



中国科学院大连化学物理研究所

DALIAN INSTITUTE OF CHEMICAL PHYSICS, CHINESE ACADEMY OF SCIENCES

Dynamic Kinetic Resolution of Allylic Azides

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Checker: Yu-Qing Bai

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Ott, A. A.; Goshey, C. S.; Topczewski, J. J. *J. Am. Chem. Soc.* **2017**, *139*, 7737

Liu, E.-C.; Topczewski, J. J. *J. Am. Chem. Soc.* **2021**, *143*, 5308

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3 Summary

CV of Prof. Joseph J. Topczewski



Background:

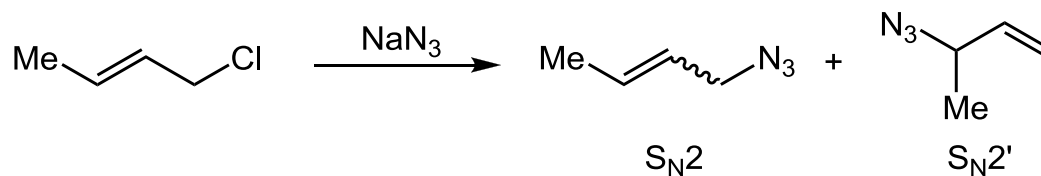
- ❑ **2007** B. S., University of Wisconsin at Parkside
- ❑ **2011** Ph. D., University of Iowa (with Prof. David Wiemer)
- ❑ **2011-2013** Postdoc., University of Iowa (with Prof. Hien M. Nguyen and Daniel M. Quinn)
- ❑ **2013-2015** Postdoc., University of Michigan (with Prof. Melanie Sanford)
- ❑ **2015-present** Assistant Professor, University of Minnesota Twin Cities

Research Interests:

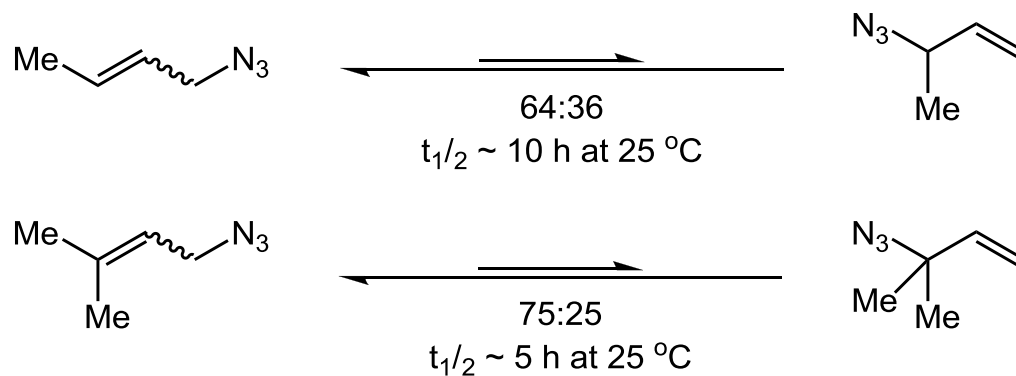
- ✓ Development of highly selective reactions, reactions that exploit dynamic systems, the selective differentiation of allylic azides.

Winstein Rearrangement

Azidation of Allylic Chloride

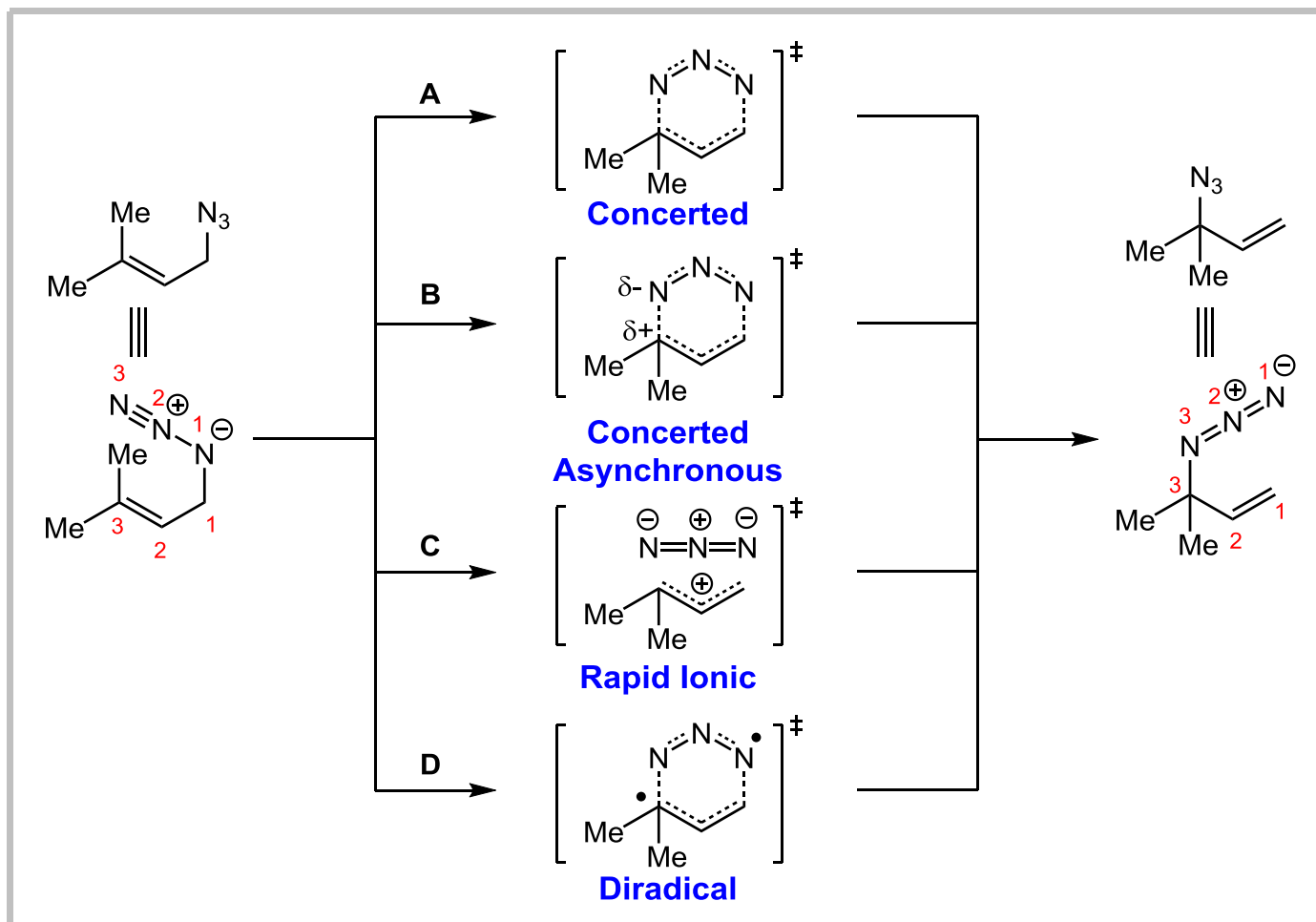


Winstein Rearrangement



Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956

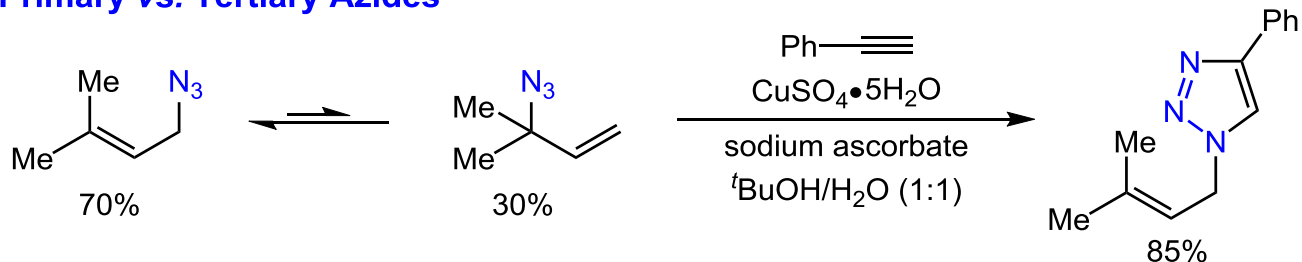
Possible Mechanism for Winstein Rearrangement



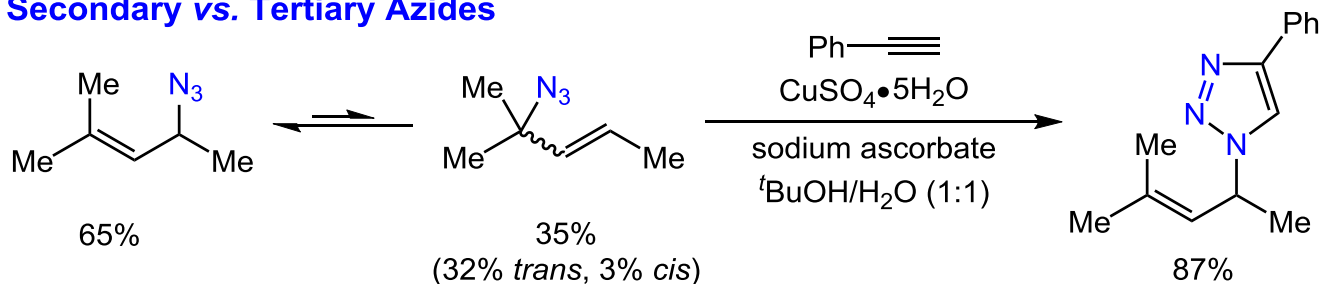
Carlson, A. S.; Topczewski, J. J. *Org. Biomol. Chem.* **2019**, *17*, 4406

Coupling with CuAAC

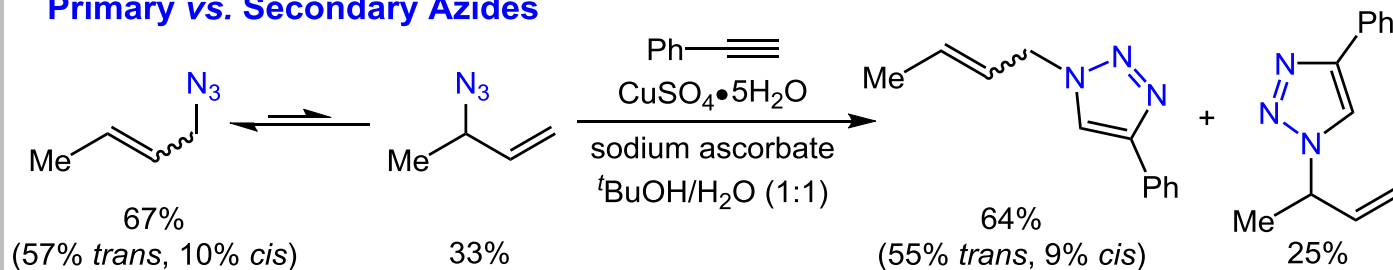
Primary vs. Tertiary Azides



Secondary vs. Tertiary Azides

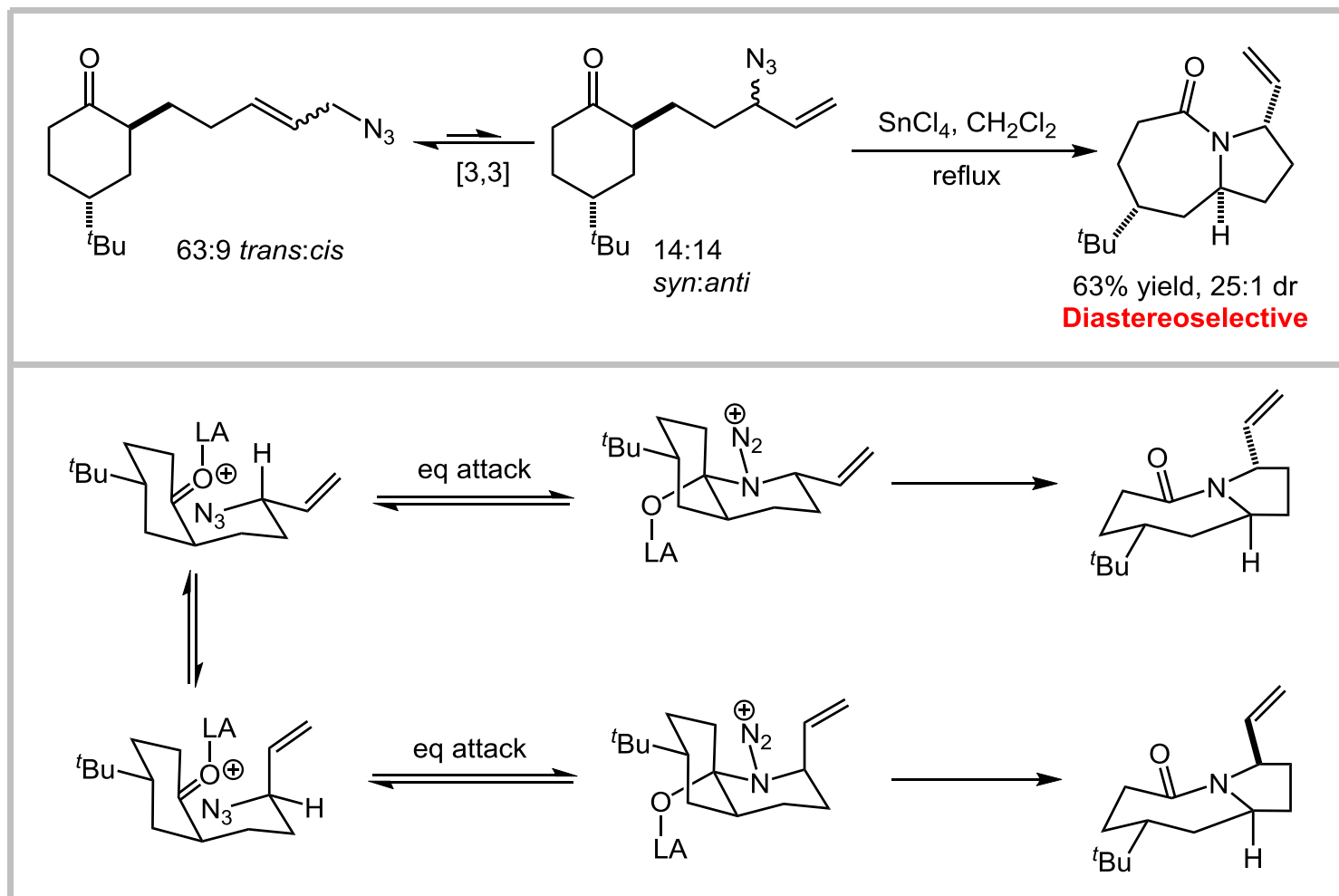


Primary vs. Secondary Azides



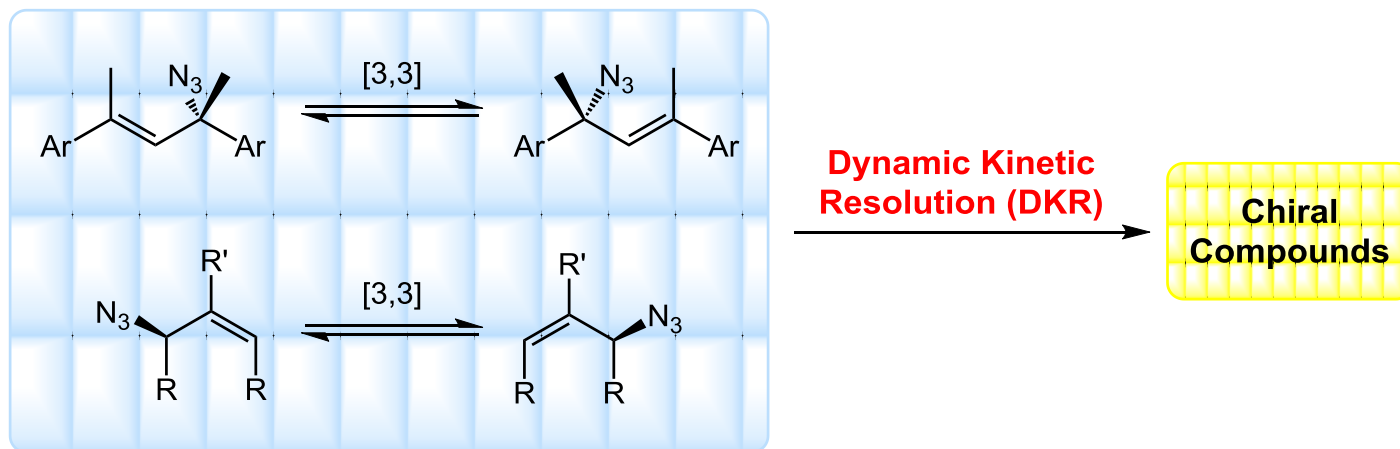
Feldman, A. K.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444

Coupling with Schmidt Reaction



Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. *J. Am. Chem. Soc.* **2012**, *134*, 6528

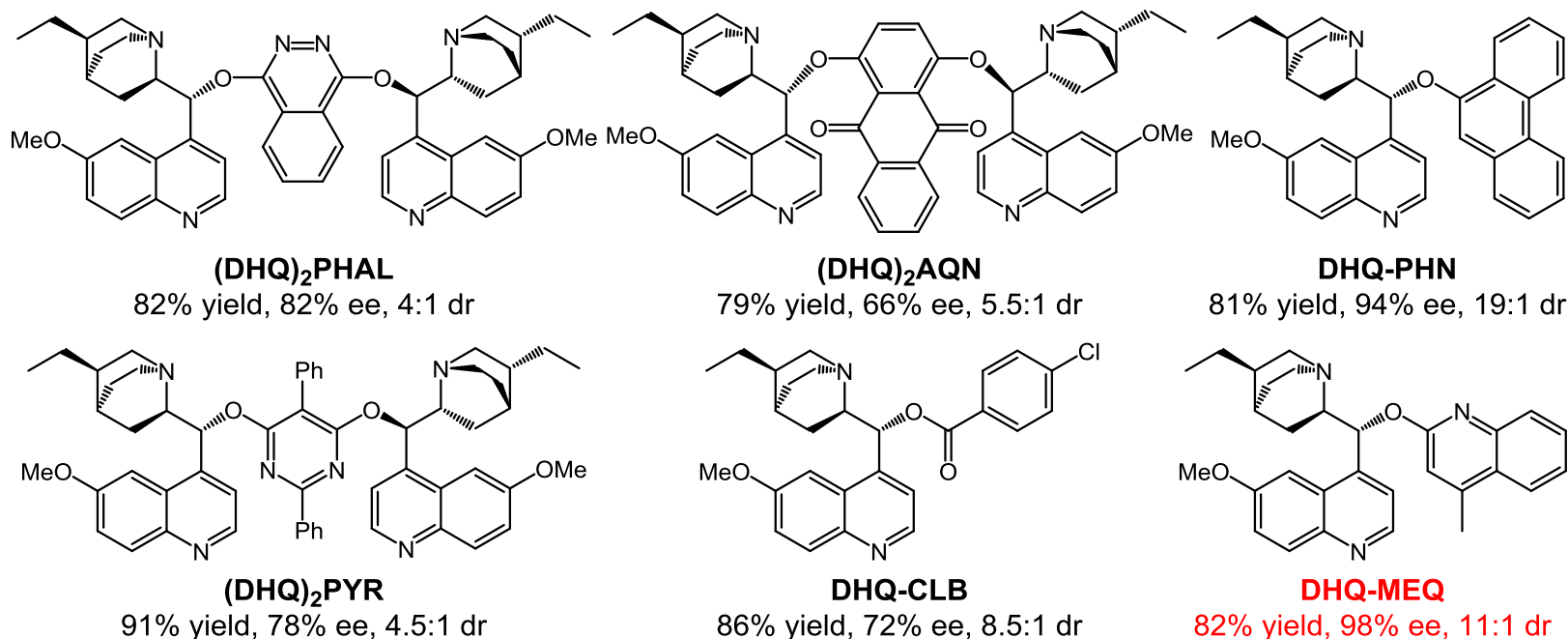
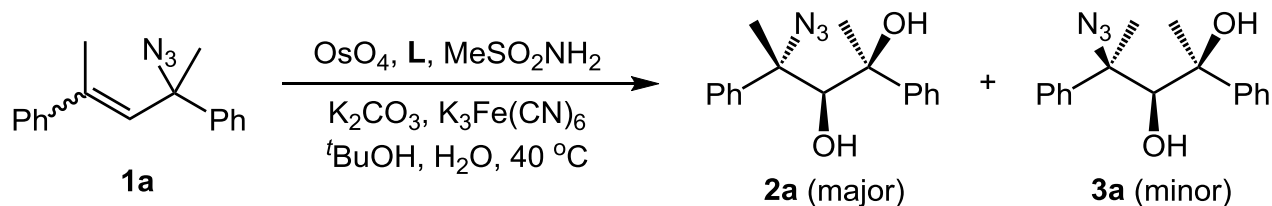
Dynamic Kinetic Resolution of Allylic Azides



Limitations of DKR:

- Requirement for a mechanistic pathway for racemization
- Common need for two separate catalysts
- Delicate balance of relative rates in the synchronized catalytic cycles

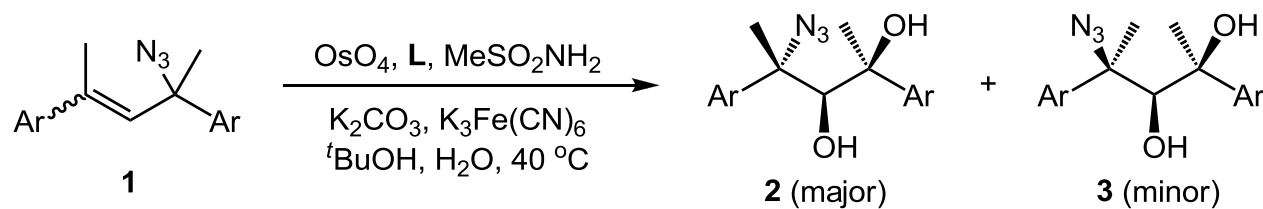
DKR of Allylic Azides via SAD



Reaction conditions: allylic azide **1a** (0.2 mmol), OsO_4 (5 mol%), **L** (10 mol%), K_2CO_3 (3 equiv.), MeSO_2NH_2 (3 equiv.), $\text{K}_3\text{Fe}(\text{CN})_6$ (3 equiv.), $t\text{BuOH}/\text{H}_2\text{O}$ (2.0/2.0 mL), under air, 48 h.

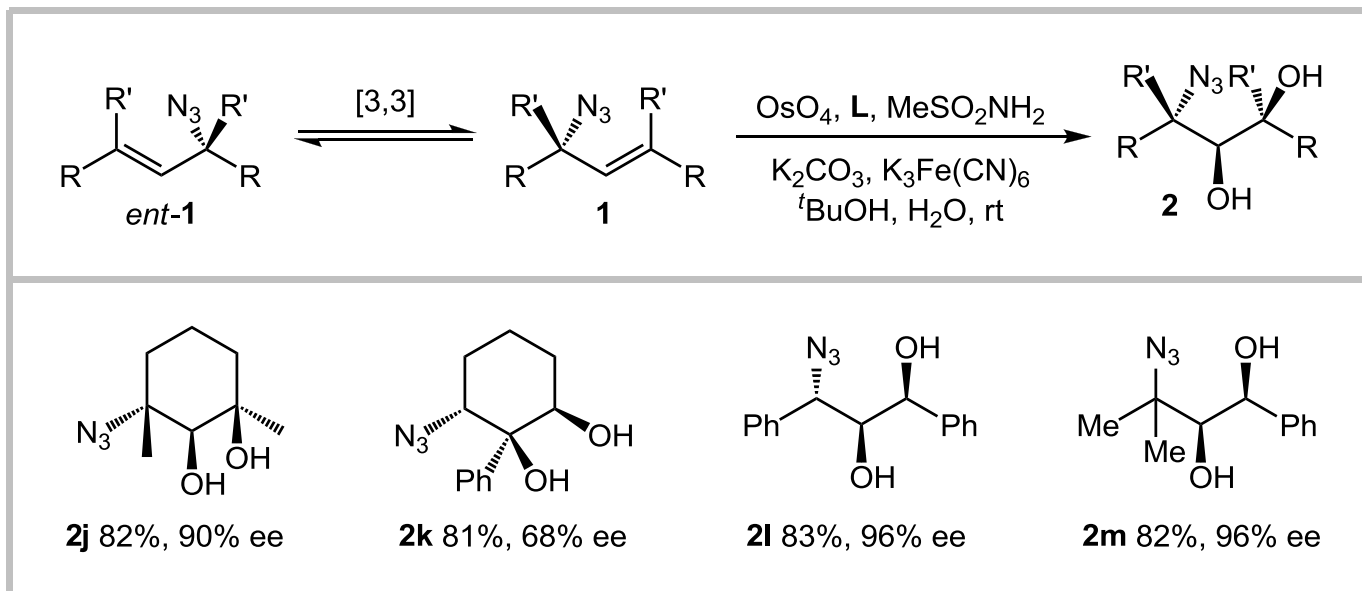
Ott, A. A.; Goshey, C. S.; Topczewski, J. J. *J. Am. Chem. Soc.* **2017**, *139*, 7737

Substrate Scope

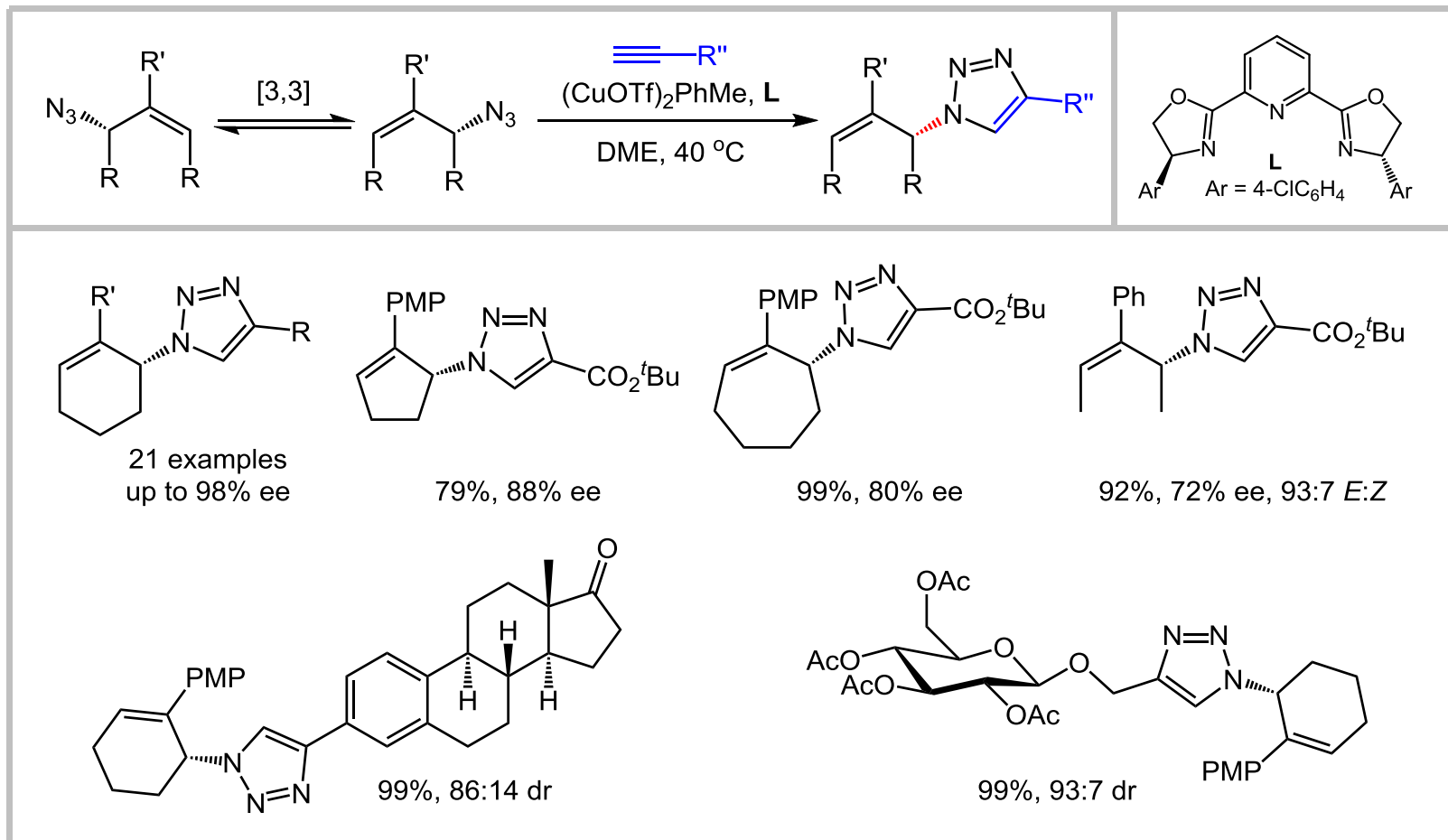


Entry	Ar	Yield (%)	Ee of 2 (%)	Dr
1	C_6H_5	79	98	11:1
2	4- $t\text{BuC}_6\text{H}_4$	77	98	10:1
3	4- $i\text{BuC}_6\text{H}_4$	81	90	10:1
4	4- FC_6H_4	75	96	9.5:1
5	4- ClC_6H_4	80	96	10:1
6	4- BrC_6H_4	72	96	9:1
7	4- $\text{F}_3\text{CC}_6\text{H}_4$	73	94	9:1
8	3- FC_6H_4	76	96	9:1
9	3- ClC_6H_4	81	94	10:1

Substrate Scope

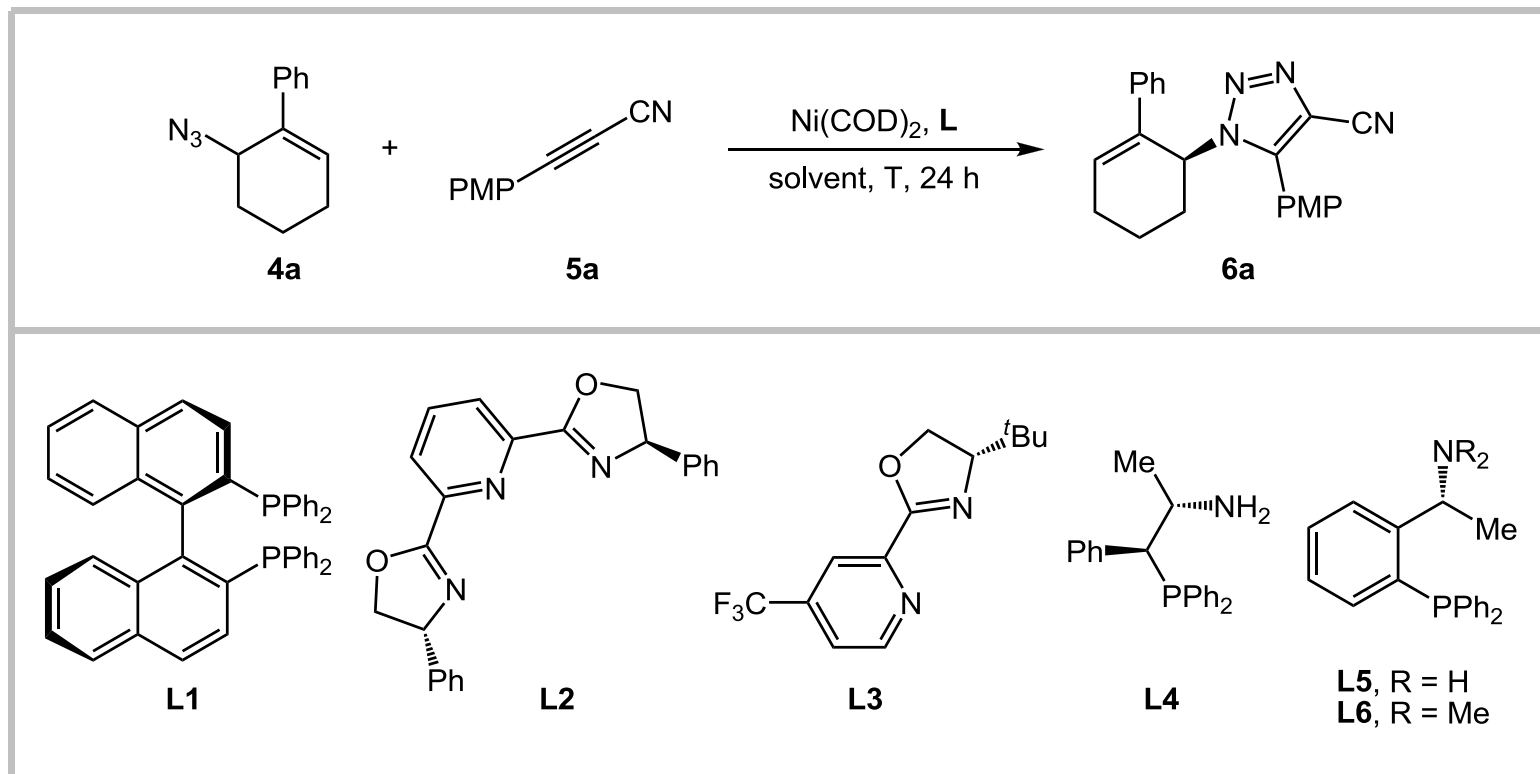


DKR of Allylic Azides via E-CuAAC



Liu, E.-C.; Topczewski, J. J. *J. Am. Chem. Soc.* **2019**, *141*, 5135

DKR of Allylic Azides via E-NiAAC



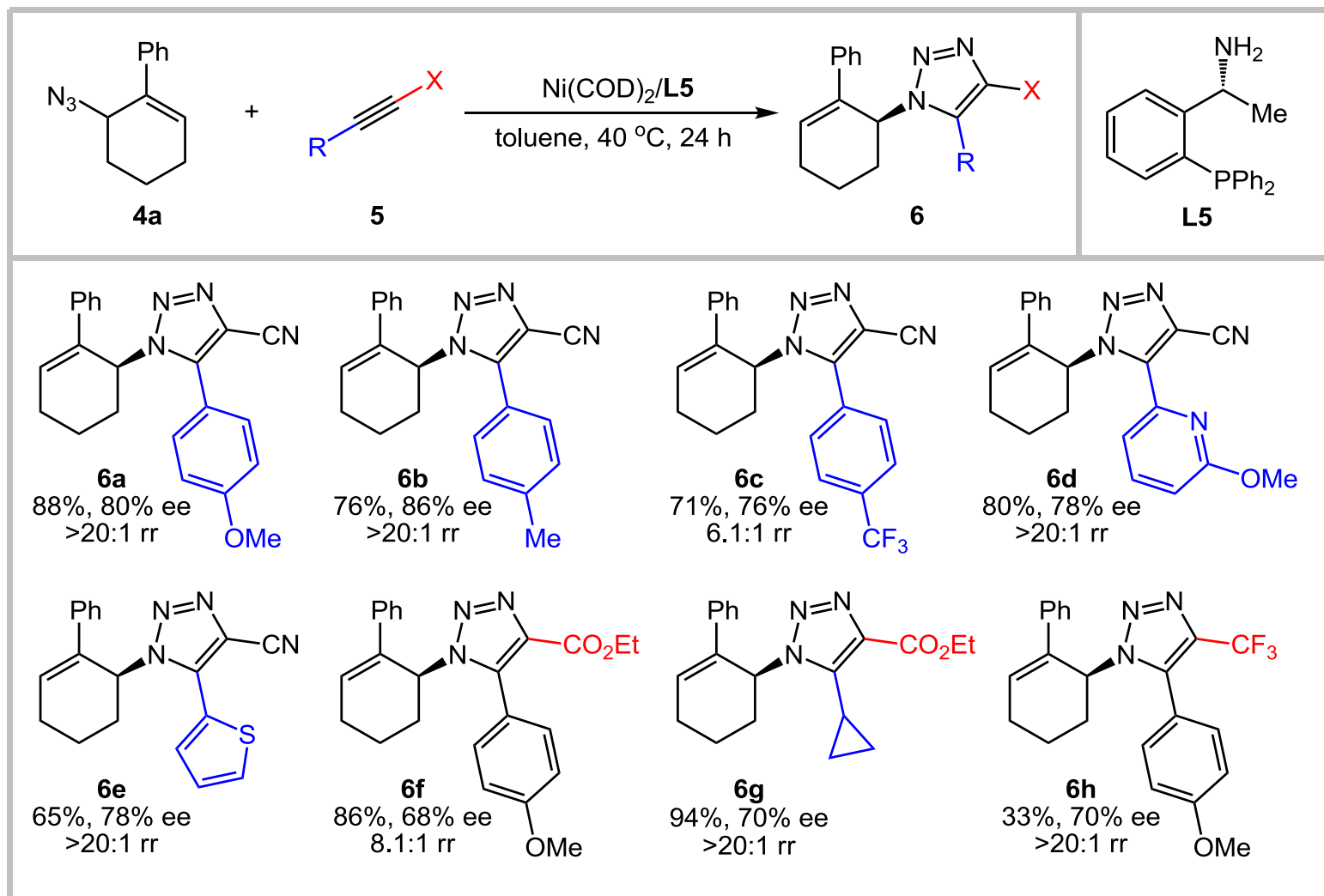
Liu, E.-C.; Topczewski, J. J. *J. Am. Chem. Soc.* **2021**, *143*, 5308

DKR of Allylic Azides via E-NiAAC

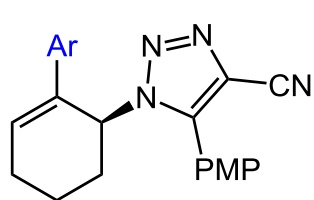
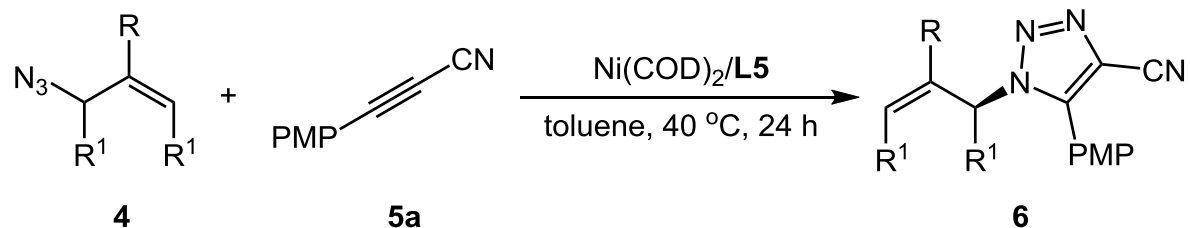
Entry ^a	L	Solvent	T (°C)	Yield (%) ^b	Ee (%) ^c
1	L1	Dioxane	50	0	--
2	L2	Dioxane	50	11	2
3	L3	Dioxane	50	27	22
4	L4	Dioxane	50	56	66
5	L5	Dioxane	50	52	74
6	L6	Dioxane	50	0	--
7	L5	Hexanes	50	82	66
8	L5	DCE	50	0	--
9	L5	Toluene	50	62	78
10	L5	Toluene	60	56	76
11	L5	Toluene	40	56	82
12 ^d	L5	Toluene	40	86	80

^a Reaction conditions: **4a** (0.05 mmol), **5a** (0.075 mmol), Ni(COD)₂ (10 mol%), **L** (10 mol%), toluene (0.50 mL). ^b Yields were determined by SFC analysis using 2',4',6'-trimethylacetophenone as an internal standard. ^c Enantiomeric ratios were determined by SFC with a chiral stationary phase. ^d Toluene (0.20 mL).

Substrate Scope



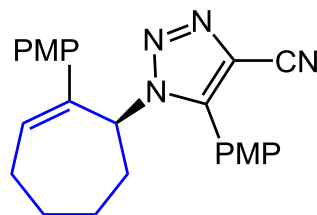
Substrate Scope



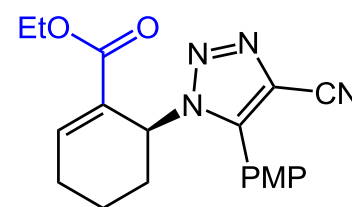
6i Ar = 4-MeOC₆H₄
88%, 78% ee, >20:1 rr

6j Ar = 4-F₃CC₆H₄
57%, 62% ee, >20:1 rr

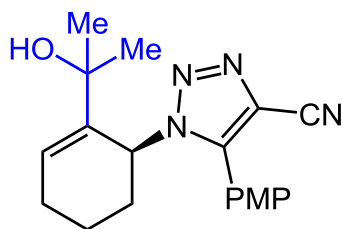
6k Ar = 4-MeSC₆H₄
74%, 72% ee, >20:1 rr



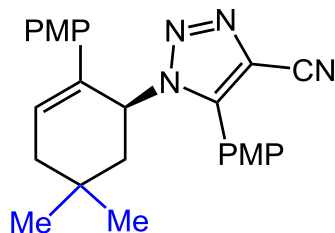
6l 85%
76% ee, >20:1 rr



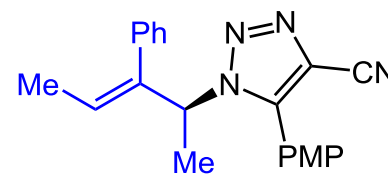
6m 86%
56% ee, >20:1 rr



6n 87%
86% ee, 8.1:1 rr

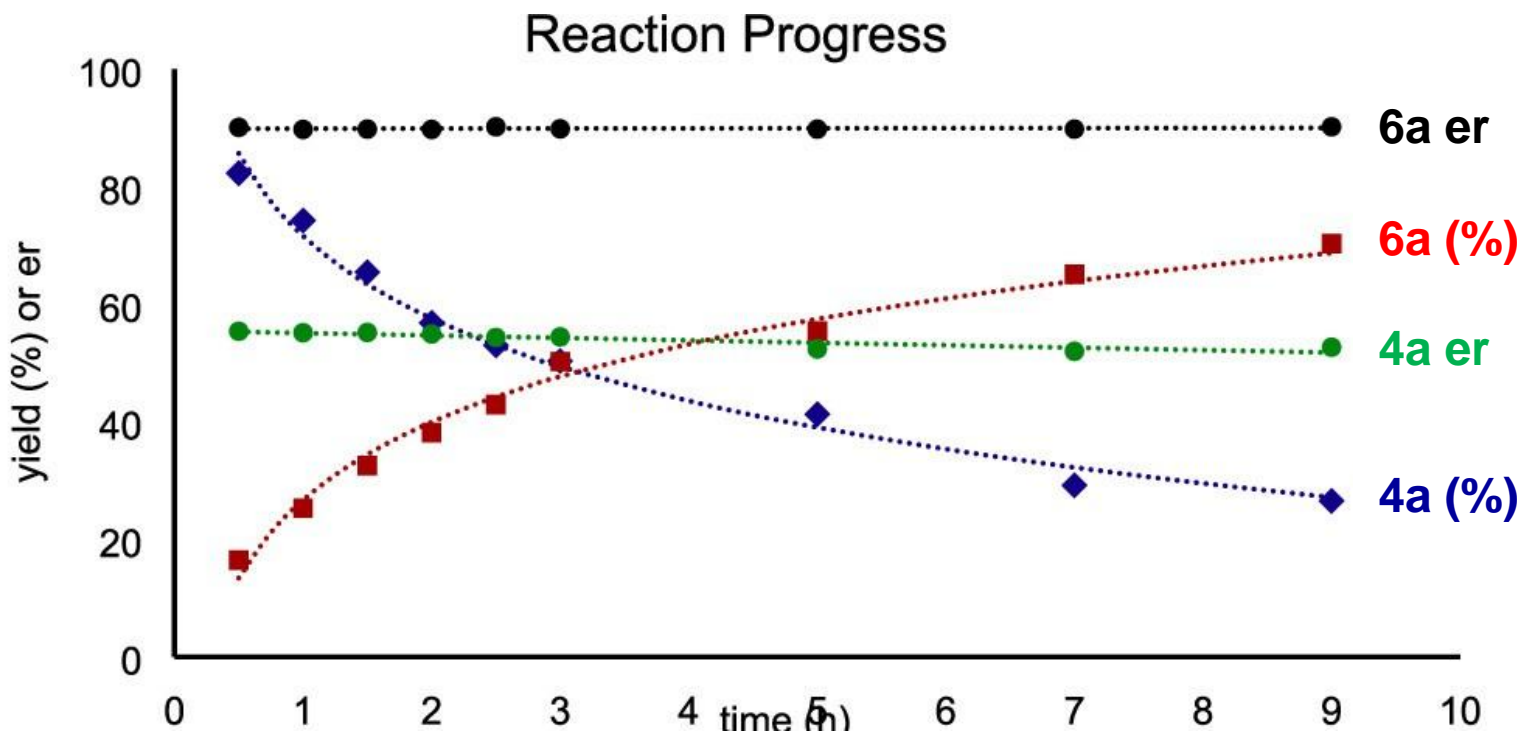


6o 89%
68% ee, >20:1 rr



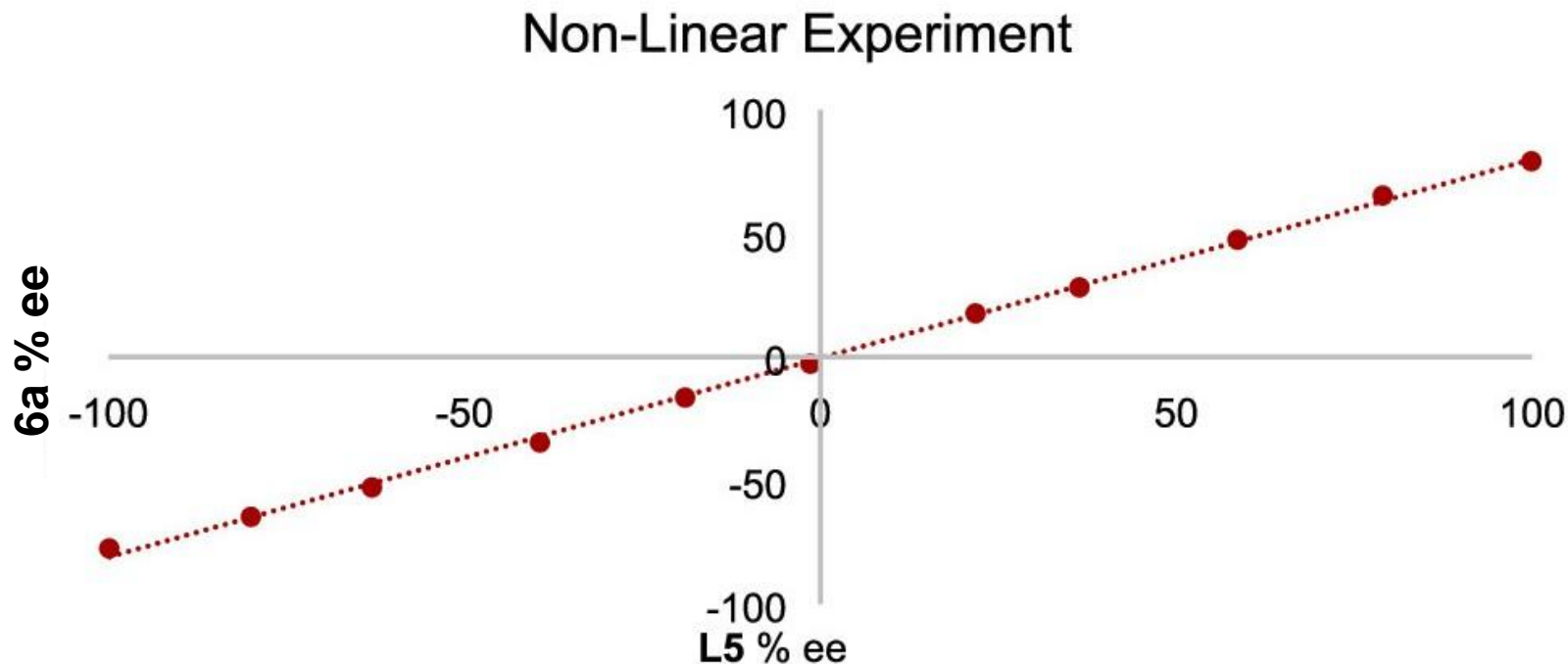
6p 94%
62% ee, >20:1 rr

Mechanistic Studies



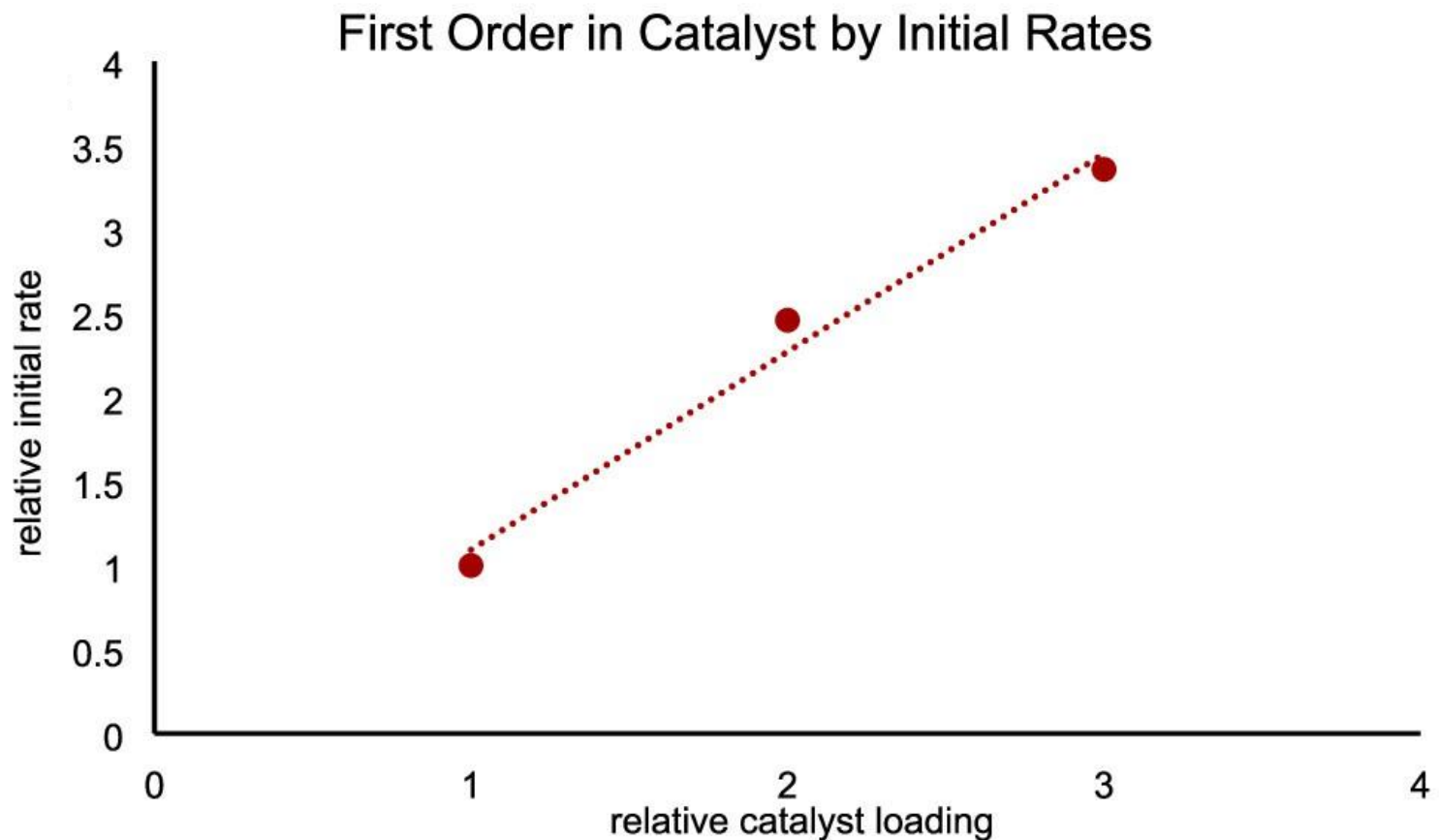
At very early time points, a slight enrichment of the azide er was measurable (up to 55:45), indicating that this DKR likely occurs in a nonideal kinetic regime.

Mechanistic Studies



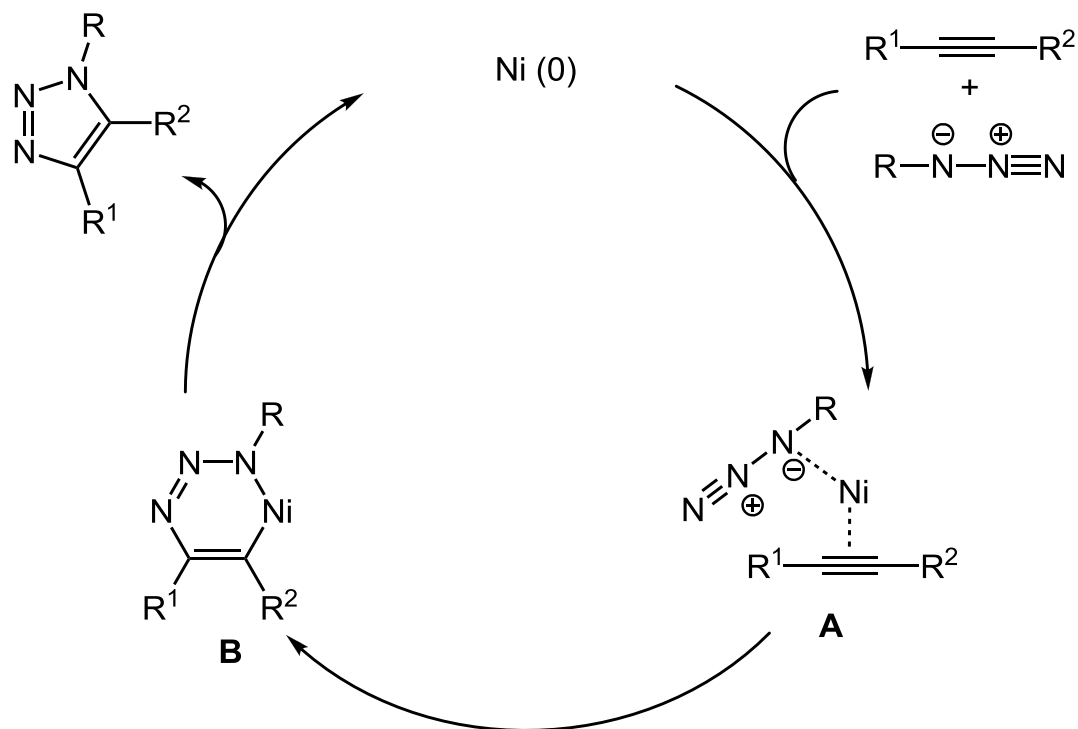
The E-NiAAC reaction did not demonstrate a nonlinear effect, indicating that only 1 equiv of ligand L5 is involved in the enantiodetermining step.

Mechanistic Studies



The reaction was found to be first-order in catalyst by initial rates.

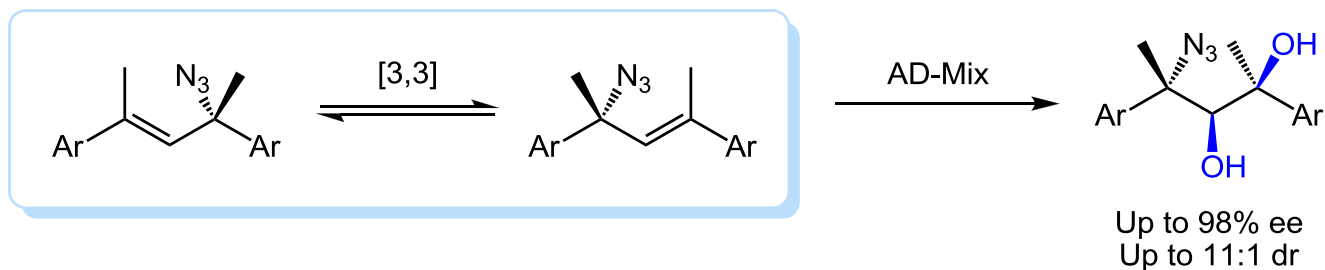
Tentative Mechanism of NiAAC



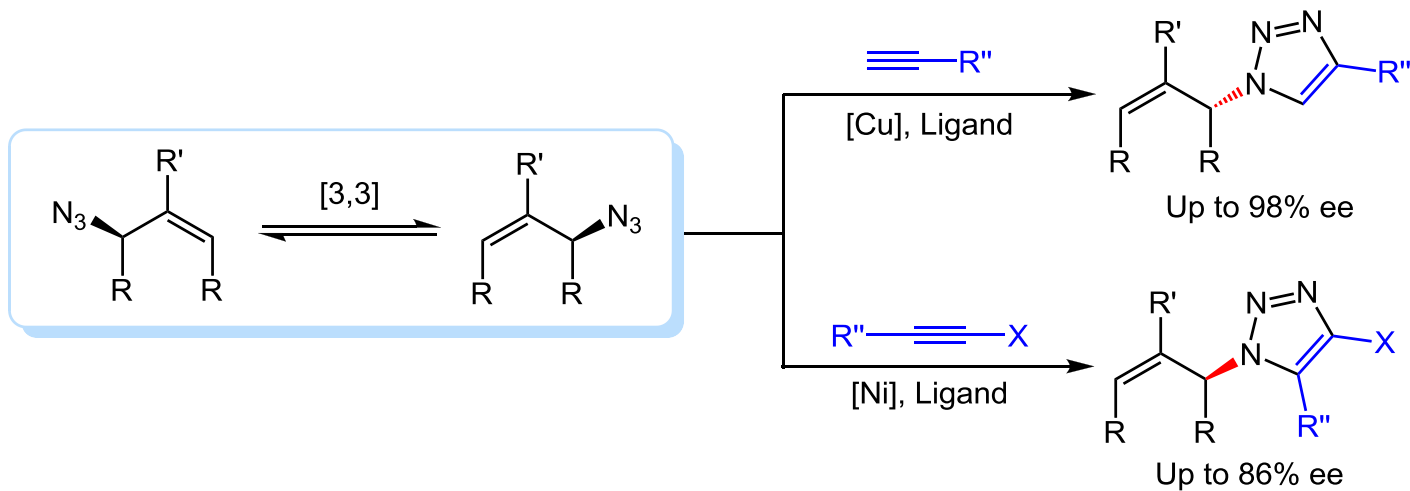
Kim, W. G.; Kang, M. E.; Hong, S. Y. *J. Am. Chem. Soc.* **2017**, *139*, 12121

Summary

DKR of Allylic Azides *via* Sharpless Asymmetric Dihydroxylation



DKR of Allylic Azides *via* Enantioselective Alkyne-Azide Cycloaddition



Title and The First Paragraph

Title

**Enantioselective Nickel-Catalyzed Alkyne-Azide
Cycloaddition *by* Dynamic Kinetic Resolution**

Writing Strategy

**The features and limitations of Cu-
catalyzed alkyne-azide cycloaddition**



**Other metal catalytic systems for alkyne-
azide cycloaddition and their features**

The First Paragraph

In 2002, Sharpless and Meldal made contemporaneous disclosures that copper could catalyze the alkyne-azide cycloaddition reaction (CuAAC). CuAAC provides exquisite regioselectivity for the 1,4-disubstituted triazole and is the quintessential “click” reaction. With a few noted exceptions, CuAAC is traditionally limited to terminal alkynes. Other metals can catalyze the alkyne-azide cycloaddition reaction, including zinc, rhodium, silver, iridium, nickel, and gold. These reactions often provide complementary selectivity or reactivity relative to CuAAC. For instance, the ruthenium-catalyzed alkyne-azide cycloaddition (RuAAC) typically affords 1,5-disubstituted 1,2,3-triazole products.

The Last Paragraph

Writing Strategy

Summary of this work



Significance of this work

The Last Paragraph

In conclusion, ligand **L5** can promote an E-NiAAC reaction by DKR. This is the first enantioselective alkyne-azide cycloaddition that is reported to be catalyzed by a metal other than copper. The E-NiAAC reaction provides synthetic access to 1,4,5-trisubstituted α -chiral triazoles that are not directly accessible by E-CuAAC. Furthermore, preliminary mechanistic experiments indicate that the nature of the NiAAC catalyst is a monometallic L_1 species, which is distinct from CuAAC.

Title and The First Paragraph

Title

**Dynamic Kinetic Resolution of Allylic Azides
via Asymmetric Dihydroxylation**

Writing Strategy

**Winstein rearrangement
and the synthetic applications**



**Hypothesis for the application of
Winstein rearrangement in DKR**

The First Paragraph

The seminal report describing the rearrangement of allylic azides was authored by Winstein in 1960. The rearrangement, which is thought to occur via a sigmatropic process, typically occurs at or near room temperature. While the Winstein rearrangement has been observed in many contexts, selectivity challenges inherent in the azide mixture have limited its synthetic applications. In 2005, Sharpless and co-workers reported that site-selectivity could be achieved in some instances by exploiting different alkene substitution patterns. Subsequently, it was shown by Aubé and co-workers that the equilibrating mixture of azides could be differentially functionalized in an intramolecular Schmidt reaction that differentiated the azides based on the relative rates of ring closure. Based on this precedent, we hypothesized that the Winstein rearrangement could be used as the racemization pathway in a dynamic kinetic resolution. Herein, we report the successful achievement of this goal.

Representative Examples

Robust synthetic access has enabled triazole incorporation into numerous discovery efforts. (阐述进展)

While E-CuAAC reactions have advanced, enantioselective variants of other metal-catalyzed alkyne–azide cycloadditions have remained elusive. (引出发展新方法的意义)

The PYBOX scaffold (**L2**) is privileged in E-CuAAC reactions; however, this reactivity did not translate to the NiAAC system. (条件优化)

Both electron-rich (**3i**) and electron-deficient (**3j**) heterocycles could be incorporated. (底物拓展)

Acknowledgement

***Thanks
for your attention***