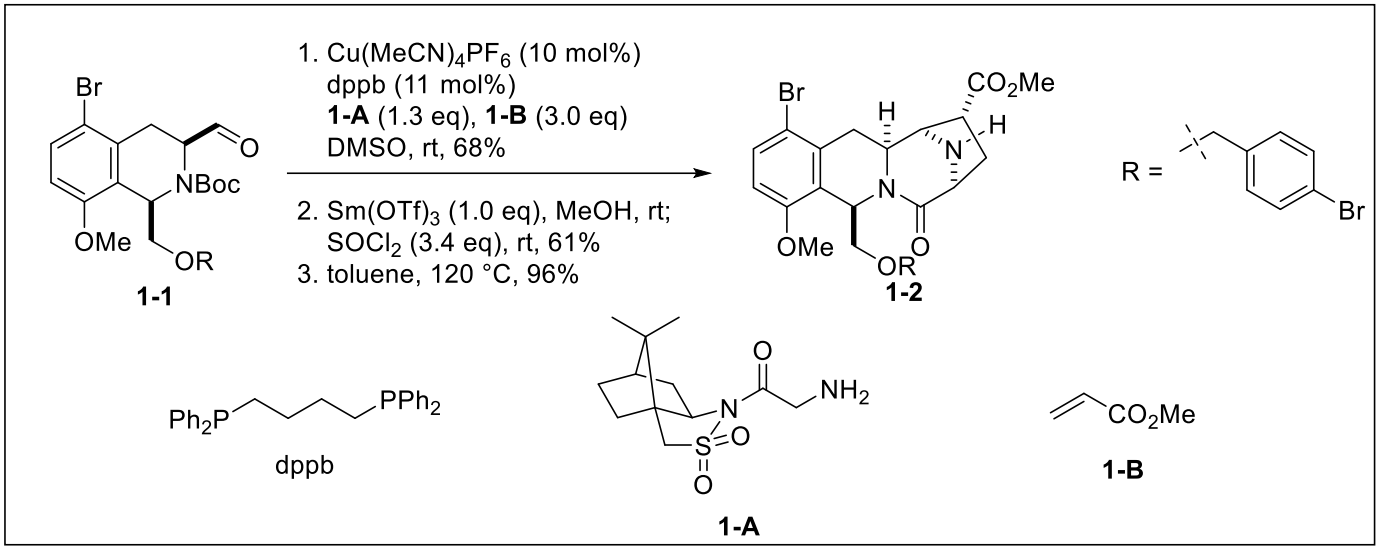
Isolation: *Streptomycse melanovinaceus*[1]
Structure features:
tetrahydroisoquinoline (AB ring)
bridged pyrrolidine-piiperazine (CD ring)
Bioactivity: antitumor activity[2]
Total synthesis:

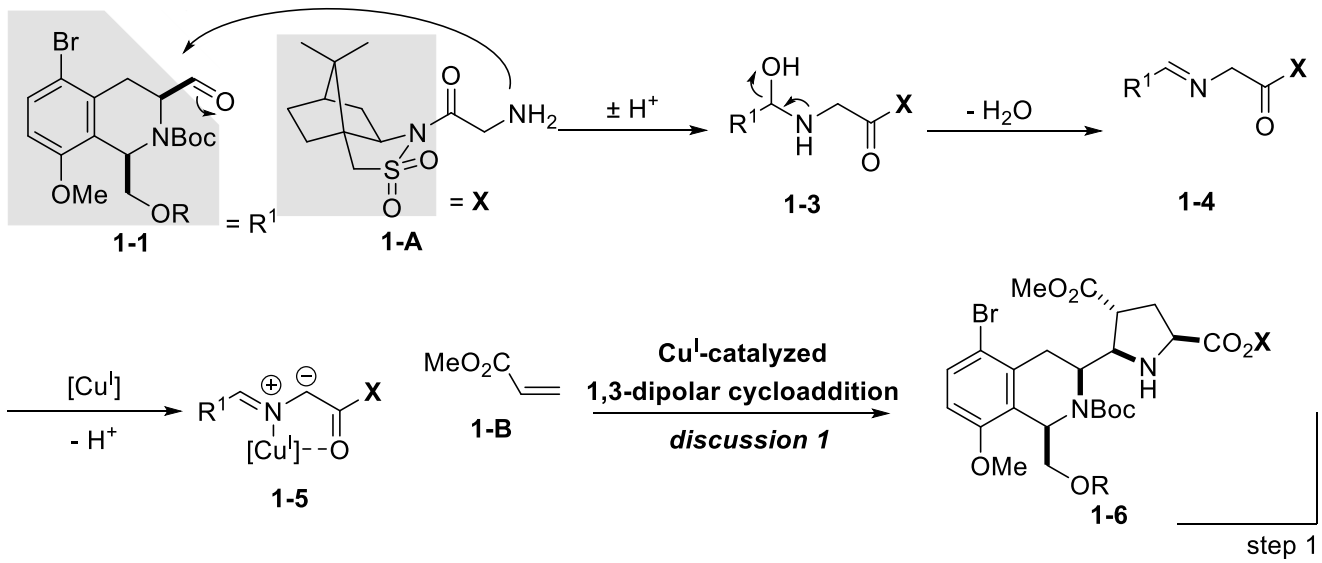


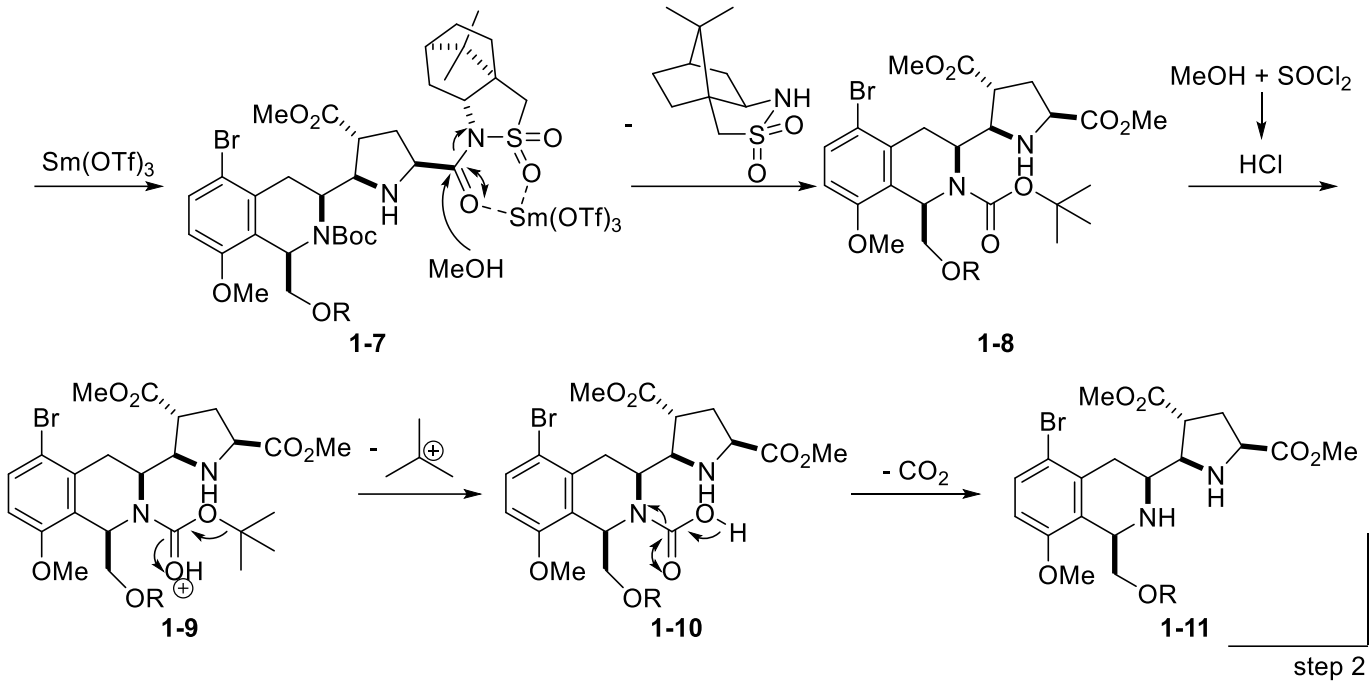
(-)-quinocaricin

Fukuyama (reacemic, *J. Am. Chem. Soc.* **1988**, *110*, 5196-5198.),
Garner (assymmetric, *J. Am. Chem. Soc.* **1992**, *114*, 2767-2768.; *J. Am. Chem. Soc.* **1993**, *115*, 10742-10753.)
Terashima (assymmetric, *Tetrahedron* **1994**, *50*, 6239–6258.; *Pure Appl. Chem.* **1996**, *68*, 703–706.)
Meyers (assymmetric, *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797.)
Zhu (assymmetric, *J. Am. Chem. Soc.* **2008**, *130*, 7148–7152.)
Stoltz (assymmetric, *J. Am. Chem. Soc.* **2008**, *130*, 17270–17271.)
Ohno (assymmetric, *Angew. Chem. Int. Ed.* **2012**, *51*, 9169–9172.; *Chem. Eur. J.* **2013**, *19*, 8875–8883.)
Shi (assymmetric, formal synthesis, *Org. Lett.* **2019**, *21*, 4609–4613.) ⇒ problem 1
Yang (assymmetric, *Org. Lett.* **2021**, *23*, 7972–7975)
Huang (assymmetric, *Angew. Chem. Int. Ed.* **2023**, in press) ⇒ problem 2

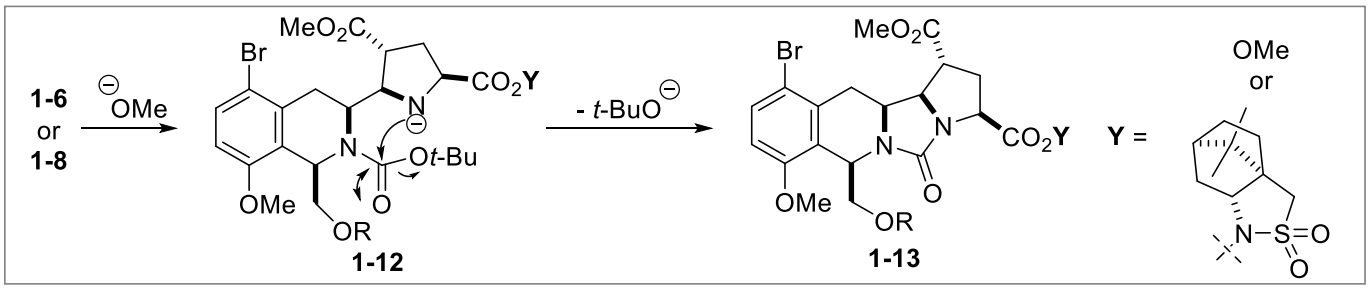
Problem 1: formal synthesis of (-)-quinocarcin by Shi

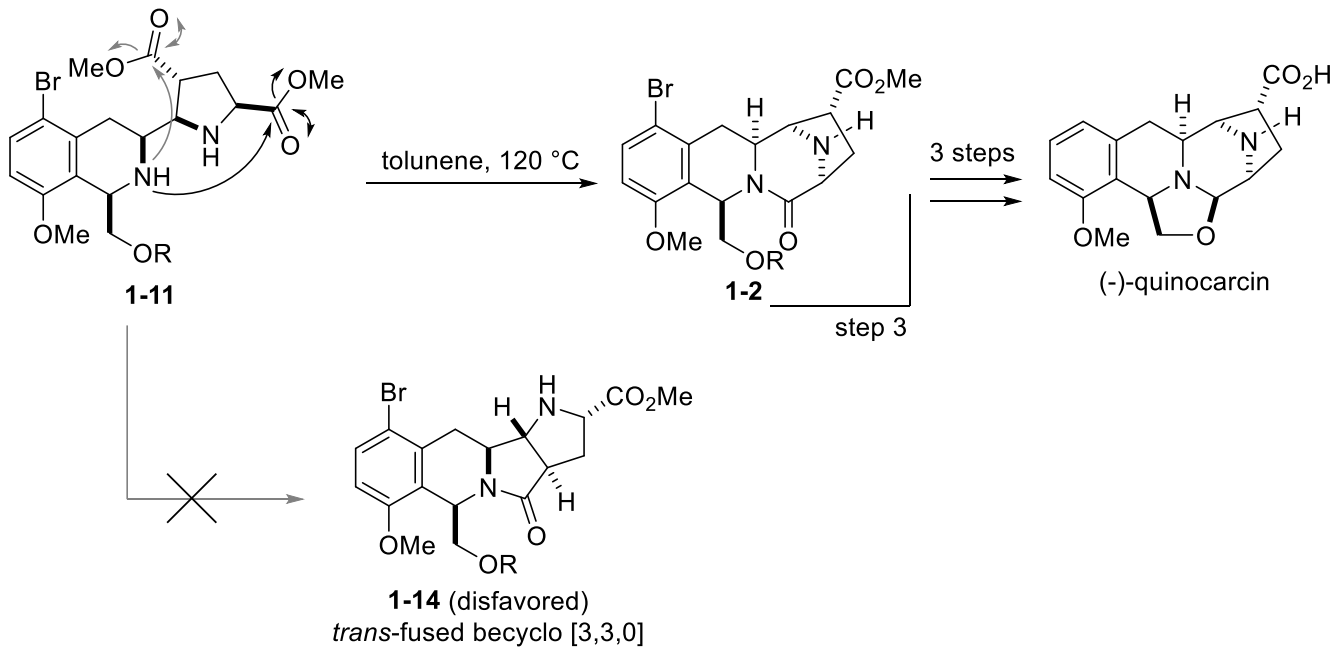






$Sm(OTf)_3$ was probably used for selective activation C=O of camphorsultam amide under neutral condition in order to prevent nucleophilic acyl substitution of N-Boc group by the pyrrolidine to give a bicyclic urea (shown below). It was reported that methanolysis of camphorsultam amide of similar compounds under basic conditions ($MeOH/Mg(OMe)_2$) was accompanied by the generation of a bicyclic urea.[3]





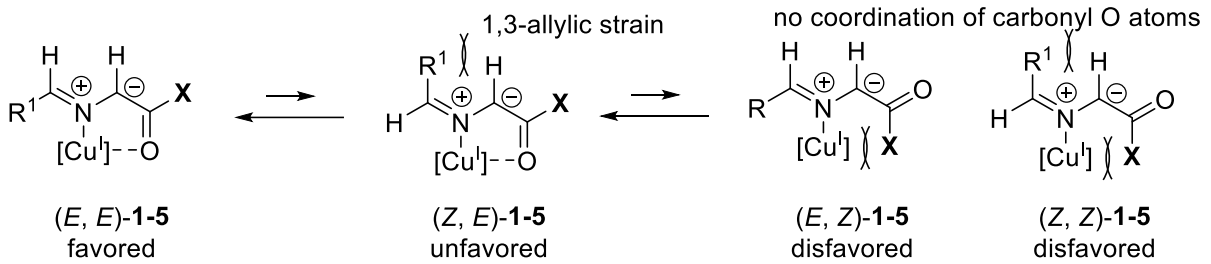
Discussion 1. Cu^{I}-catalyzed asymmetric 1,3-dipolar cycloaddition using chiral camphorsultam amide

1-1. Regioselectivity

1,3-dipolar cycloaddition of azomethine ylide is generally classified as Type I (HOMO-controlled, normal electron demand).

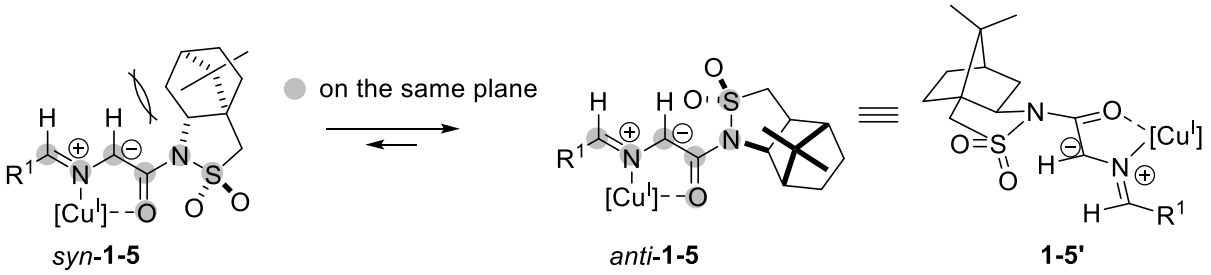
1-2. Stereoselectivity

1-2-1. Geometric isomerism of metalated azomethine ylide

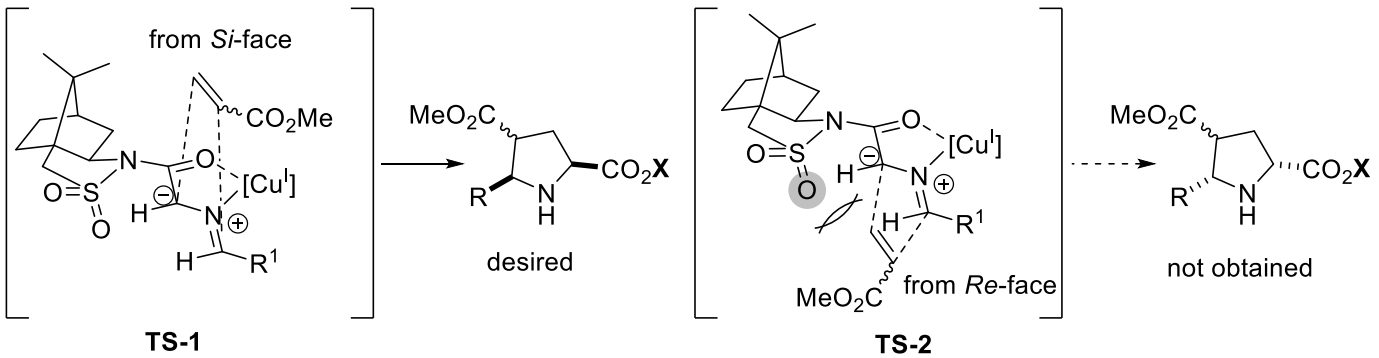


(*E*, *E*)-azomethine ylide is most favored, resulting in the generation of 2,5-cis substituted pyrrolidine.

1-2-2. Direction of approaching of dipolarophile **1-B**

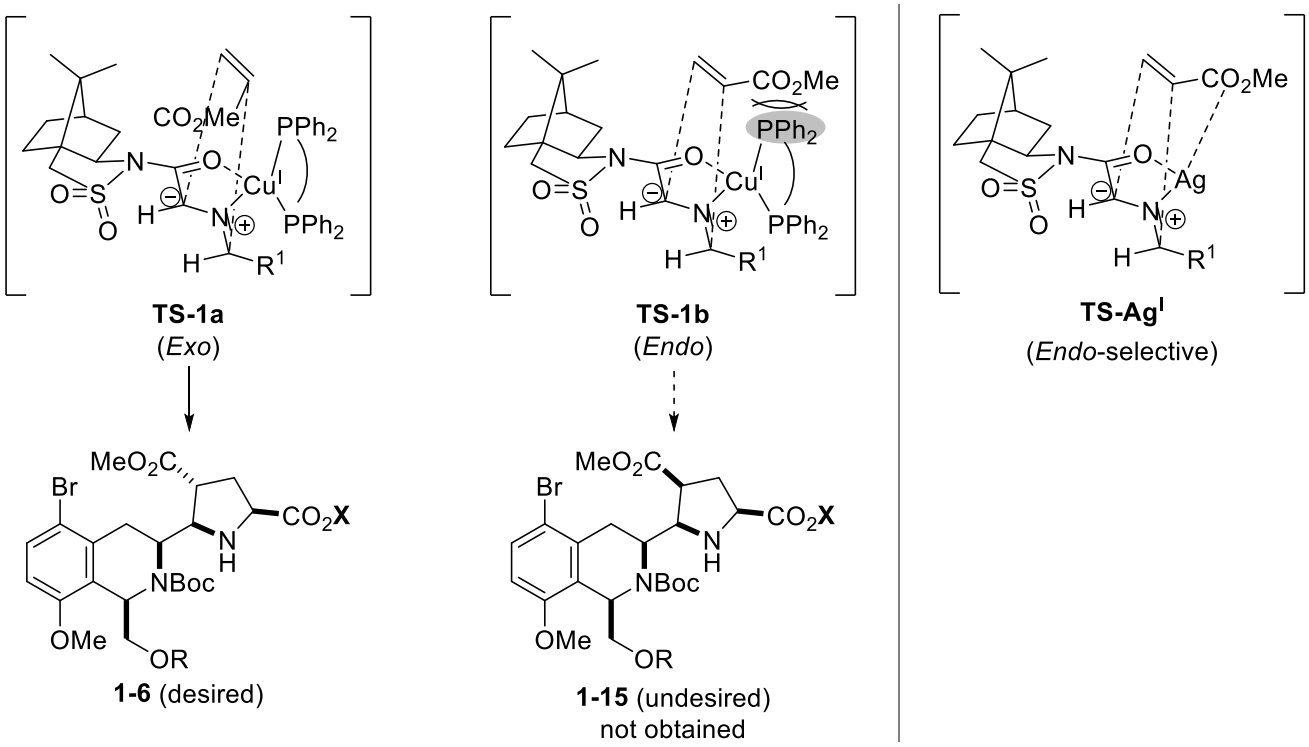


C=O bond of amide and N-S bond of camphorsultam directs *anti* to minimize the steric repulsion.



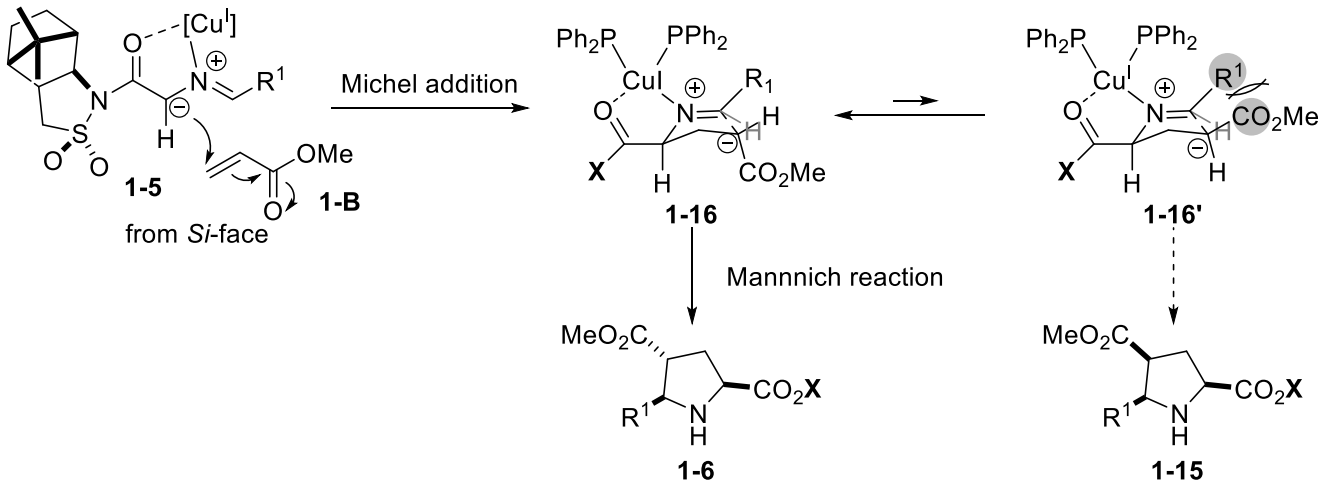
Dipolarophile **1-B** approaches to the azomethine ylide from *Si*-face (opposite to the pro-S sulfomimide oxygene).

1-2-3. *Exo* selectivity



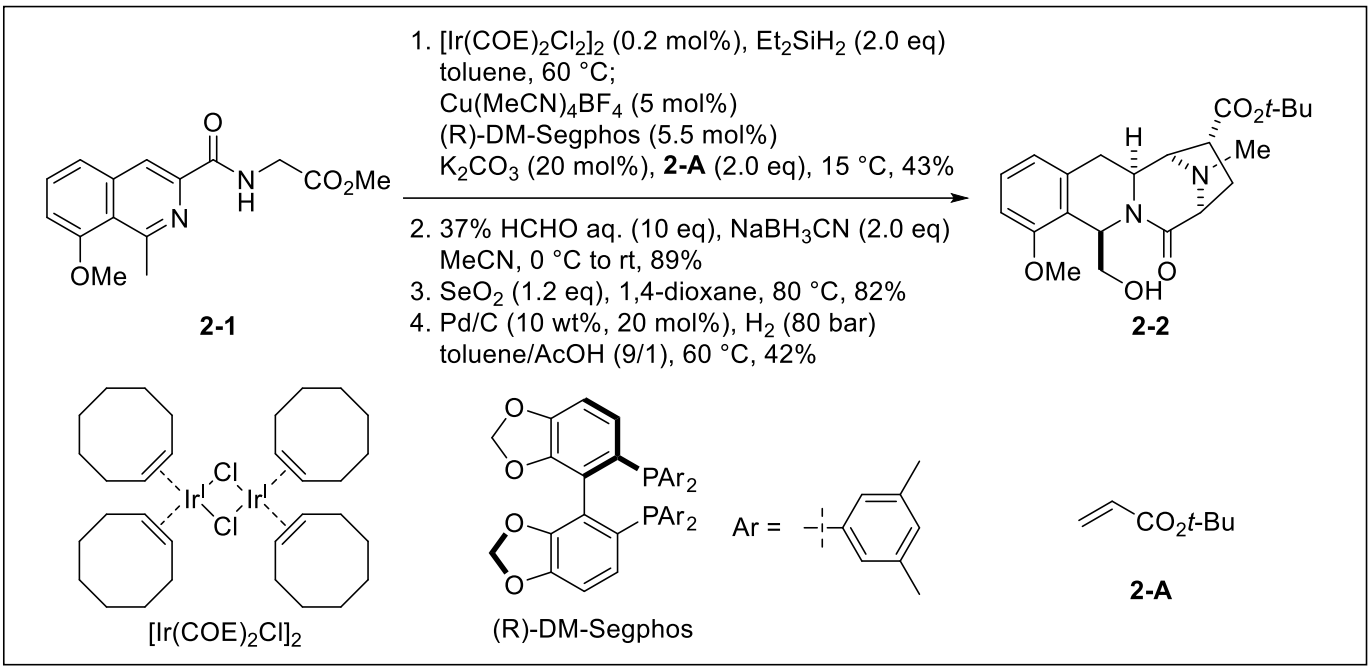
Cu^I-bispohsphine catalyst system would favor the *exo*-TS to minimize the steric repulsion between phosphine ligand and electron-withdrawing group. (In contrast, Ag^I catalyst system would favor the *endo*-TS by coordination with carbonyl group.[4])

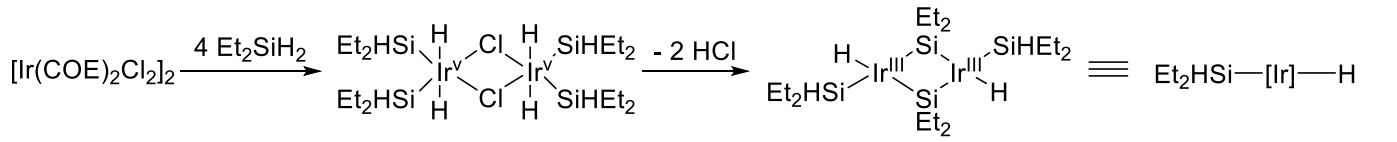
1-4. Another pathway for **1-6** (stepwise)

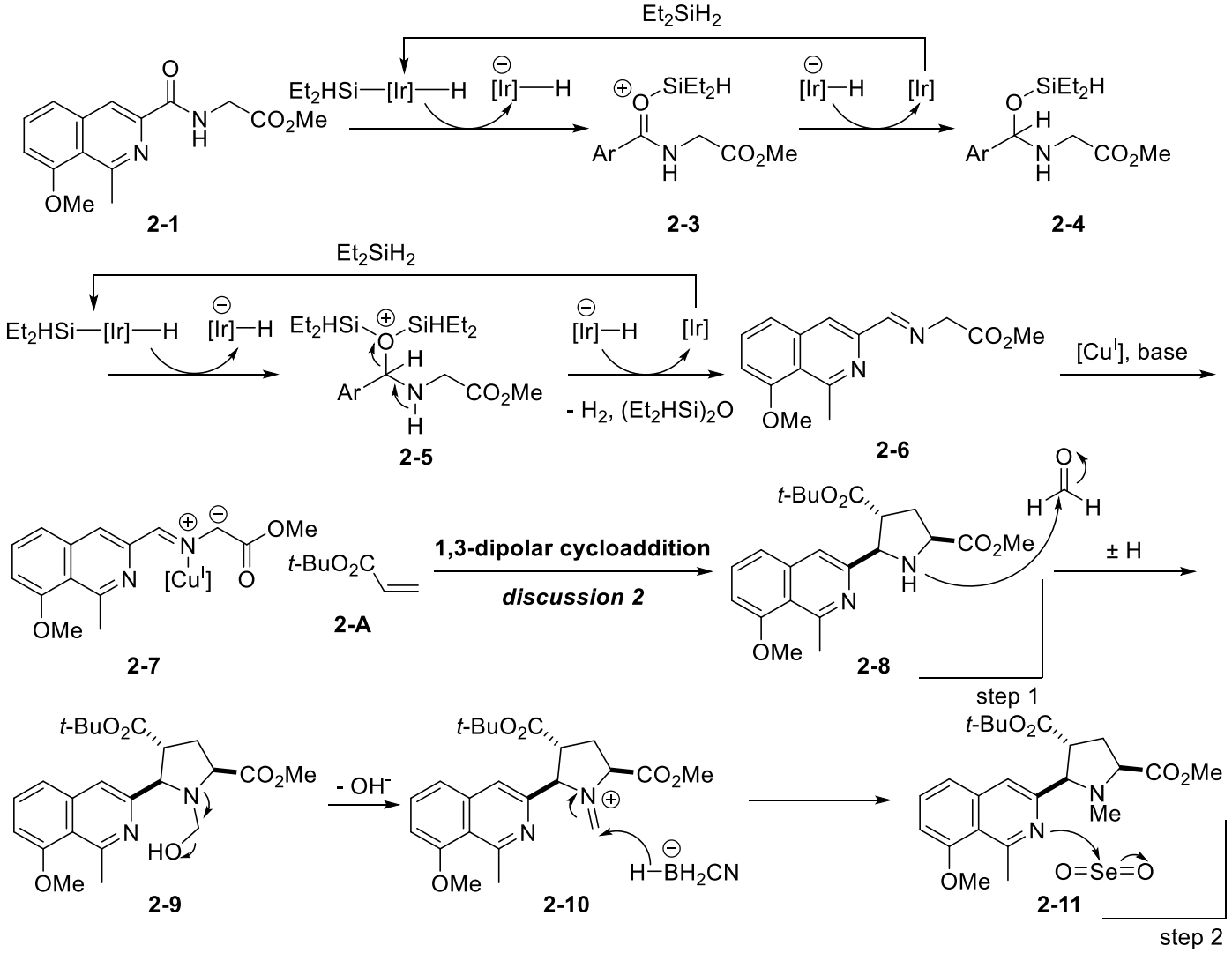


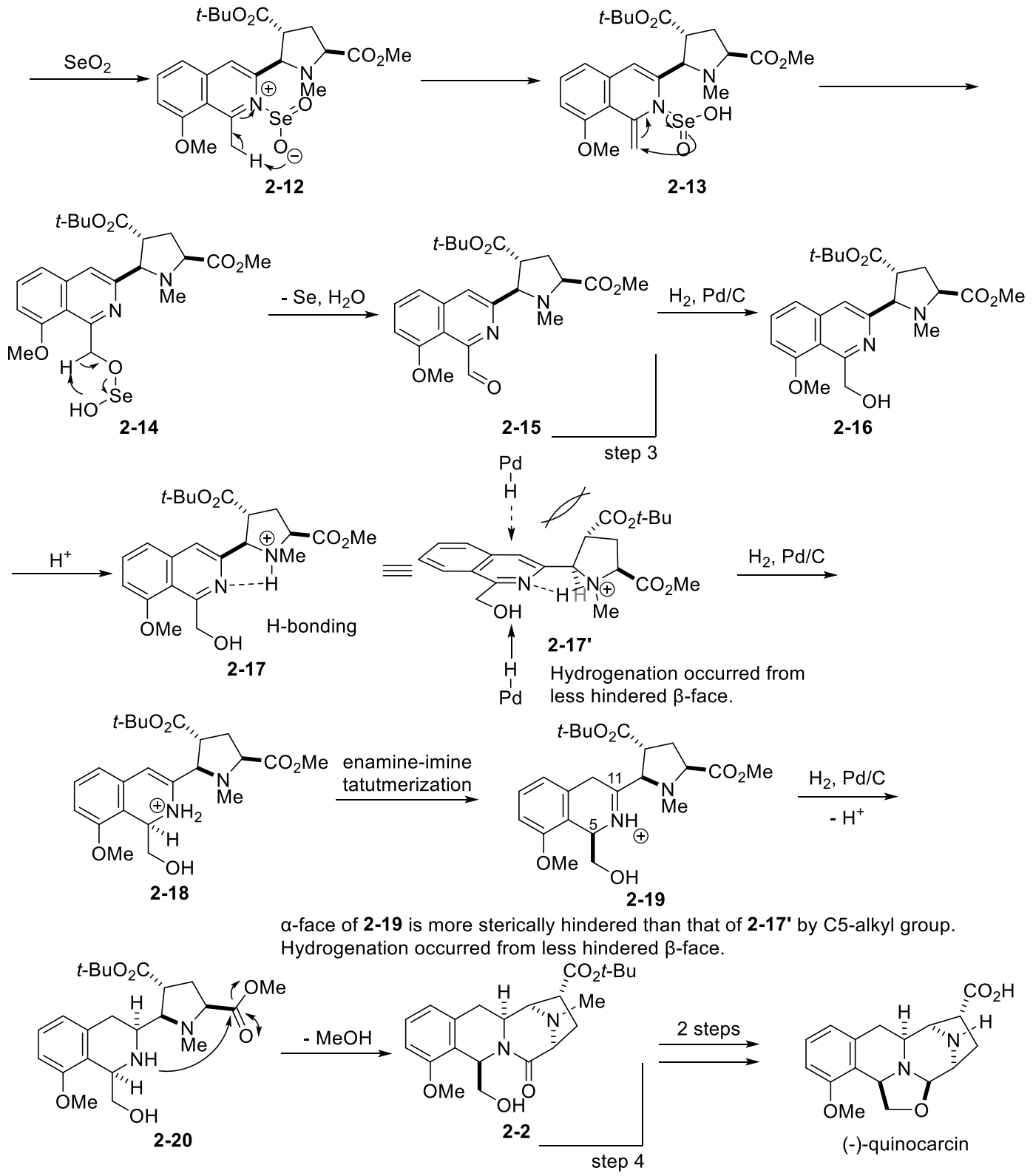
Stepwise pathway via zwitterionic intermediate **1-16** (or **1-16'**) is also possible. 4,5-trans product **1-6** results from the minimization of a steric repulsion between CO_2Me and R^1.

Problem 2: total synthesis of (-)-quinocarcin by Huang





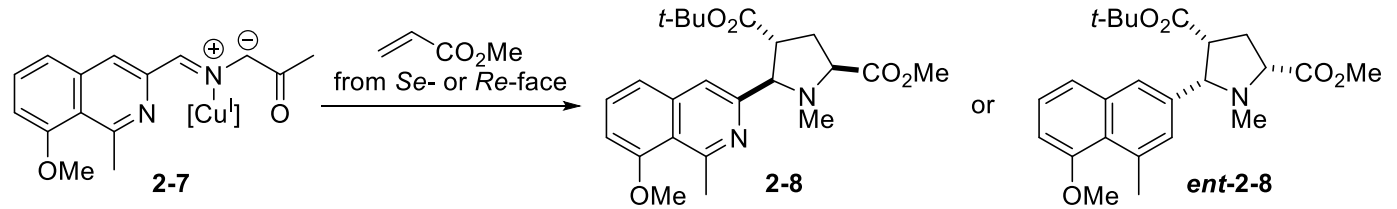


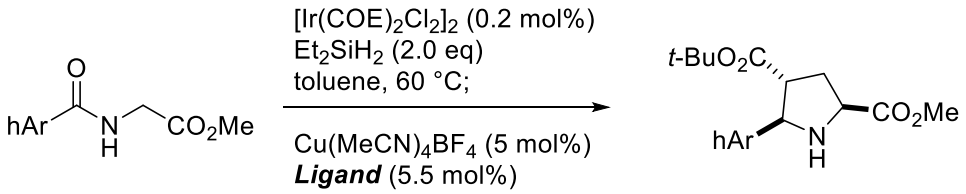


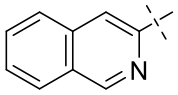
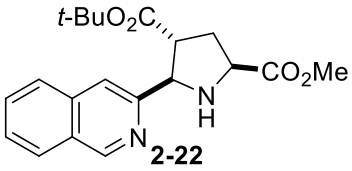
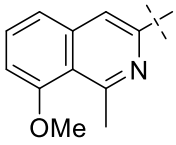
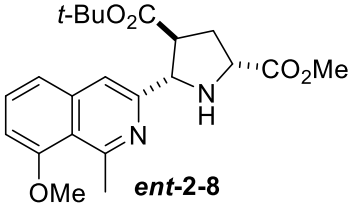
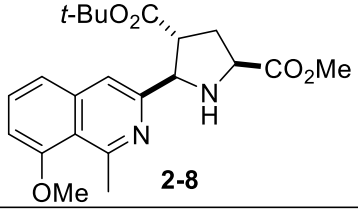
Discussion 2. Cu^{I}-catalyzed asymmetric 1,3-dipolar cycloaddition using chiral ligand

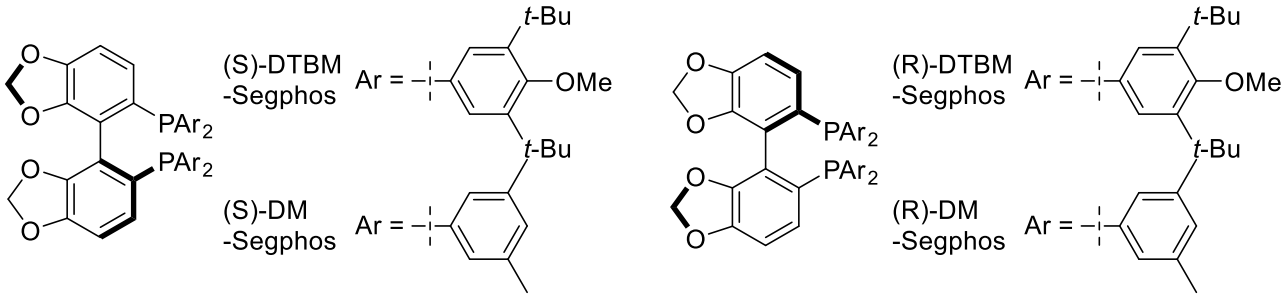
2-1. Reversed enantioselectivity of 1,3-dipolar cycloaddition

Stereoselectivity other than that derived from the direction of dipolarophile approaching can be provided in the same manner as described in problem 1. The enantioselectivity shown below is discussed in this section.



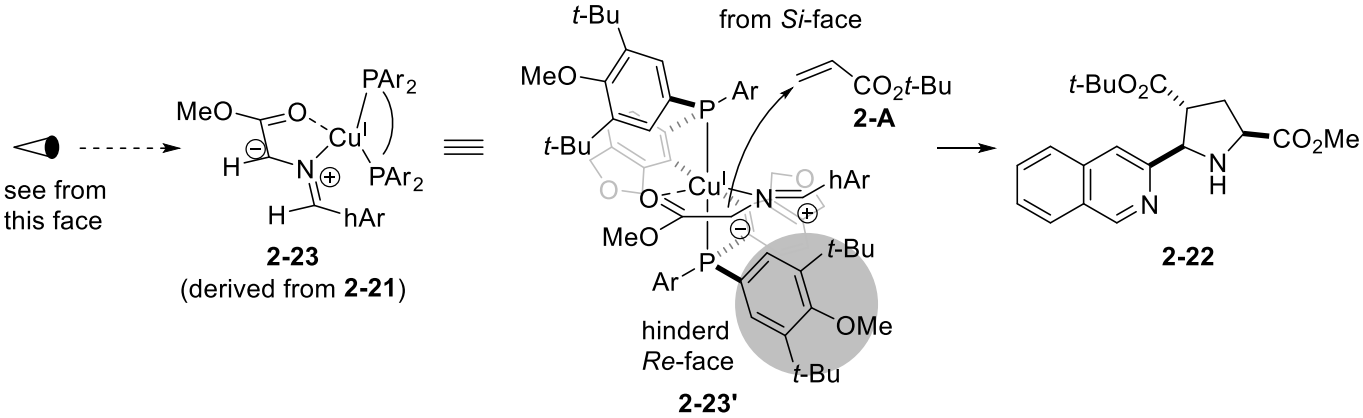


hAr	*Ligand*	*base*	major product	yield
 **2-21**	(S)-DTBM-Segphos	*i*-Pr_2NEt (2.0 eq)	 **2-22**	70%, 92% ee
 **2-1**	(S)-DTBM-Segphos	*i*-Pr_2NEt (2.0 eq)	 ***ent*-2-8**	35%, 65% ee
	(S)-DM-Segphos	*i*-Pr_2NEt (2.0 eq) K_2CO_3 (0.2 eq)		32%, 76% ee 45%, 94% ee
	(R)-DM-Segphos	K_2CO_3 (0.2 eq)	 **2-8**	43%, 93% ee



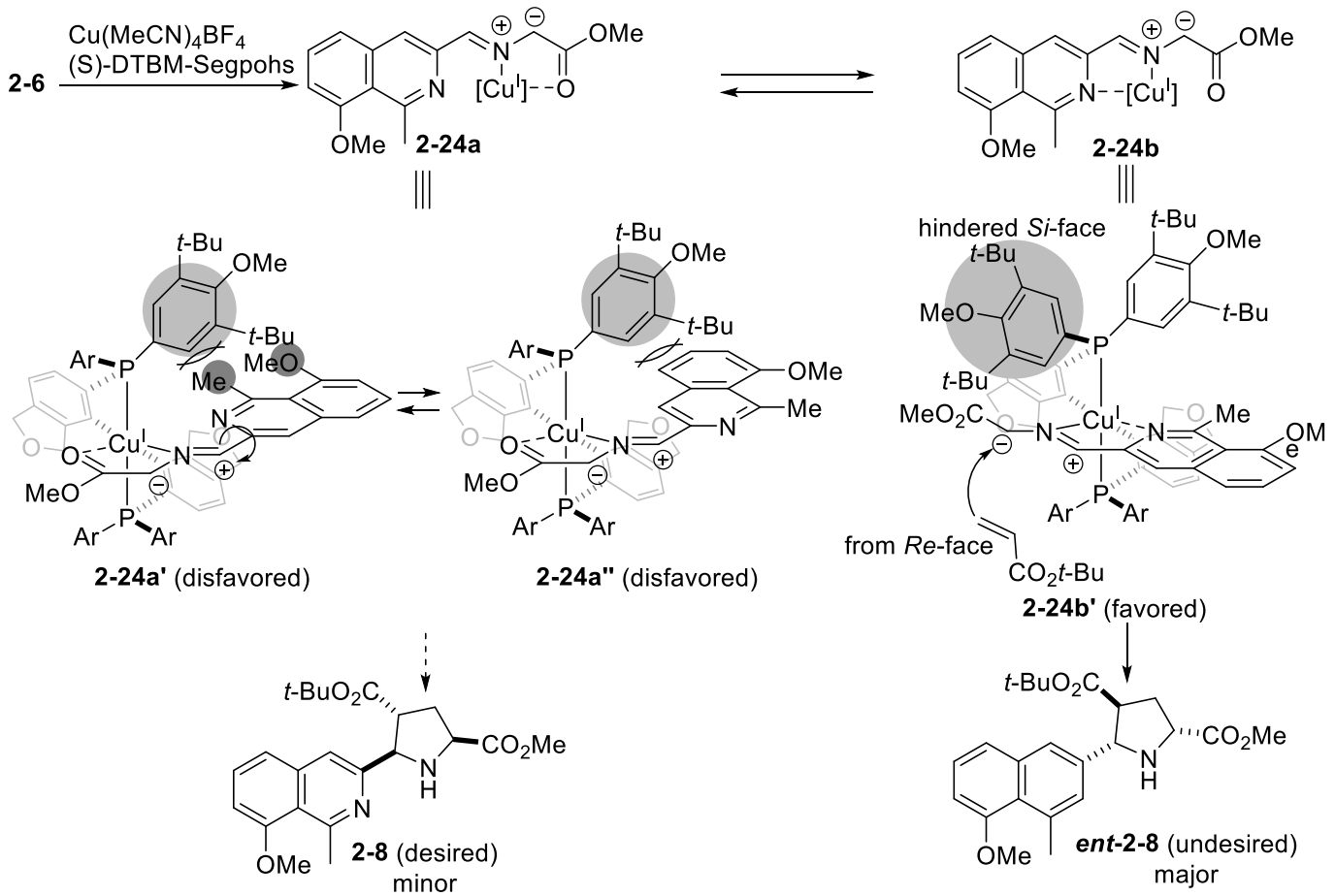
Despite the similarity of the structures of **2-22** and **2-23**, 1,3-cycloaddition products with opposite absolute configurations were generated. The reversal of enantioselectivity could be explained by the difference of the coordination manner of the azomethine ylides to the Cu^I (section 2-2, 2-3).

2-2. Transition state for **2-23**



Tetrahedral complex is formed to minimize the repulsion between the chelating components (azomethine ylide and bisphosphine ligand). Enantioselectivity was addressed to the blockage of *Re*-face by the chiral phosphine ligand.[5]

2-3. Rationale for the generation of ***ent*-2-8** using (S)-DTBM-Segphos (my proposal)

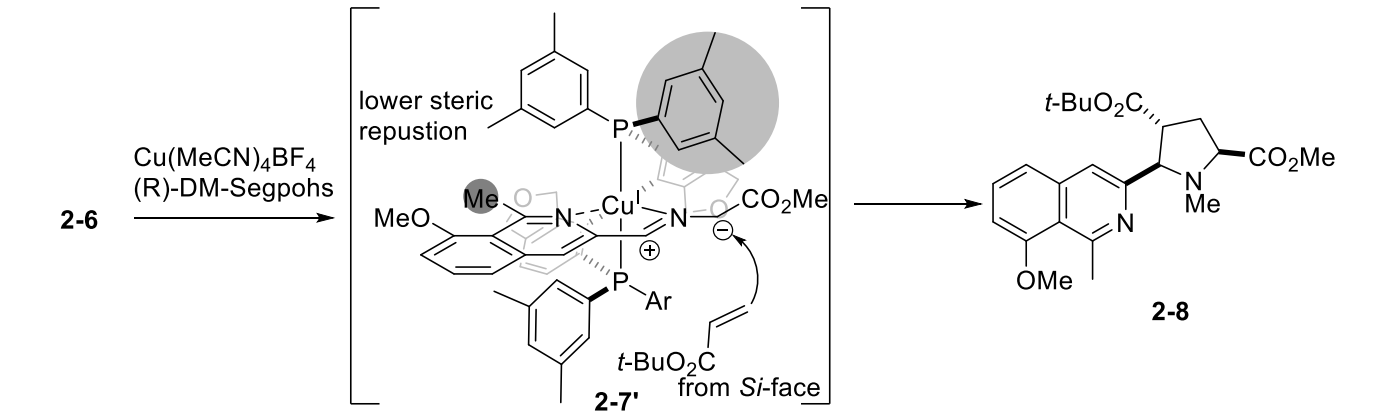


The difference of favored coordination mode of the azomethine ylide derived from **2-22** and **2-1** can be explained by comparing the effect of coordinating affinity and that of steric repulsion.

2-21: The effect of coordinating affinity (carbonyl O > isoquinoline N) is major. → **2-23** (coordination by carbonyl O)

2-1: The effect of steric repulsion (bulky groups at peri- posions) is major. → **2-24b** (coordination by isoquinoline N)

2-3. 1,3-dipolar cycloaddition for **2-8** using (R)-DM-Segphos



Less bulky phosphine ligand probably enhanced the binding affinity among the catalyst and azomethine ylide, resulting in increased the yield and stereoselectivity.

References

1) Tomita, T.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463–467.

2) Tomita, T.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 468–470.

3) Garner, P.; Kaniskan, H. U.; Keyari, C. M.; Weerasinghe, L. *J. Org. Chem.* **2011**, *76*, 5283–5294.

4) Garner, P.; Kaniskan, H. U.; Hu, J.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 3647–3650.

5) Caleffi, G. S.; Larrañaga, O.; Ferrándiz-Saperas, M.; Costa, P. R. R.; Nájera, C.; de Cózar, A.; Cossío, F. P.; Sansano, J. M. *J. Org. Chem.* **2019**, *84*, 10593–10605.