Literature Report IX

Catalytic Enantioconvergent Allenylation of Aldehydes with Propargyl Halides

Reporter: Xiao-Qing Wang
Checker: Yi-Xuan Ding
Date: 2022-3-21

Wang, Z. *et al. Angew. Chem. Int. Ed.* **2022**, *61,* 10.1002/anie.202117114

CV of Prof. Zhaobin Wang

Research Interests:

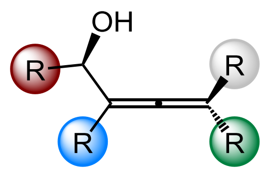
- Transition metal catalysis
- Organocatalysis
- Radical chemistry

Education and Employment:

- **2007–2011** B.S., Nanjing University
- **2011–2015** Ph.D., The Hong Kong University of Science and Technology
- **2016–2019** Postdoc., California Institute of Technology
- **Now** Distinguished Researcher, Westlake University

Contents

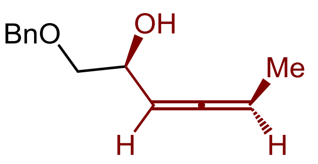
Introduction



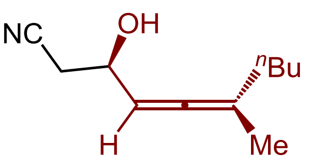
central & axial chirality

Advanced Synthon

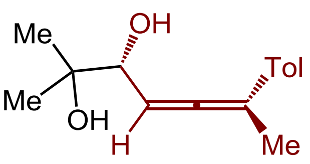
- Cycloaddition
- Cycloisomerization
- Electrophilic addition
- Pd-Catalyzed coupling



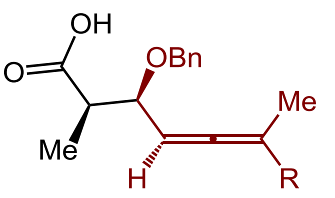
synthesis of
(+)-Varitriol



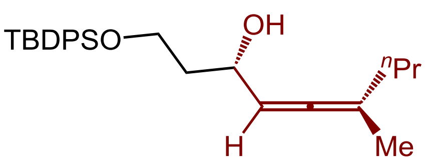
synthesis of
Hagen's gland lactone



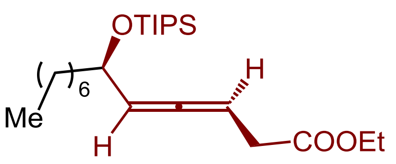
synthesis of
Boivinianin B



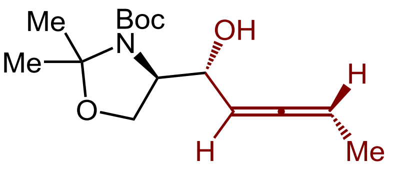
synthesis of
Dihydroerythronolide A



synthesis of
Amphidinolide X



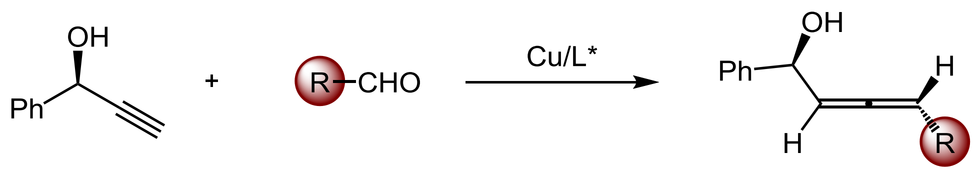
synthesis of
Clavepictines A & B



synthesis of
(+)-Furanomycin

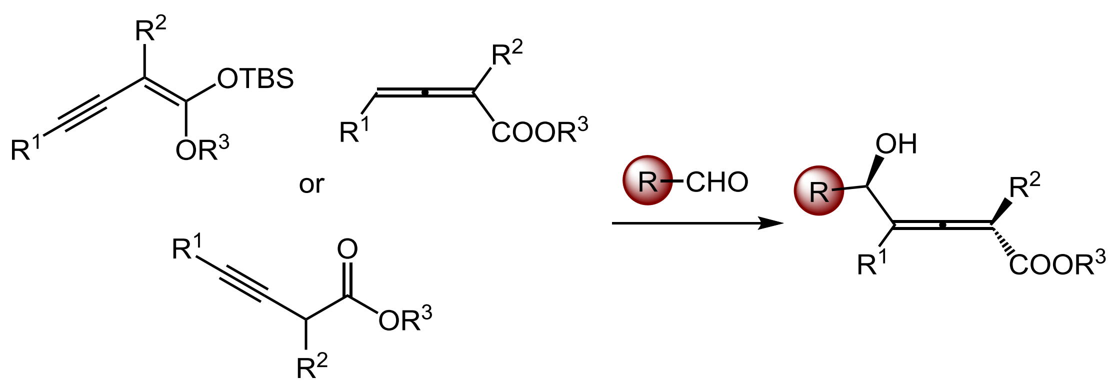
Synthesis of Chiral α-Allenols

A. Use of chiral starting materials to access chiral α-allenols



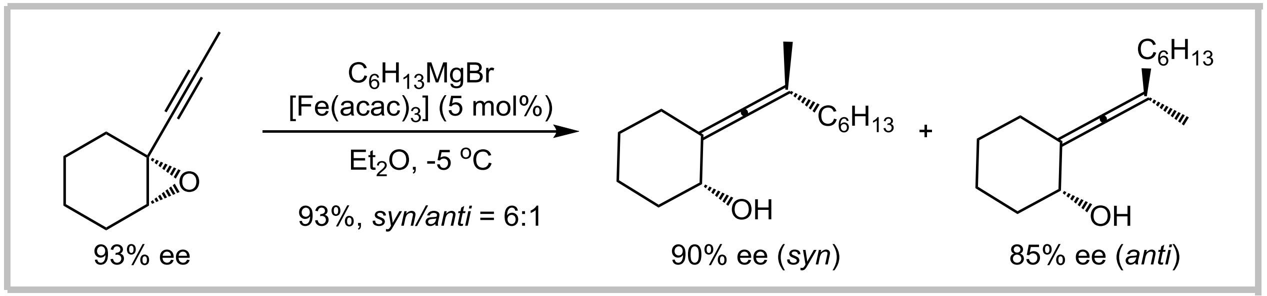
B. Use of activated nucleophiles to access chiral α-allenols

1) Asymmetric alkynylogous aldol reaction

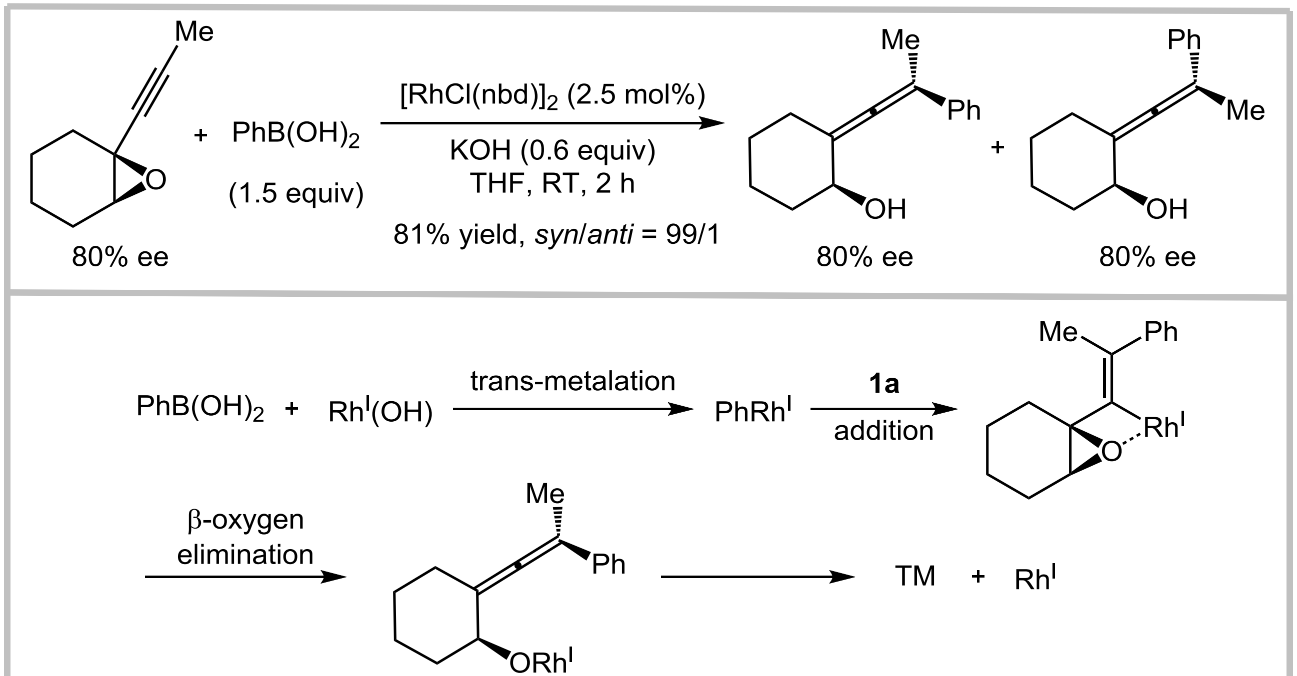


2) Asymmetric conjunctive cross-coupling reaction

Use of Chiral Starting Materials

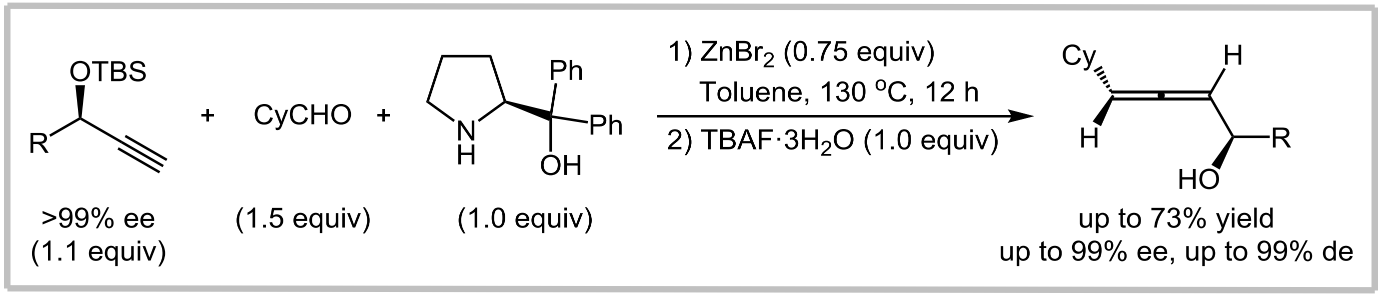


Furstner, A. *et al. Angew. Chem. Int. Ed.* **2003**, *42,* 5355

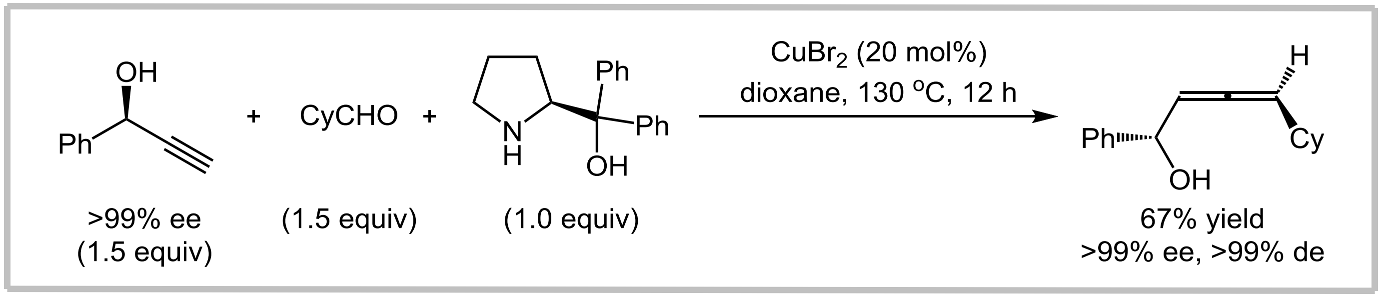


Murakami, M. *et al. Angew. Chem. Int. Ed.* **2007**, *46,* 7101

Use of Chiral Starting Materials

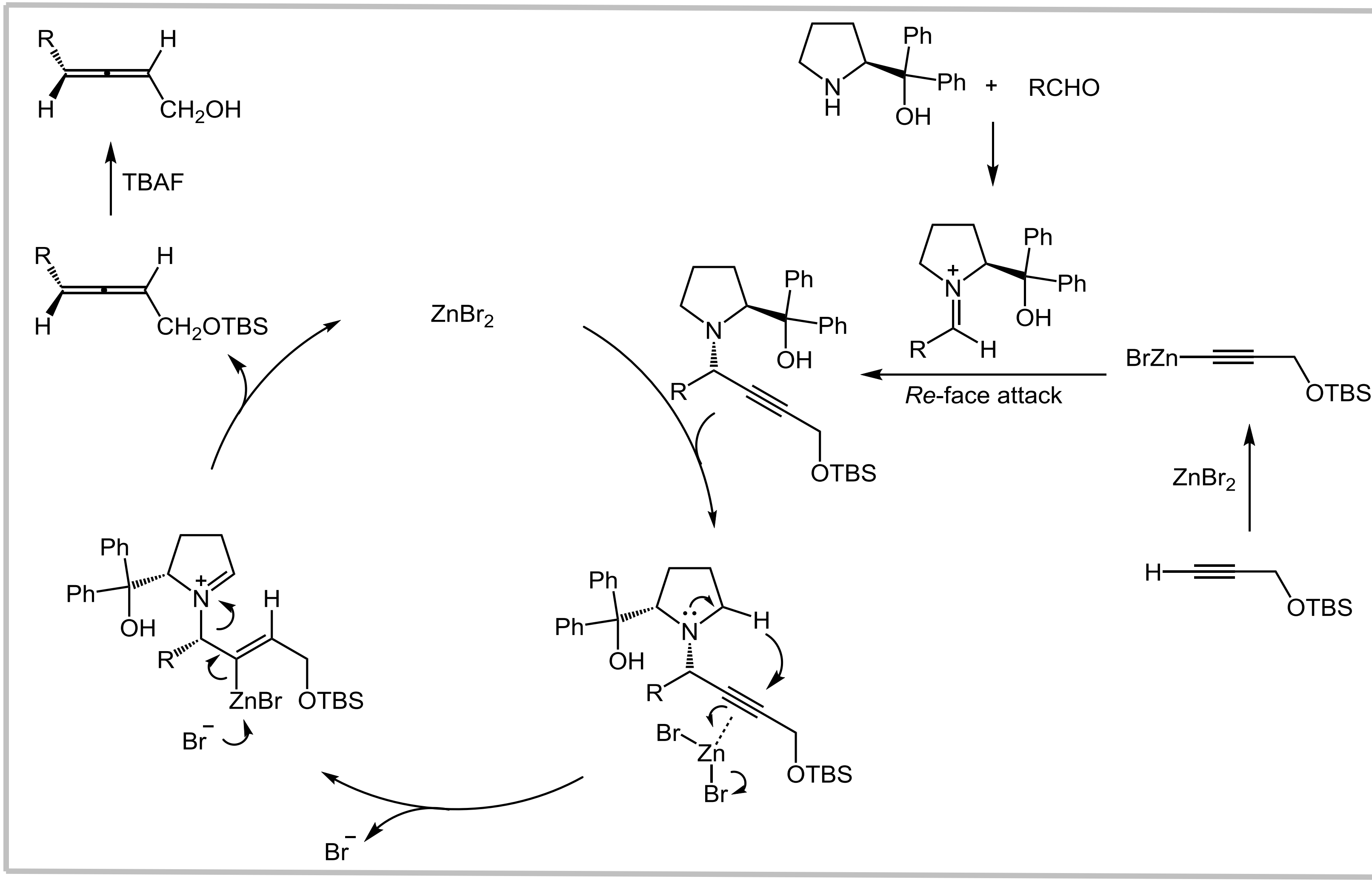


Ma, S. *et al. Chem. Eur. J.* **2013**, *19,* 716

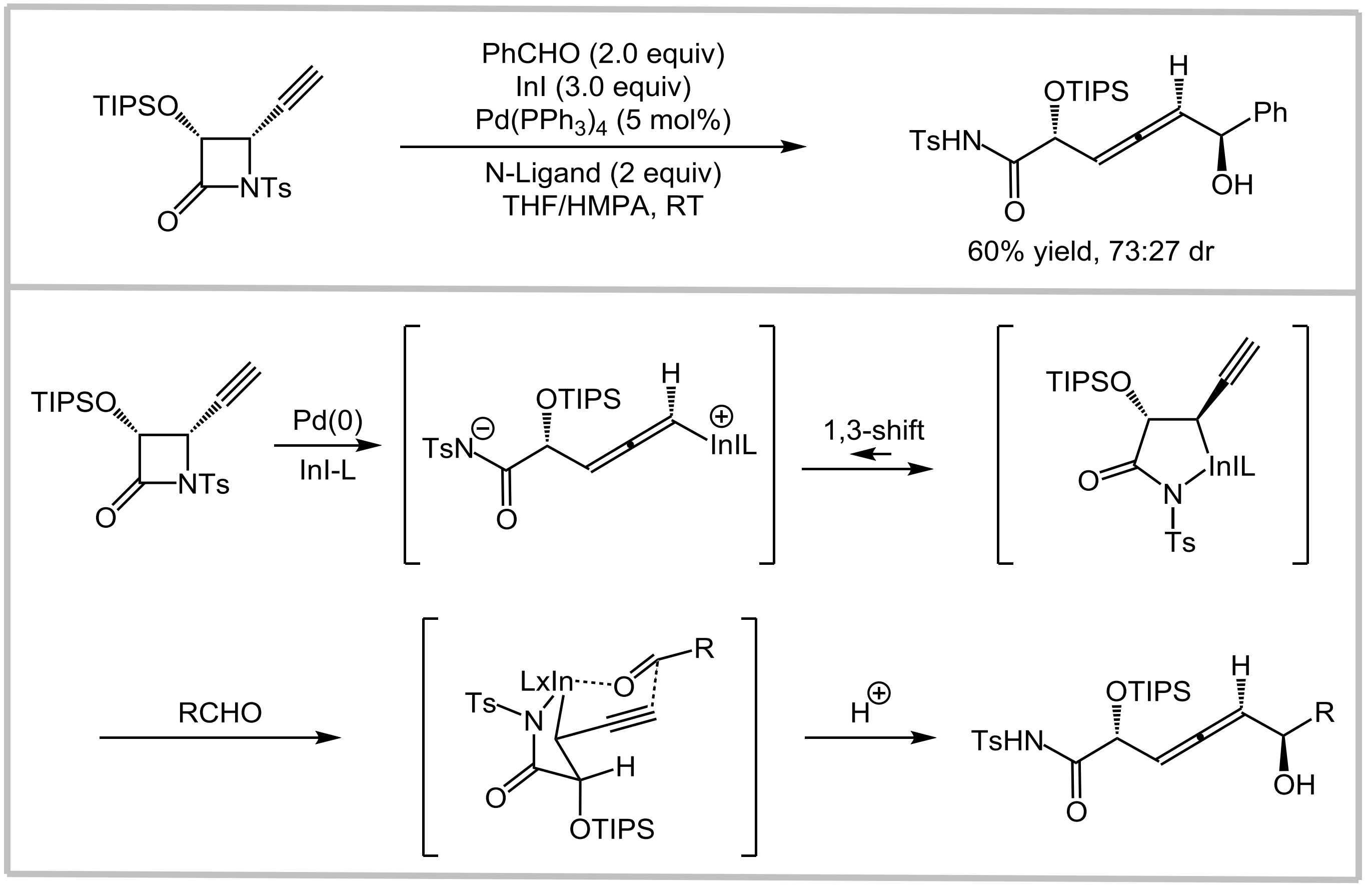


Ma, S. *et al. Chem. Commun.* **2015**, *51,* 6956

Use of Chiral Starting Materials

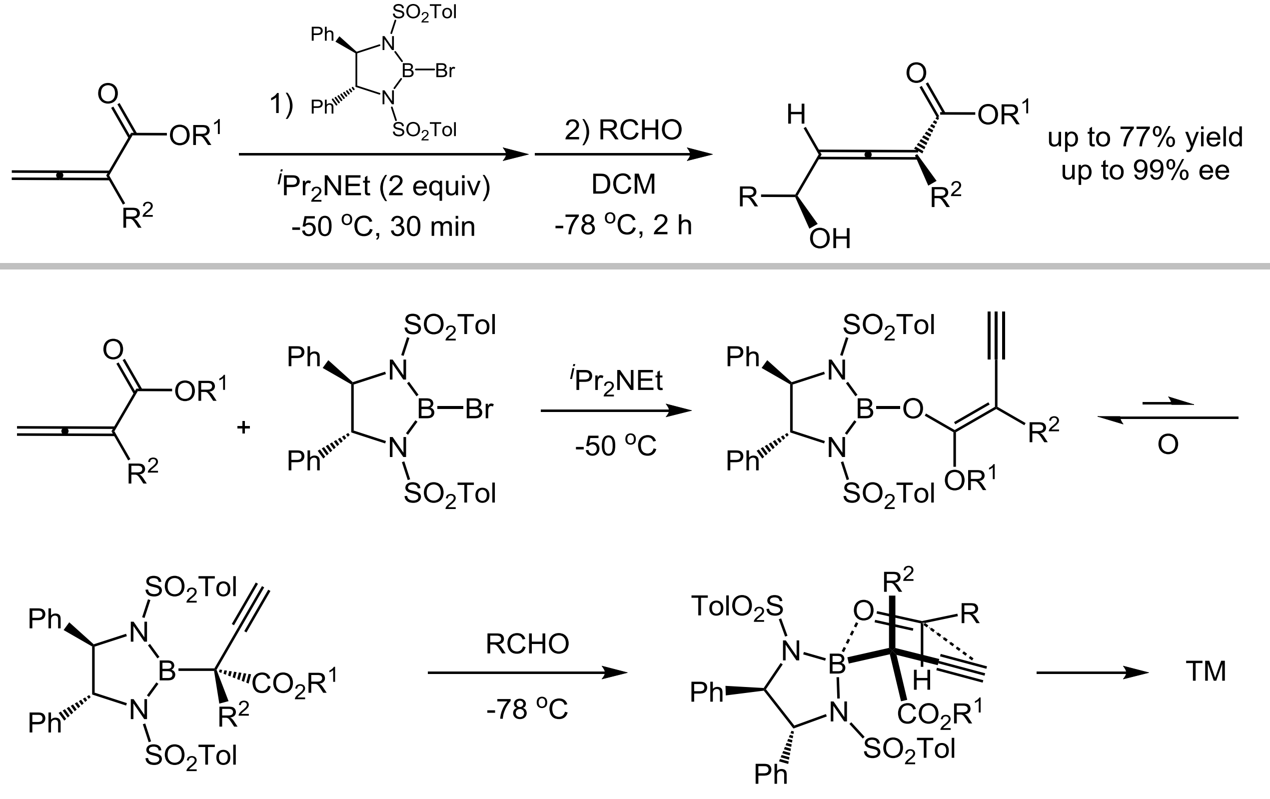


Use of Chiral Starting Materials



Zambron, B. K. *et al. Org. Lett.* **2019**, *21,* 3904

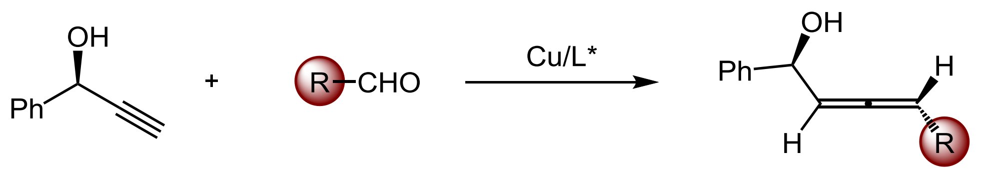
Use of Chiral Starting Materials



Yu, C.-M. *et al. Org. Lett.* **2018**, *20,* 1521

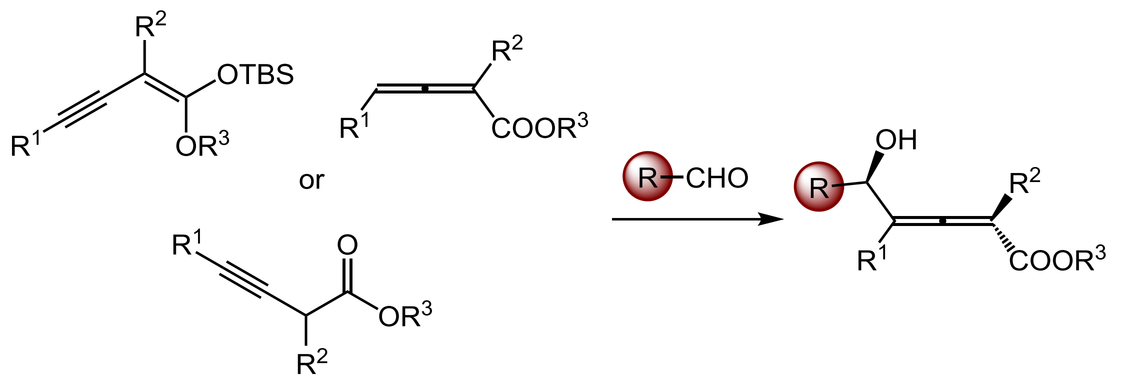
Synthesis of Chiral α-Allenols

A. Use of chiral starting materials to access chiral α-allenols

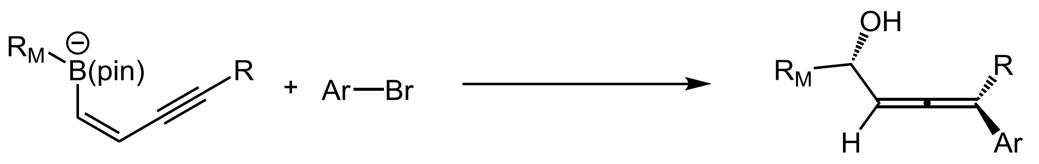


B. Use of activated nucleophiles to access chiral α-allenols

1) Asymmetric alkynylogous aldol reaction

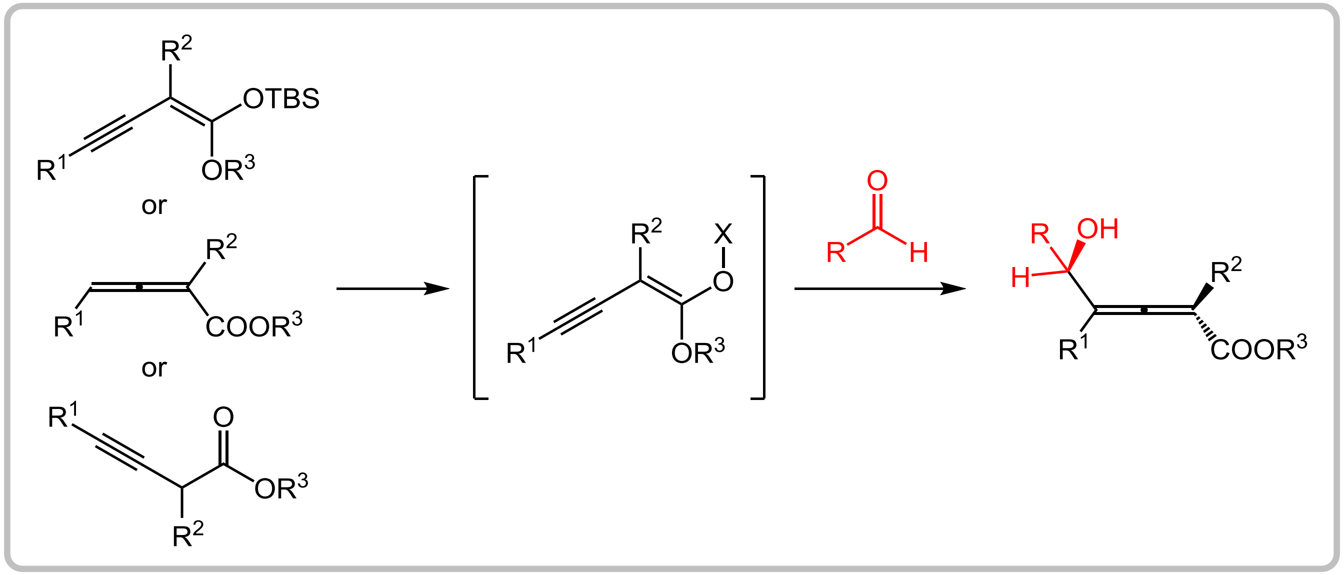


2) Asymmetric conjunctive cross-coupling reaction

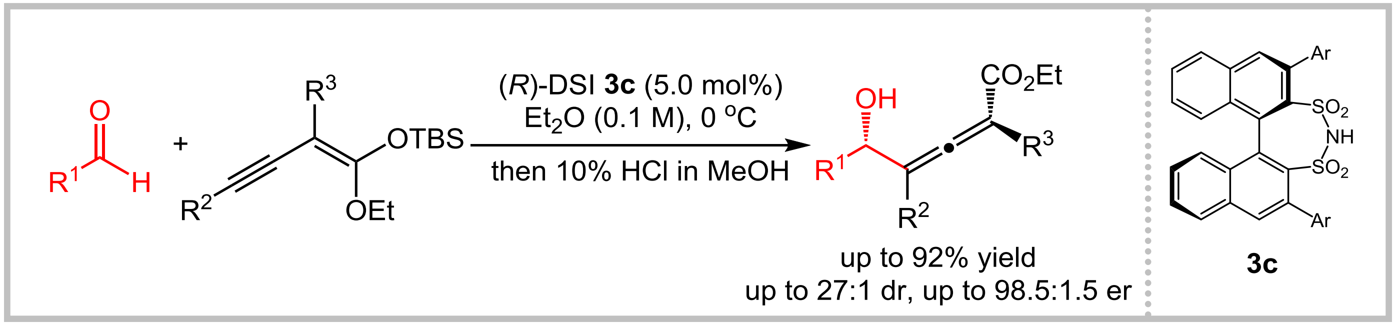


Asymmetric Alkynylogous Aldol Reaction

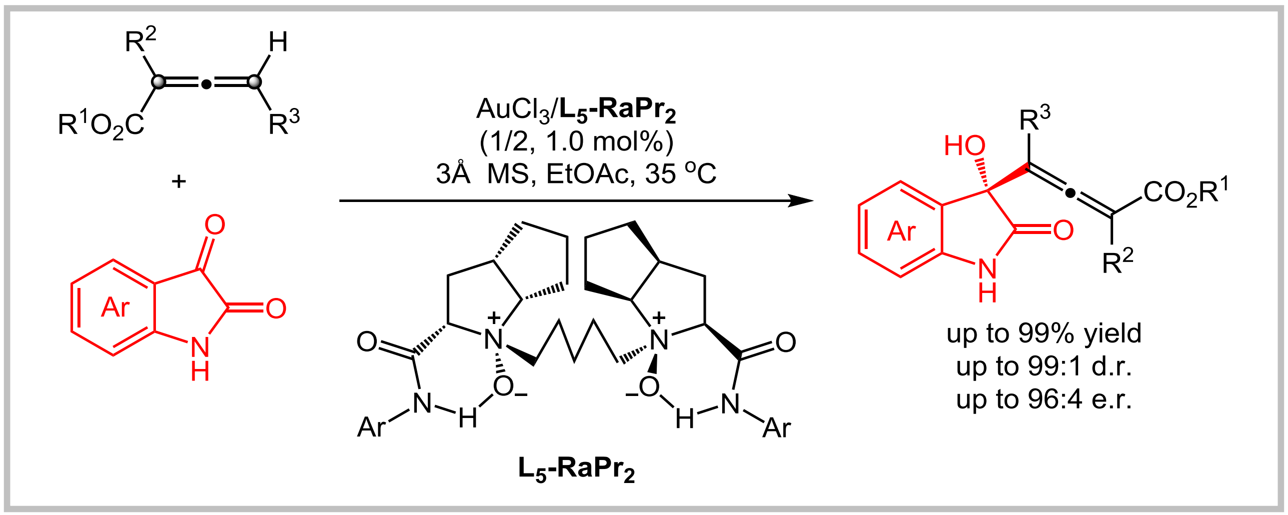
Construction of Chiral α-Allenols via Asymmetric Alkynylogous Aldol Reaction



Asymmetric Alkynylogous Aldol Reaction

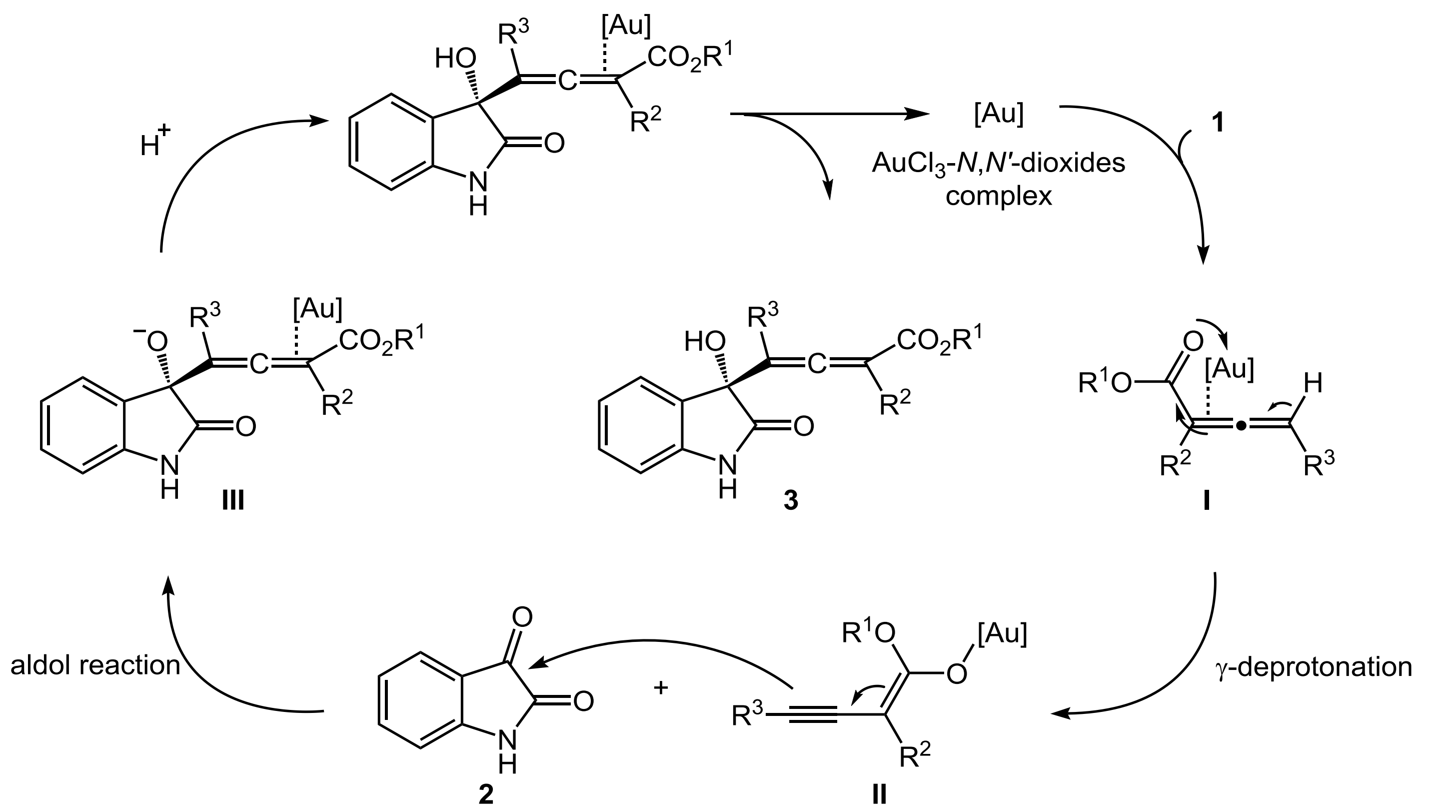


List, B. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 8962



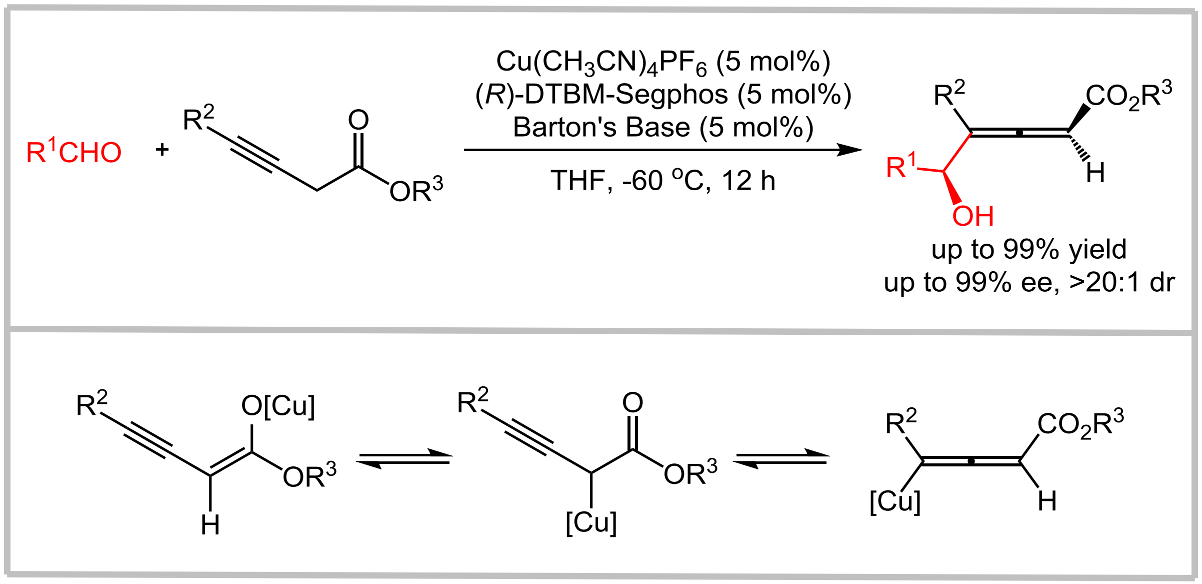
Feng, X. *et al. ACS Catal.* **2016**, *6*, 2482

Asymmetric Alkynylogous Aldol Reaction



Feng, X. *et al. ACS Catal.* **2016**, *6*, 2482

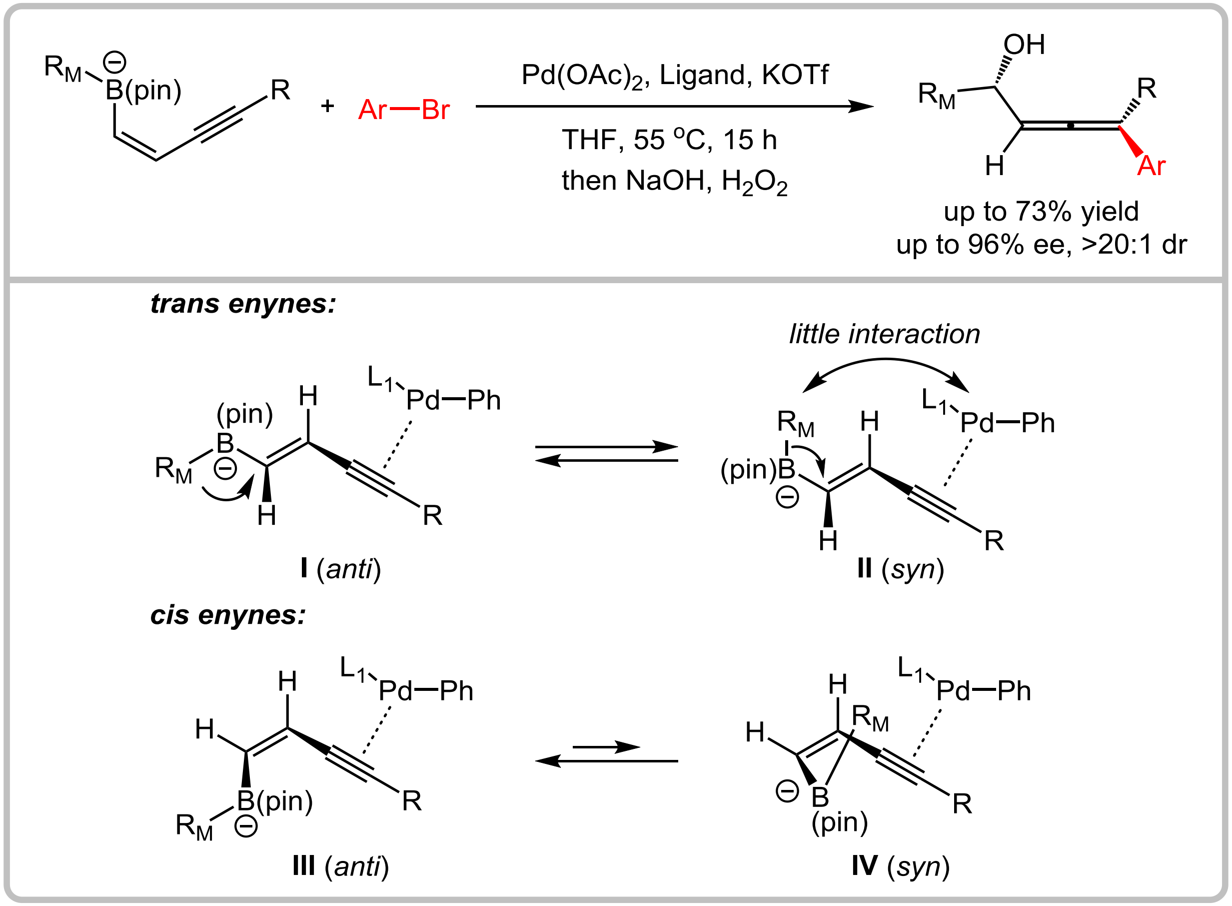
Asymmetric Alkynylogous Aldol Reaction



Yin, L. *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 1562

Asymmetric Conjunctive Cross-coupling Reaction

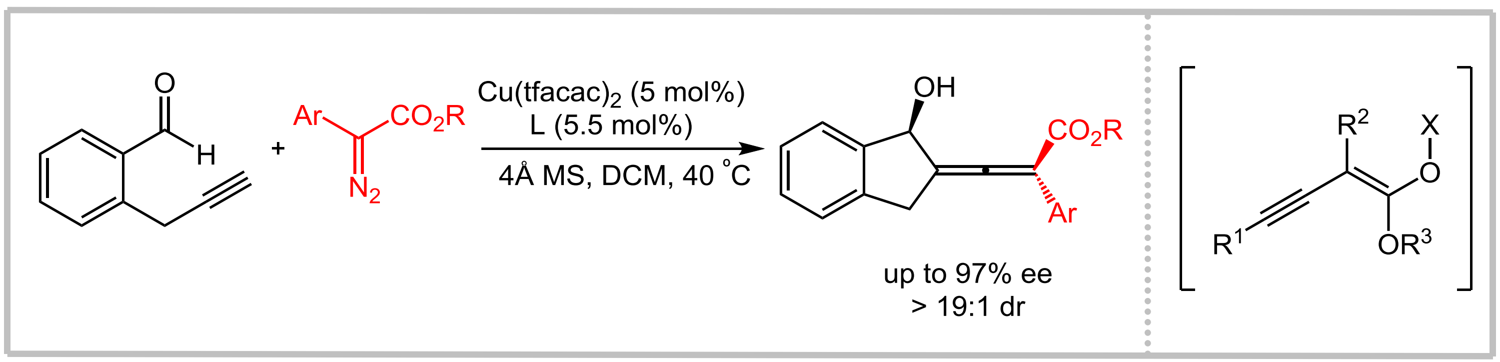
Construction of Chiral α-Allenols via Asymmetric Conjunctive Cross-coupling Reaction



Morken, J. P. *et al. Angew. Chem. Int. Ed.* **2020**, *59,* 10311

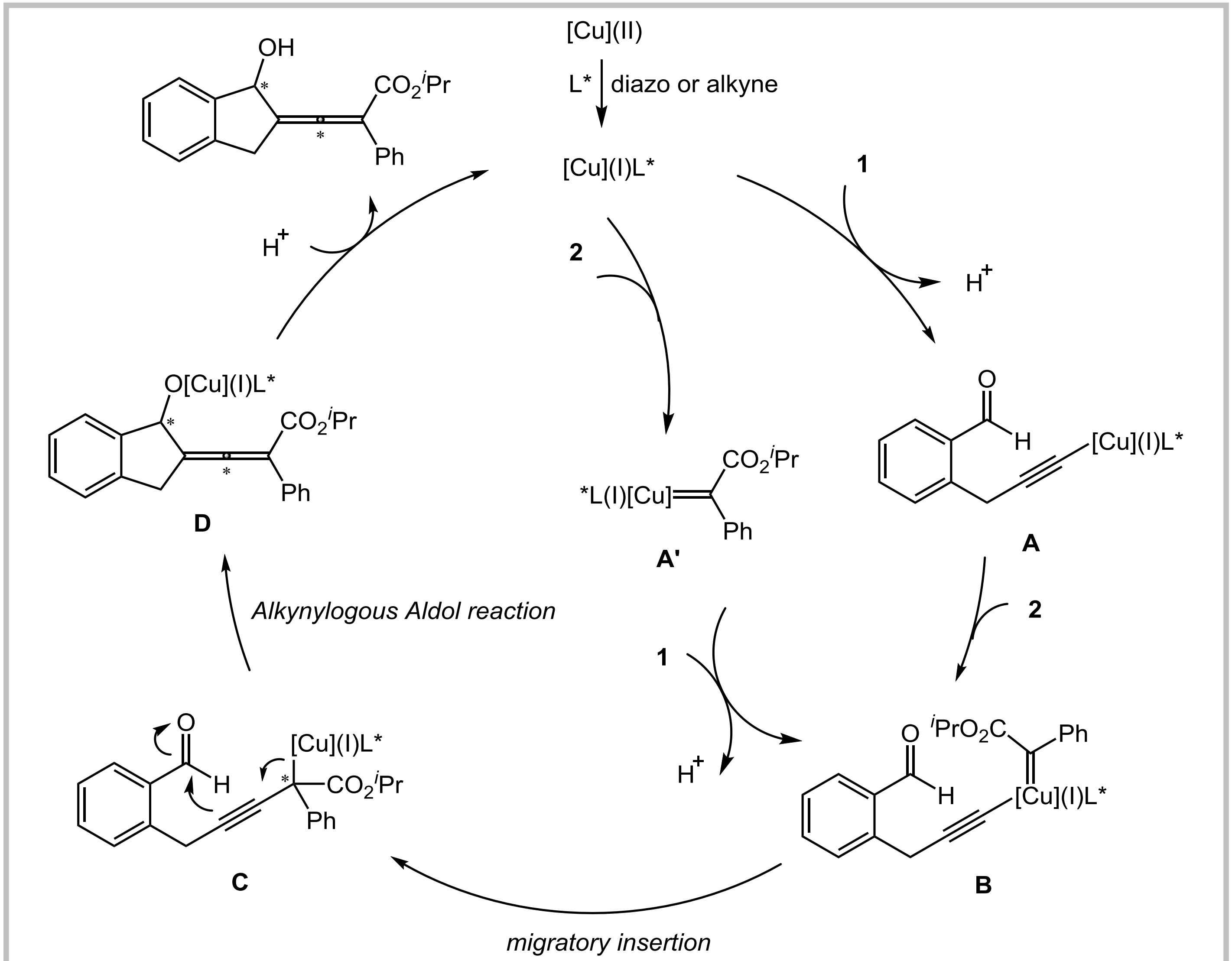
Asymmetric Tandem Reaction

Construction of Chiral α-Allenols via Asymmetric Tandem Cross-coupling and Alkynylogous Aldol Reaction

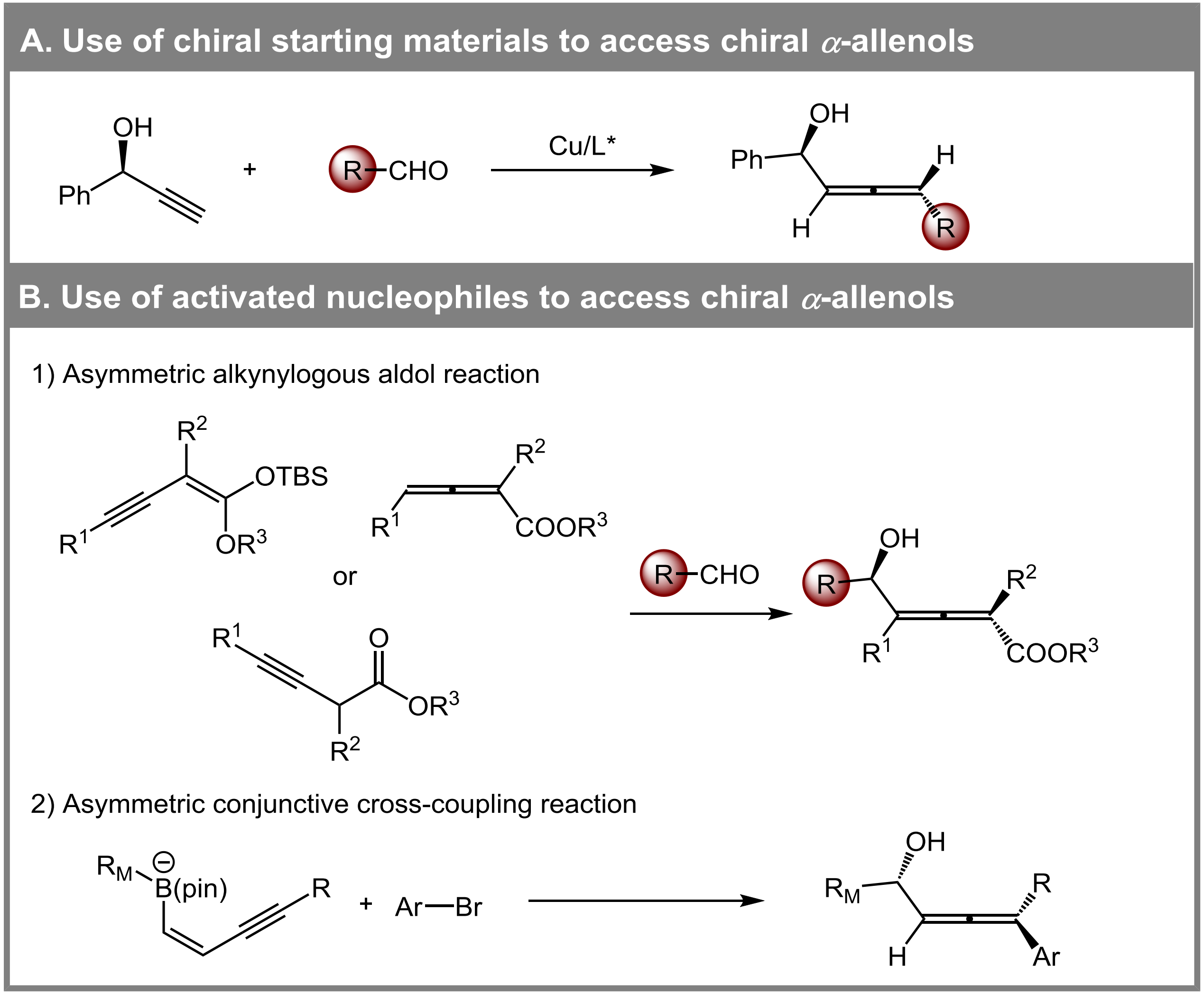


Sun, J. *et al. Org. Lett.* **2021**, *23,* 5175

Asymmetric Tandem Reaction

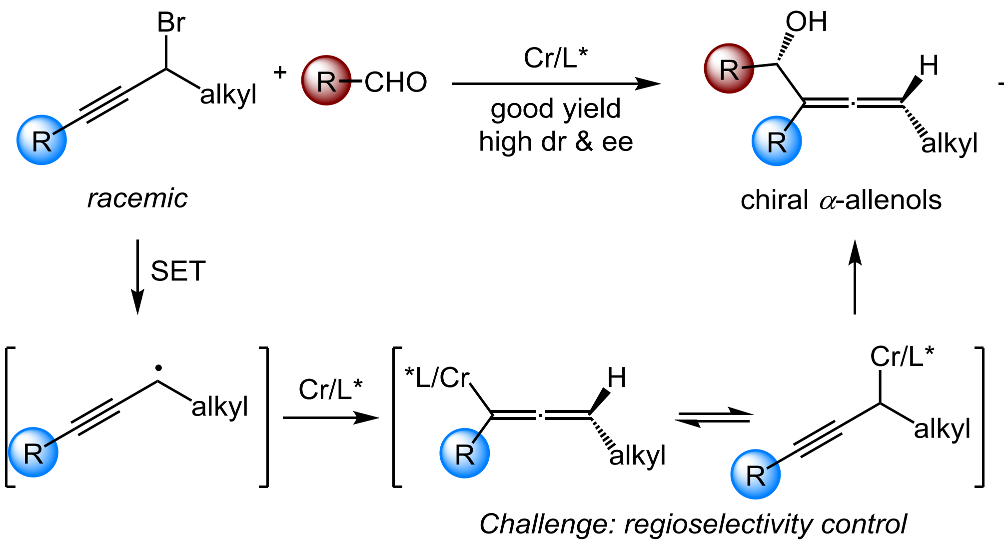


Synthesis of Chiral α-Allenols



Asymmetric Synthesis of α-Allenols

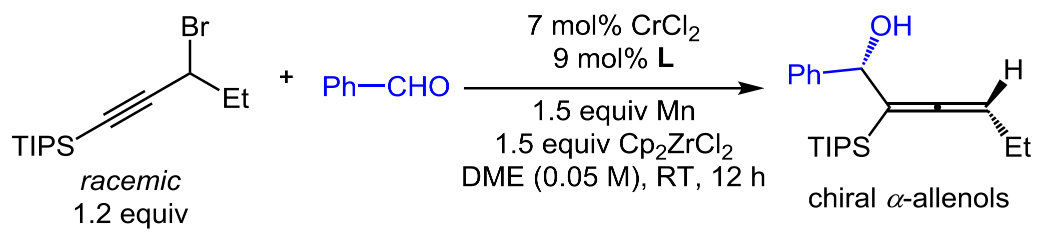
Asymmetric synthesis of α-allenols from secondary propargyl bromides

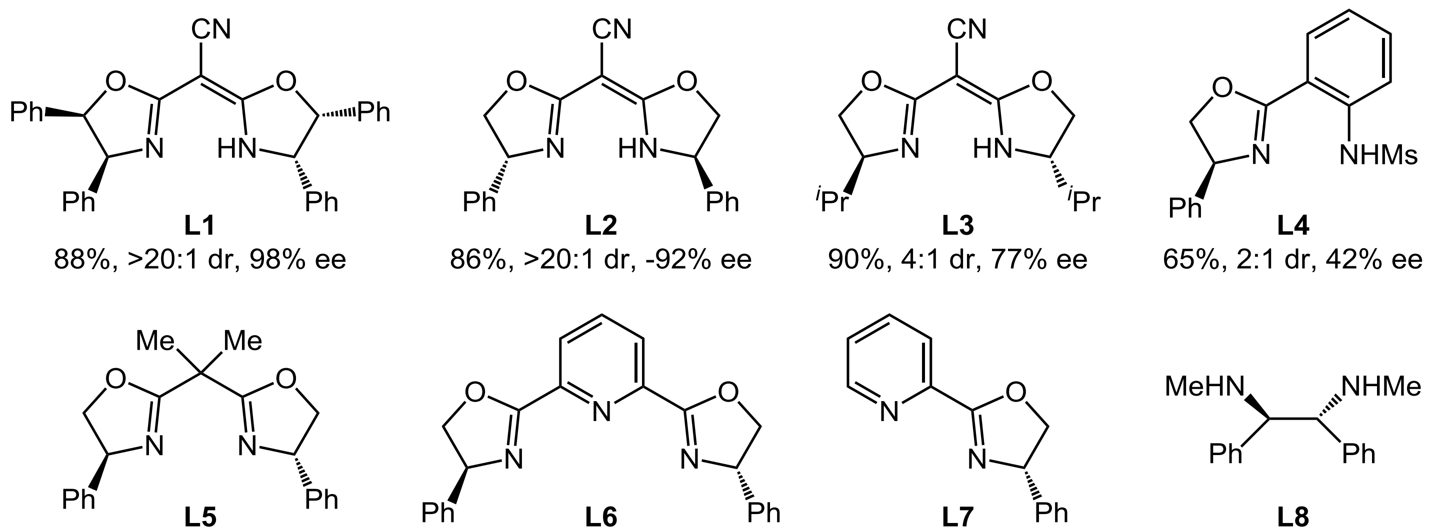


- ♥Efficient construction of central & axial chirality
- ♥Good regio-, diastereo- & enantioselectivity
- ♥All stereoisomers accessible
- ♥Mild reaction condition & broad substrate scope

Wang, Z. *et al. Angew. Chem. Int. Ed.* **2022**, *61,* 10.1002/anie.202117114

Reaction Conditions Optimization





L1 88%, >20:1 dr, 98% ee

L2 86%, >20:1 dr, -92% ee

L3 90%, 4:1 dr, 77% ee

L4 65%, 2:1 dr, 42% ee

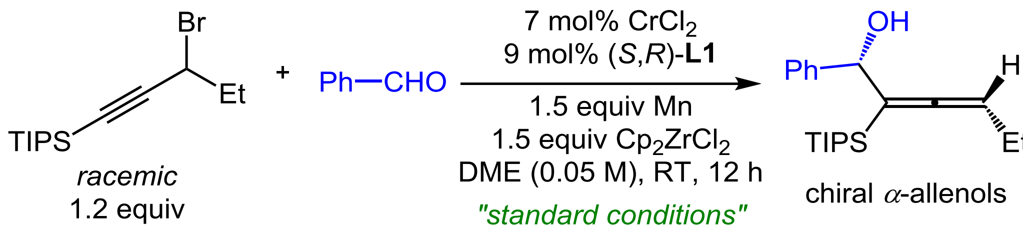
L5 23%, 2:1 dr, - ee

L6 <2%, - dr, - ee

L7 <2%, - dr, - ee

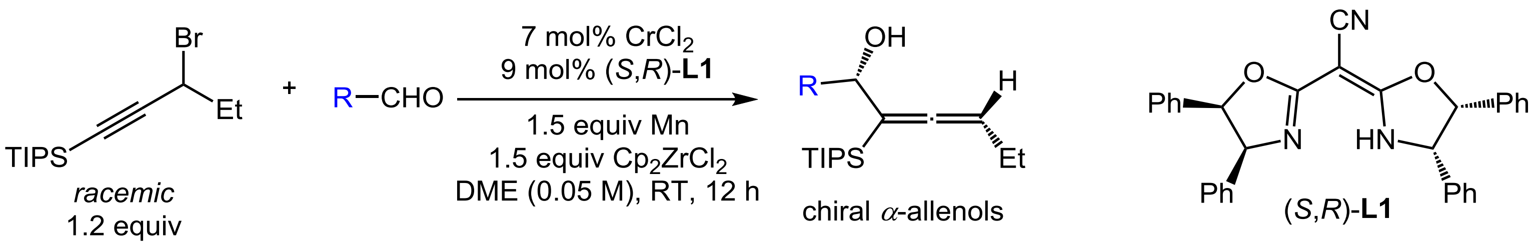
L8 68%, 12:1 dr, 41% ee

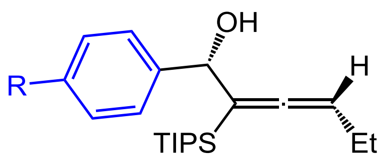
Reaction Conditions Optimization



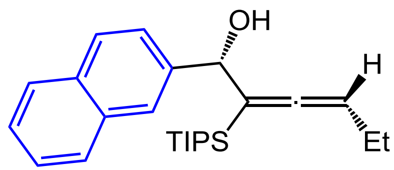
Entry	Variation from the "*standard conditions*"	Yield (%)	dr	ee (%)
1	**none**	**88**	**>20:1**	**98**
2	no $CrCl_2$	<2	-	-
3	no (*S*,*R*)-**L1**	24	1:1	-
4	Propargyl Cl, instead of Br	76	>20:1	98
5	TMSCl, instead of Cp_2ZrCl_2	18	>20:1	-
6	TESCl, instead of Cp_2ZrCl_2	<2	-	-
7	Me_2SiCl_2, instead of Cp_2ZrCl_2	60	20:1	96
8	Zn, instead of Mn	9	15:1	-
9	THF, instead of DME	72	>20:1	95
10	MeCN, instead of DME	75	11:1	90
11	0.1 M, instead of 0.05 M, in DME	81	>20:1	95
12	1.0, instead of 1.5, equiv Cp_2ZrCl_2	70	>20:1	99
13	5 mol% $CrCl_2$, 6 mol% (*S*,*R*)-**L1**	84	>20:1	99

Scope of Substrates-Aromatic Aldehydes

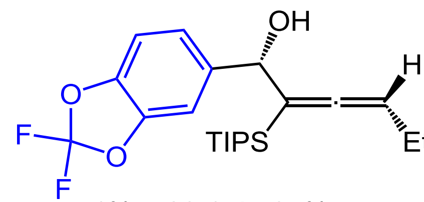




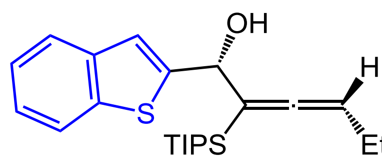
R = H	81%, >20:1 dr, 98% ee
R = F	78%, >20:1 dr, 98% ee
R = Cl	75%, >20:1 dr, 95% ee
R = Br	70%, >20:1 dr, 96% ee
R = OMe	57%, >20:1 dr, 97% ee
R = SMe	71%, >20:1 dr, 95% ee
R = Bpin	58%, >20:1 dr, 96% ee
R = SO_2Me	68%, >20:1 dr, 94% ee
R = CF_3	65%, >20:1 dr, 95% ee
R = COOMe	72%, >20:1 dr, 96% ee
R = CN	61%, >20:1 dr, 95% ee



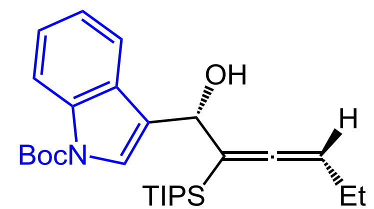
88%, >20:1 dr, 98% ee



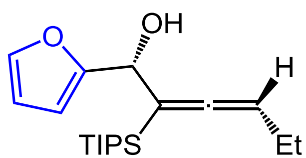
71%, >20:1 dr, 95% ee



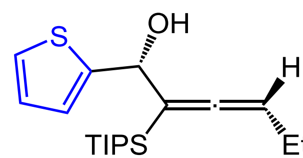
84%, >20:1 dr, 97% ee



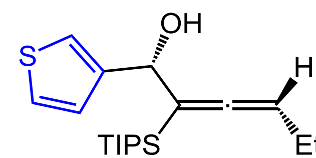
53%, >20:1 dr, 95% ee



83%, >20:1 dr, 96% ee

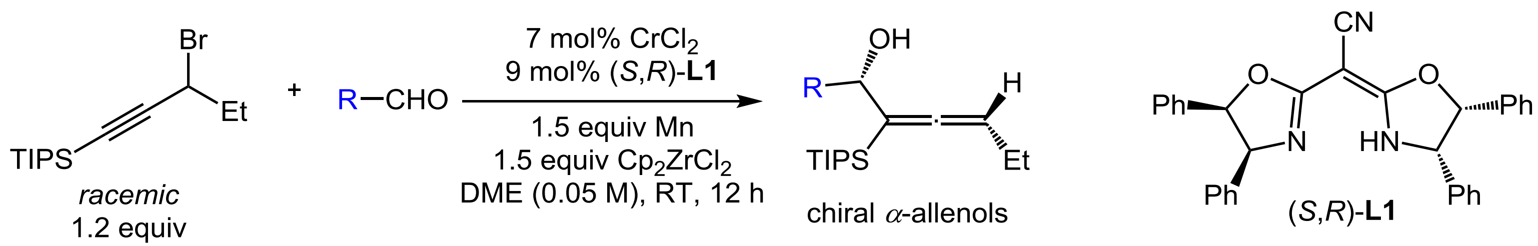


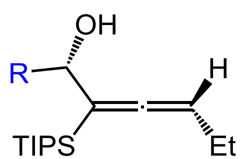
85%, >20:1 dr, 98% ee



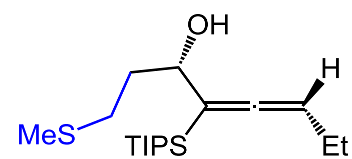
76%, >20:1 dr, 95% ee

Scope of Substrates-Aliphatic Aldehydes

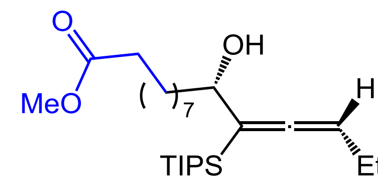




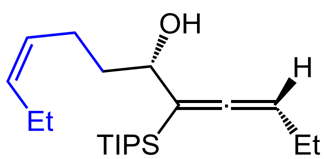
R = CH_2Bn 78%, >20:1 dr, 94% ee
R = $CH_2{}^iPr$ 82%, >20:1 dr, 96% ee
R = ^iPr 88%, >20:1 dr, 98% ee
R = Cy 82%, >20:1 dr, 97% ee



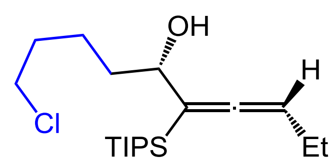
78%, >20:1 dr, 93% ee



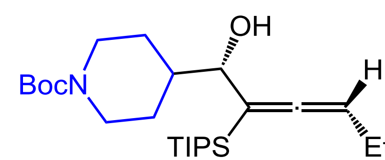
79%, >20:1 dr, 97% ee



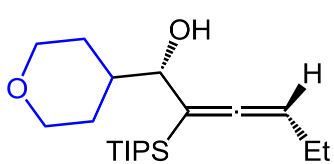
84%, >20:1 dr, 95% ee



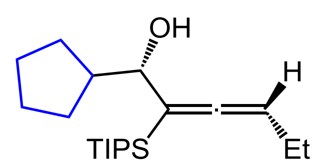
80%, >20:1 dr, 92% ee



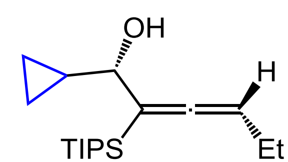
84%, >20:1 dr, 99% ee



78%, >20:1 dr, 97% ee

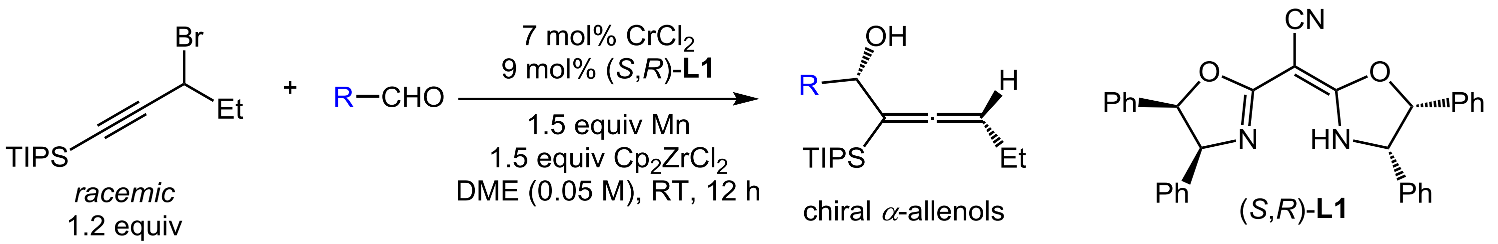


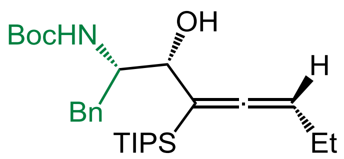
79%, >20:1 dr, 97% ee



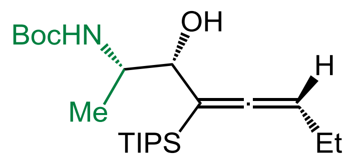
74%, >20:1 dr, 97% ee

Scope of Substrates-Chiral Aldehydes

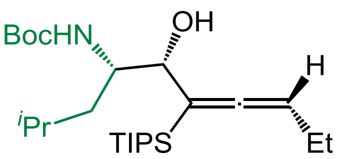




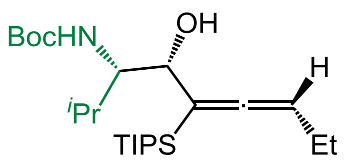
from ***L*-Phenylalanine**
60%, >20:1 dr



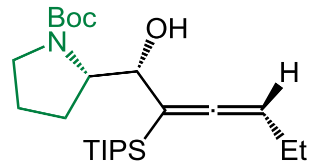
from ***L*-Alanine**
84%, >20:1 dr



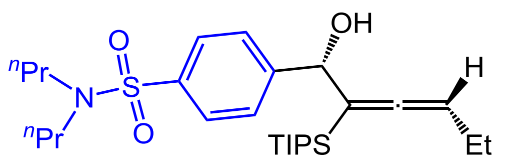
from ***L*-Leucine**
77%, >20:1 dr



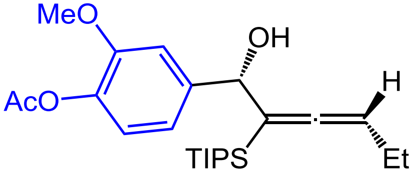
from ***L*-Valine**
60%, 6:1 dr



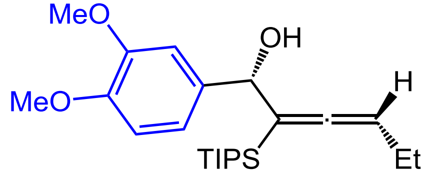
from ***L*-Proline**
30%, >20:1 dr



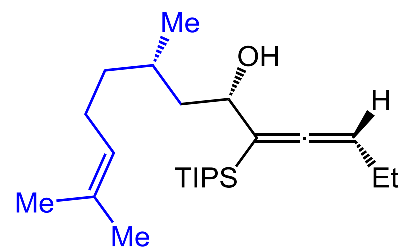
from **Probenecid**
75%, >20:1 dr, 96% ee



from **Vanillin acetate**
80%, >20:1 dr, 96% ee

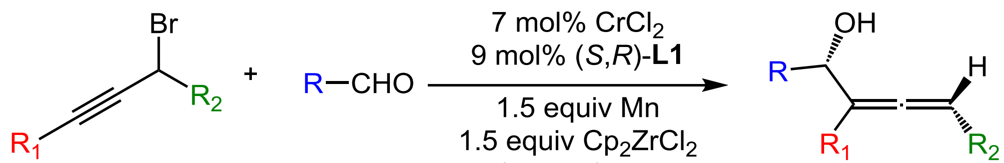


from **Veratraldehyde**
70%, >20:1 dr, 96% ee



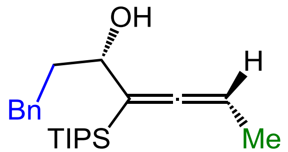
from **(-)-Citronellal**
81%, >20:1 dr

Scope of Substrates

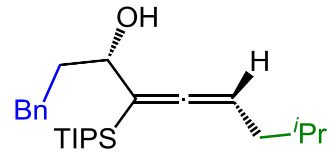


racemic
1.2 equiv

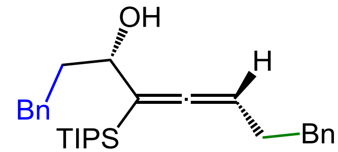
chiral α-allenols



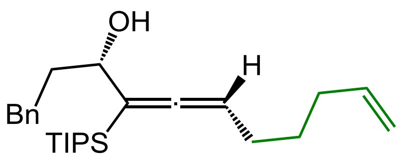
81%, >20:1 dr, 93% ee



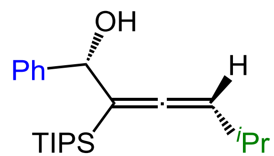
71%, >20:1 dr, 89% ee



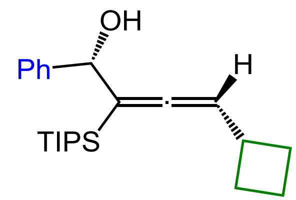
69%, 10:1 dr, 89% ee



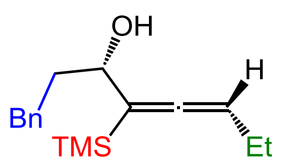
82%, >20:1 dr, 92% ee



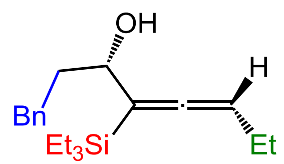
51%, >20:1 dr, 94% ee



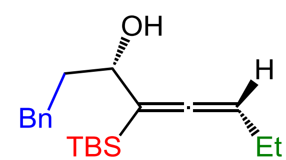
64%, >20:1 dr, 94% ee



68%, >20:1 dr, 98% ee



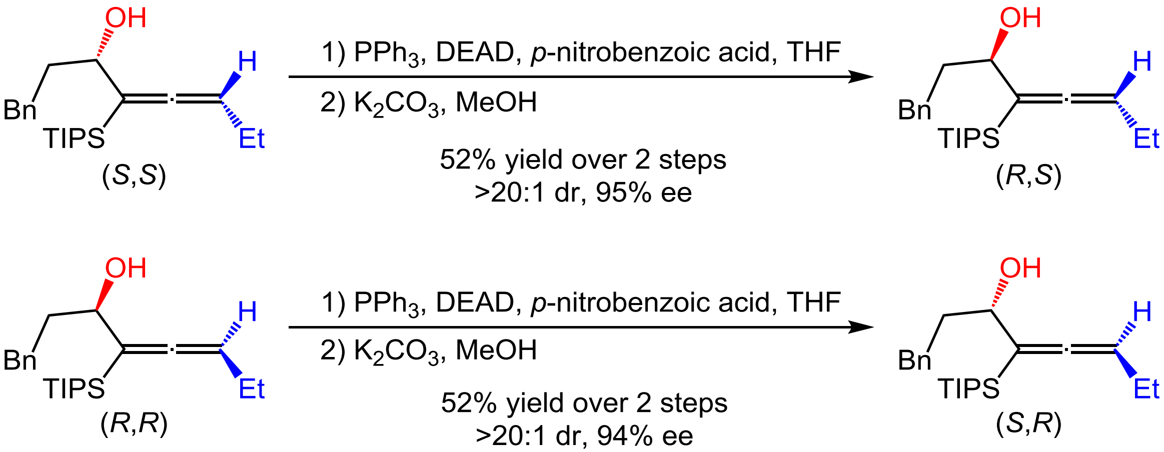
73%, >20:1 dr, 96% ee



85%, >20:1 dr, 96% ee

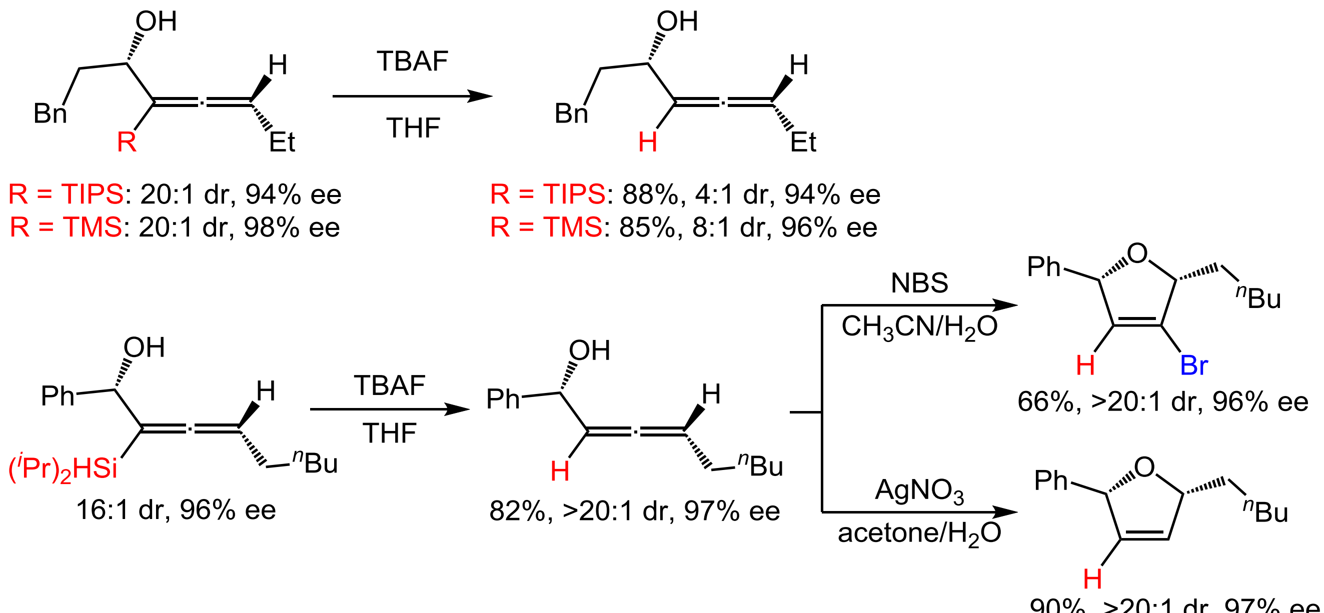
Access to All Stereoisomers

a) Access to all stereoisomers

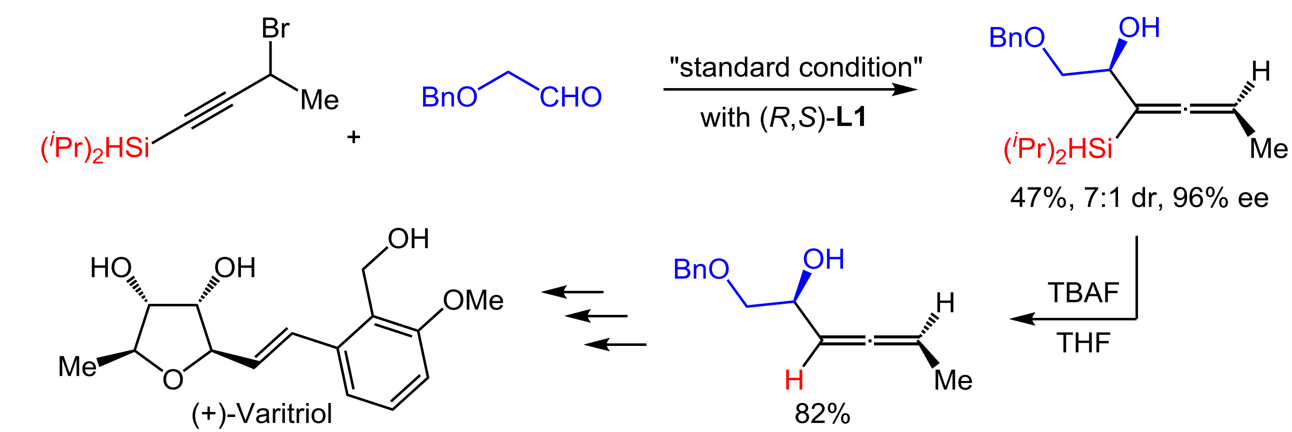


Post-functionalizations

b) Synthetic transformations

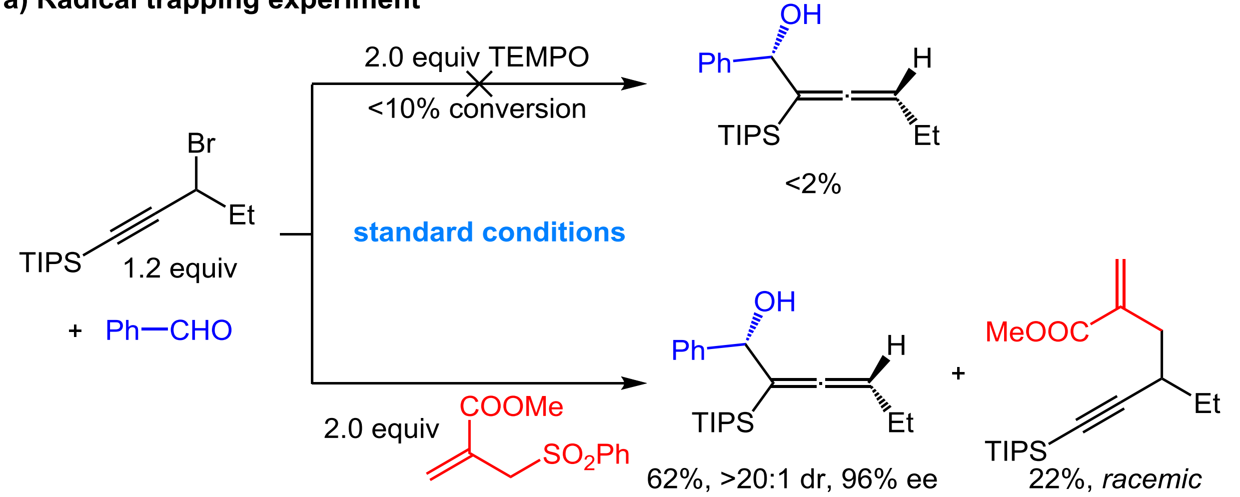


c) Application in formal total synthesis

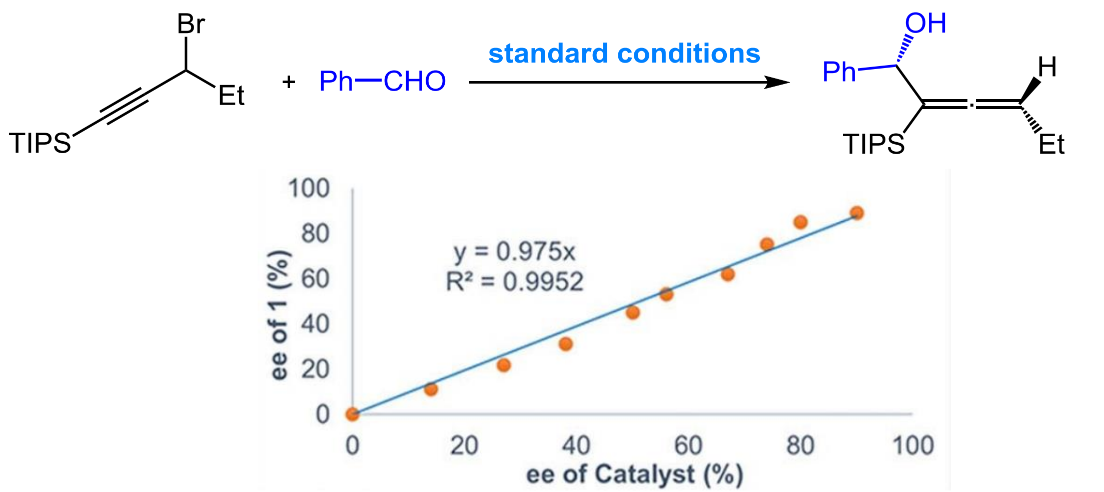


Preliminary Mechanistic Study

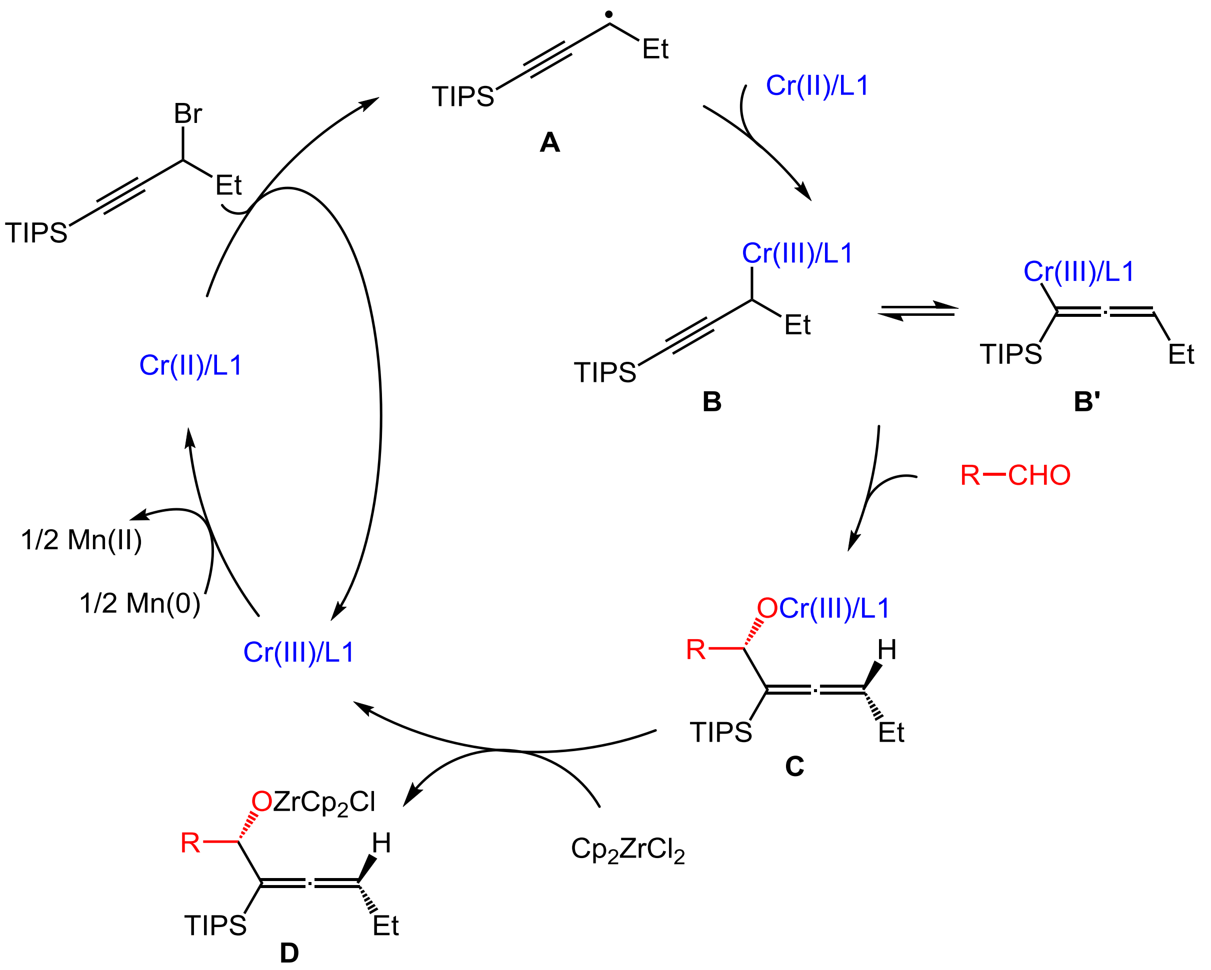
a) Radical trapping experiment



b) Non-linear effect study



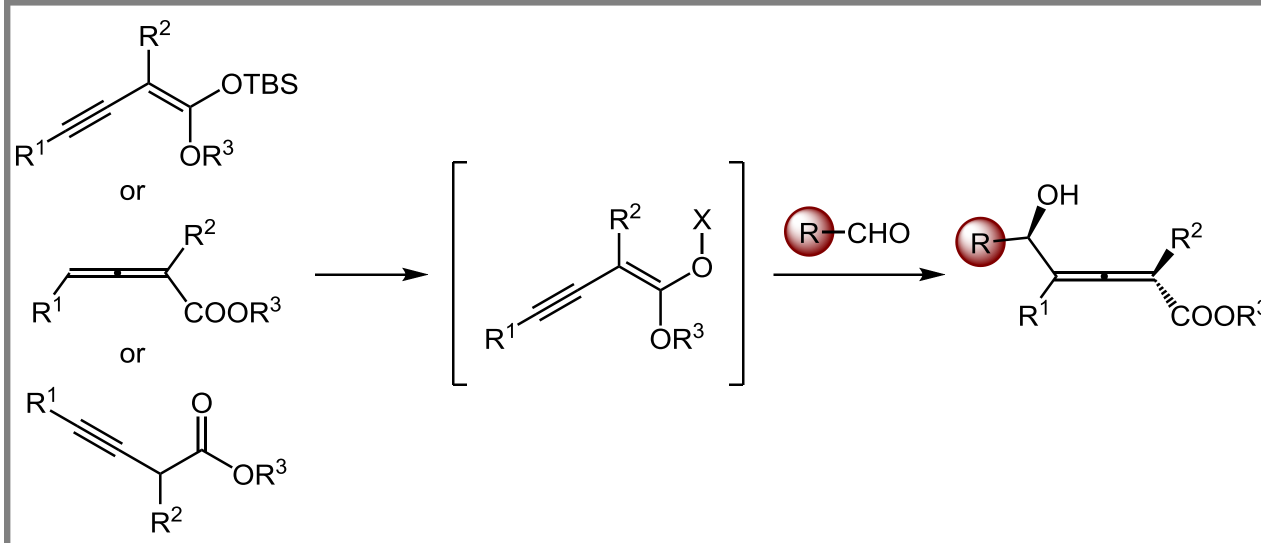
Proposed Mechanism



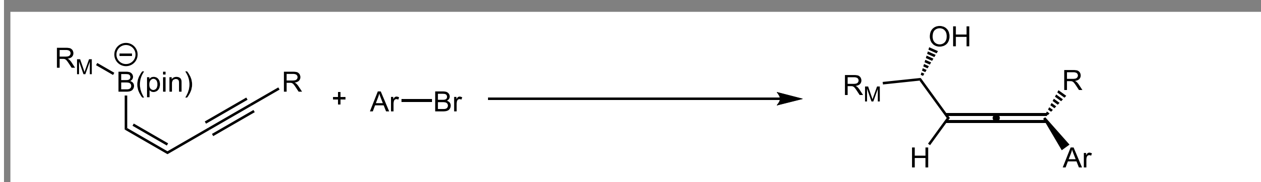
Summary

Catalytic asymmetric synthesis of *α*-allenols

1) Asymmetric alkynylogous aldol reaction

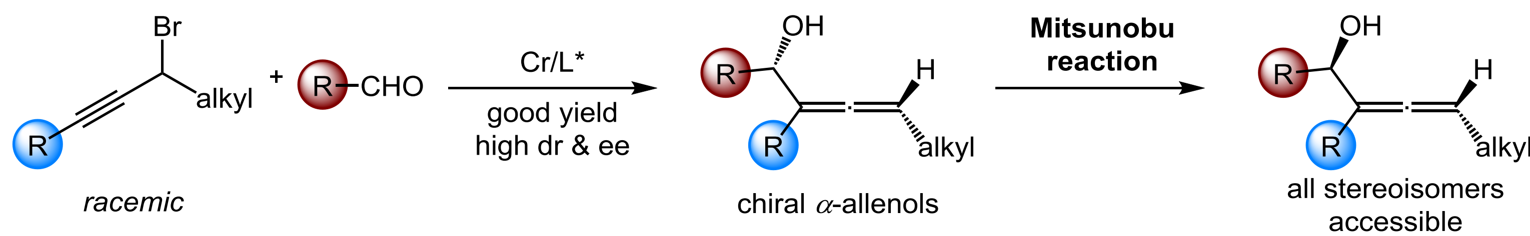


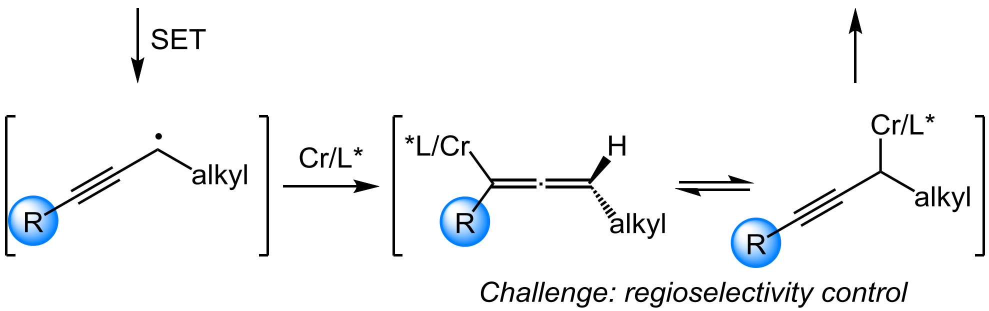
2) Asymmetric conjunctive cross-coupling reaction



Summary

Asymmetric synthesis of *α*-allenols from secondary propargyl bromides





- ♥Efficient construction of central & axial chirality
- ♥Good regio-, diastereo- & enantioselectivity
- ♥All stereoisomers accessible
- ♥Mild reaction condition & broad substrate scope

Wang, Z. *et al. Angew. Chem. Int. Ed.* **2022**, *61,* 10.1002/anie.202117114

The First Paragraph

写作思路

介绍手性联烯醇
的重要性

↓

介绍常用的合成方法
及前人工作的受限性

↓

引出自己的工作

The First Paragraph

Allenol has emerged as a common building block in organic synthesis in the last few decades. Structurally, allenols are composed of allene and alcohol functional groups with variable connectivity. The presence of both functionalities endows the rich chemical reactivity of such molecules. Among the diverse allenols, α-allenols bear the hydroxyl unit at the α-position and represent the most useful and studied subclass regarding synthesis and application. Due to the orthogonal distribution of cumulene molecular orbitals, α-allenols can have both axial and central chiralities when differently substituted. These chiral α-allenols have served as valuable substrates in a wide range of transformations, including cycloaddition, cycloisomerization, electrophilic addition, and Pd-catalyzed coupling reactions. Moreover, they have also been used as key intermediates in the synthesis of many natural products and bioactive molecules.

The Last Paragraph

写作思路

铬催化手性汇聚式
α–联烯醇的合成

↓

介绍工作亮点

The Last Paragraph

In summary, we have developed a Cr-catalyzed enantioconvergent allenylation reaction of aldehydes with racemic propargyl halides. This robust method employs simple and readily accessible materials, exhibits exceptional functional group tolerance and broad substrate scope, and provides facile access to a wide range of valuable optically enriched α-allenols with two or three continuous chiral centers, including both central and axial chirality. Further efforts are underway to develop generally efficient catalytic systems for radical-involved asymmetric alkylations of carbonyl compounds.

Representative Examples

In sharp contrast, the simultaneous efficient control over both axial and central chiralities **remains an elusive challenge.** (然而，…仍具挑战)

Its catalytic asymmetric variants have also received considerable attention, and **substantial** progress has been achieved. (重大的)

From a practical point of view, it is noteworthy that the yield of the allenylation product is only modestly diminished, if the concentration is increased from 0.05 M to 0.1 M, 1.0 equivalent of Cp_2ZrCl_2 is used, or 5 mol% $CrCl_2$ is used. (从实用的角度)

Thanks
for your attention