Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines

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Checker: Zhang-Pei Chen

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Ma, S. *et al.*
Angew. Chem. Int. Ed. **2013**, *52*, 441.

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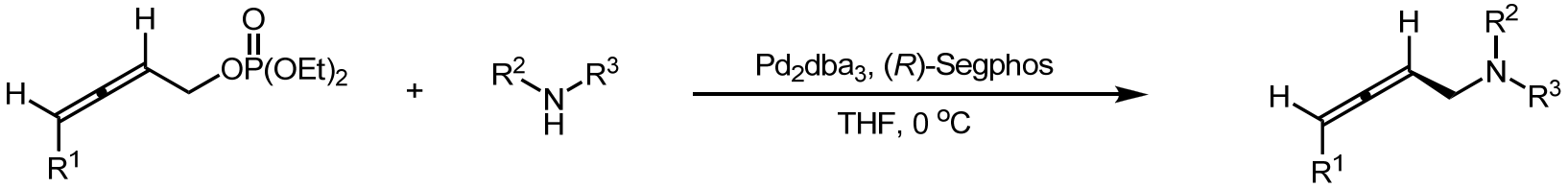
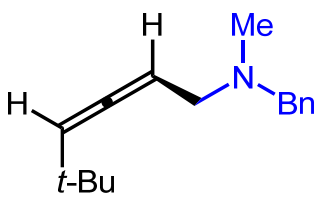
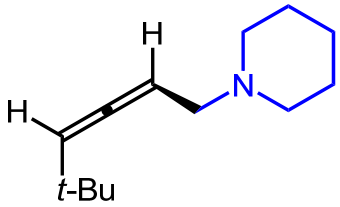
Asymmetric Amination and Imidation of Phosphates

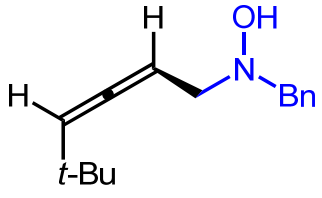




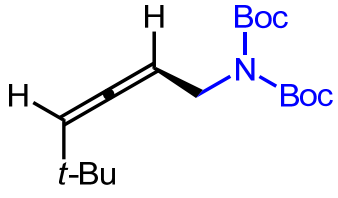
72%, 84% ee



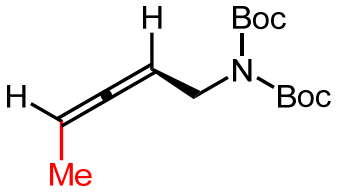
56%, 91% ee



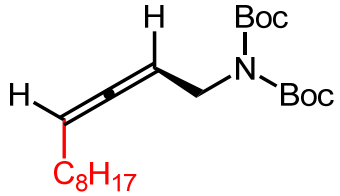
59%, 76% ee



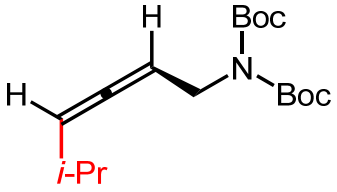
77%, 97% ee



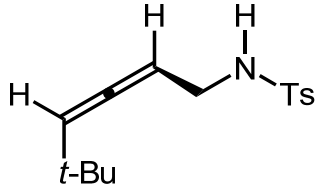
60%, 85% ee



85%, 82% ee



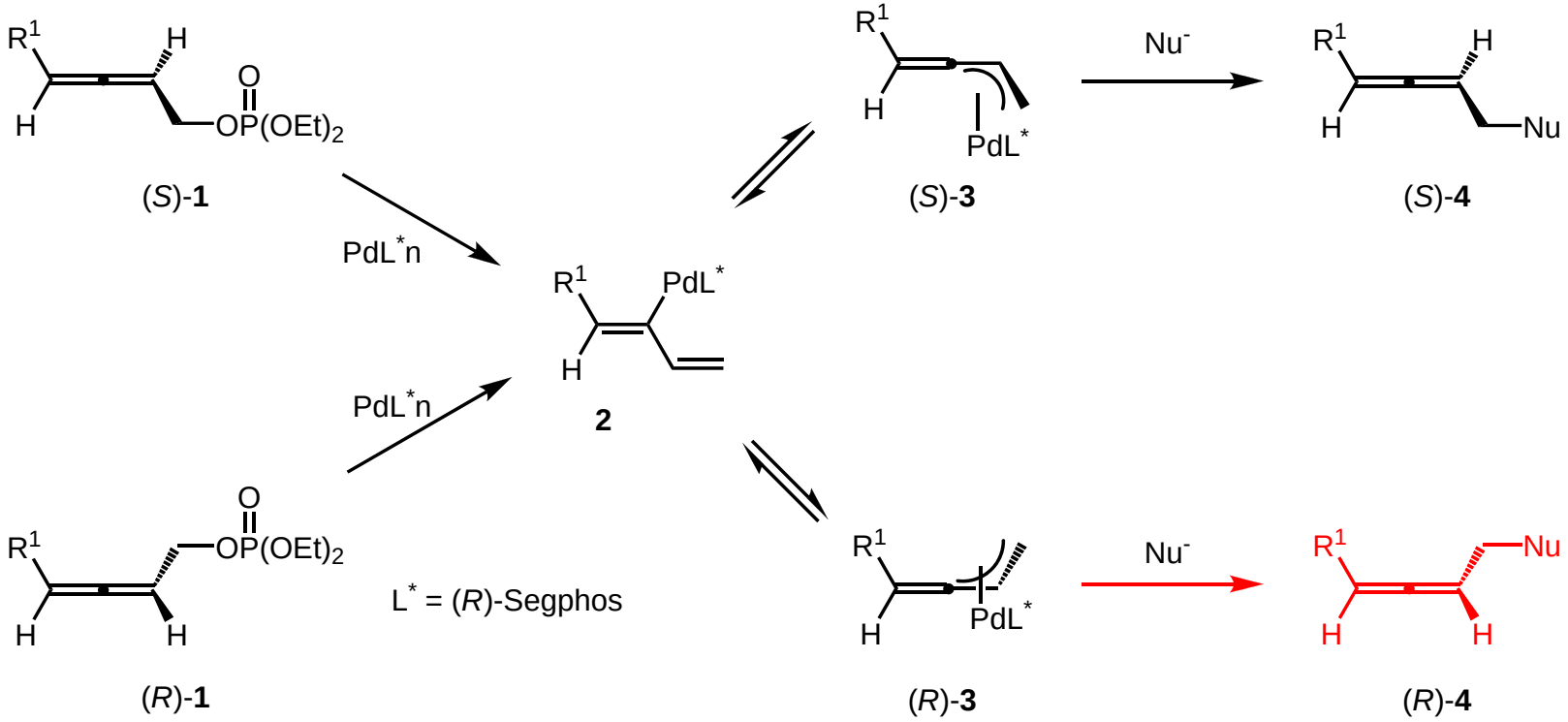
51%, 87% ee



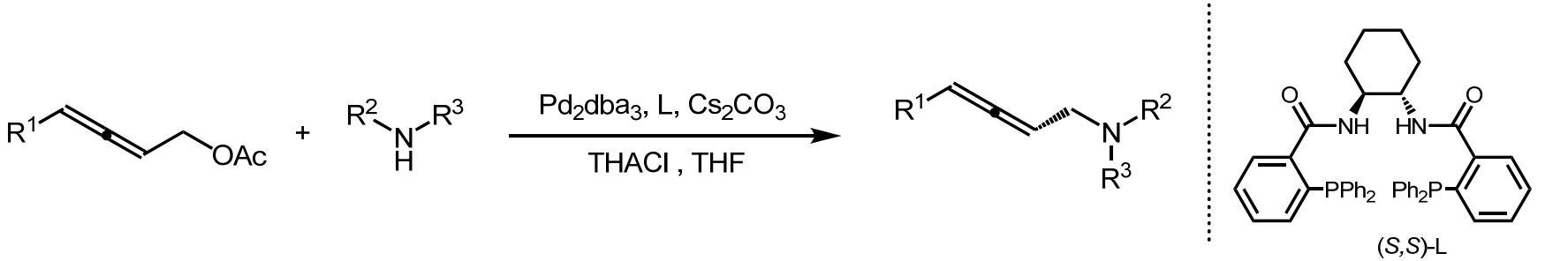
26%, 80% ee

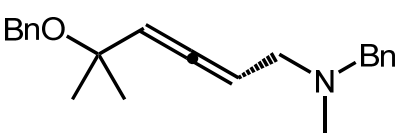
Imada, Y. *et al.* Org. *Lett.* **2005**, *7*, 5837.

Proposed Mechanism

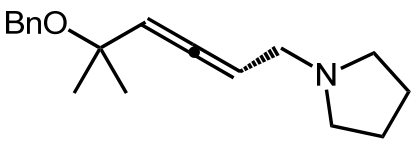


Asymmetric Amination of Acetates

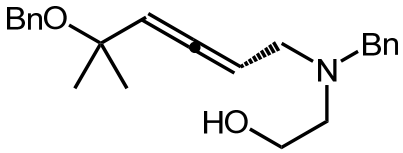




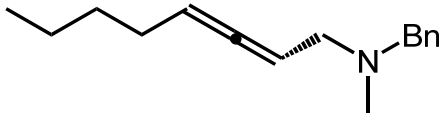
98%, 95% ee



86%, 89% ee



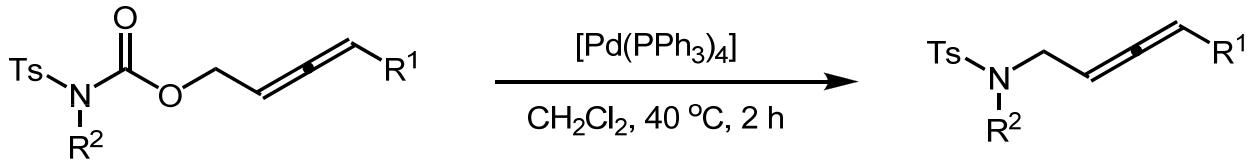
89%, 90% ee

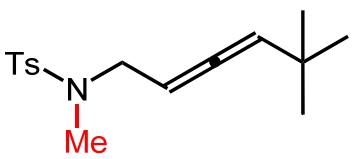


56%, 90% ee

Trost, B. M. *et al. J. Am. Chem. Soc.* **2005**, 127, 14186.

Decarboxylative Amination





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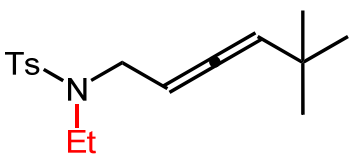
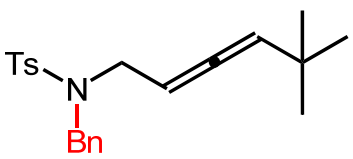


90%



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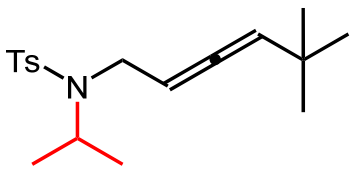

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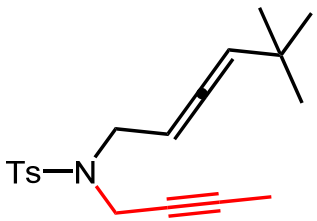

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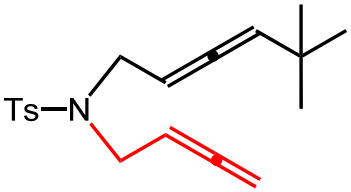
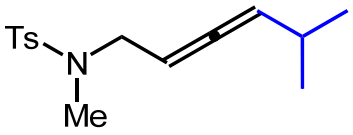
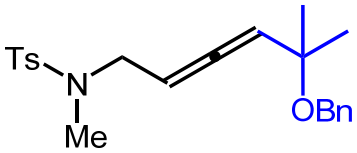


80%



77%



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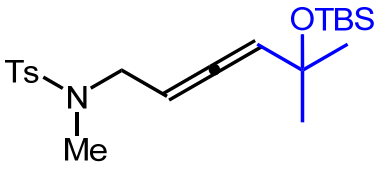
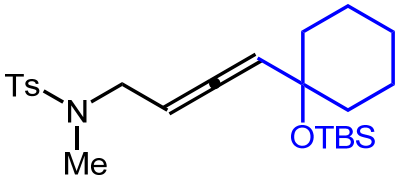


89%



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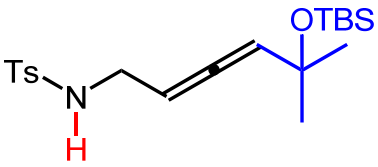
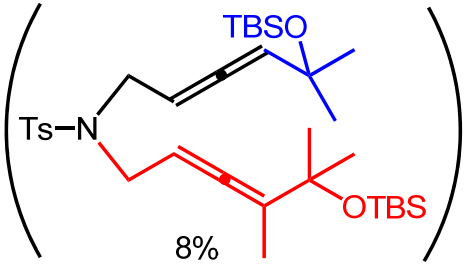


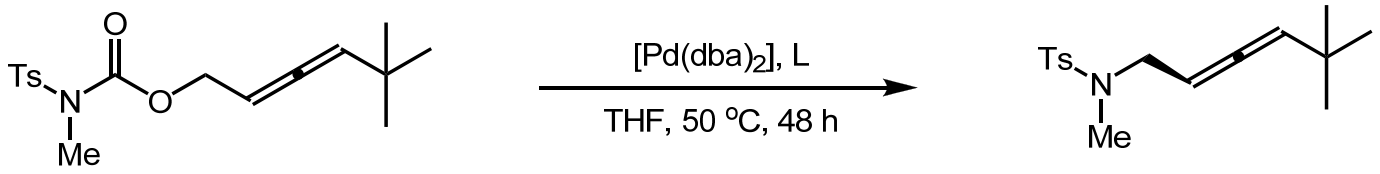
73%

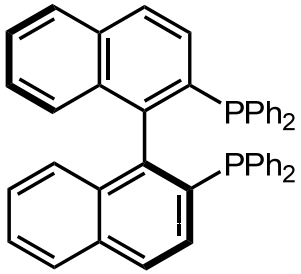


8%

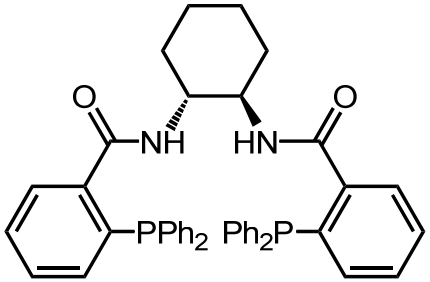
Ma, S. *et al*. *Angew. Chem. Int. Ed.* **2013**, *52*, 441.

Enantioselective Decarboxylative Amination

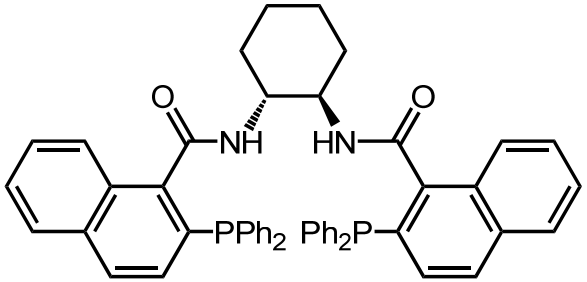




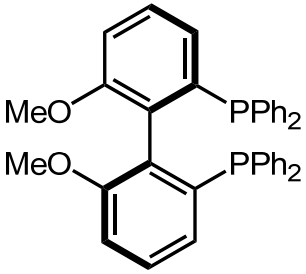
(*S*)-L1
80% yield, 22% ee



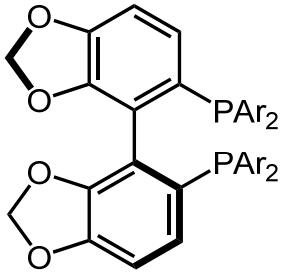
(*R*,*R*)-L2
n.d.



(*R*,*R*)-L3
n.d.

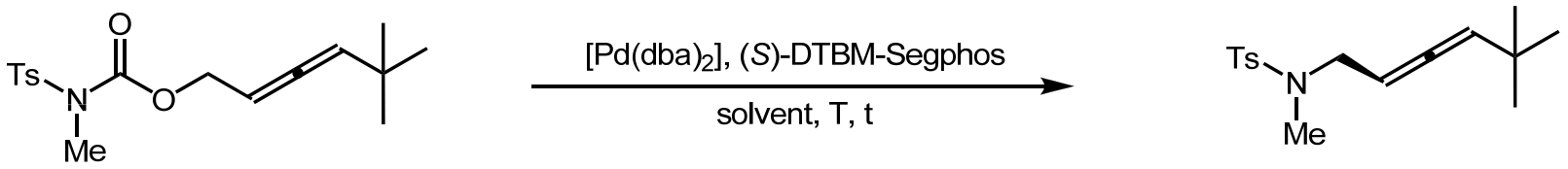


(*R*)-L4
79% yield, -63% ee



(*S*)-Segphos: Ar = Ph, 87% yield, 66% ee
(*S*)-DM-Segphos: Ar = 3,5-$Me_2C_6H_3$, 81% yield, 66% ee
(*S*)-DTMB-Segphos: Ar = 3,5-*t*Bu_2-4-$MeOC_6H_2$, 33% yield, 86% ee

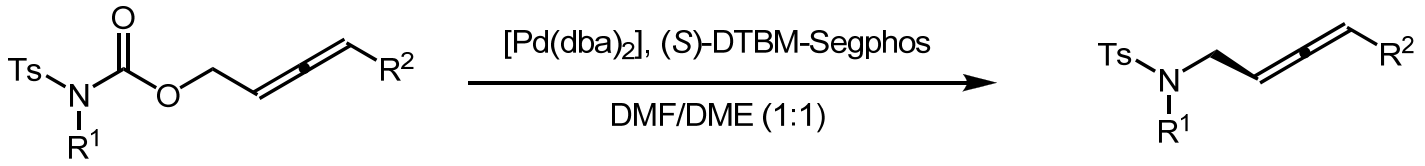
Enantioselective Decarboxylative Amination

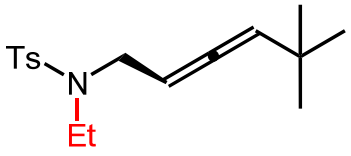


5a **6a**

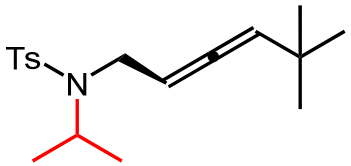
Entry	Solvent	T (°C)	t (h)	5a (rec.) (%)	6a	
					Yield (%)	Ee (%)
1	THF	50	48	52	33	86
2	1,4-Dioxane	50	48	12	75	82
3	DME	50	48	29	40	87
4	CH_2Cl_2	50	48	67	20	74
5	Toluene	50	48	17	70	84
6	DMF	50	48	0	85	88
7	DMF	25	96	0	79	91
8	DMF/DME	25	84	0	88	92

Enantioselective Decarboxylative Amination

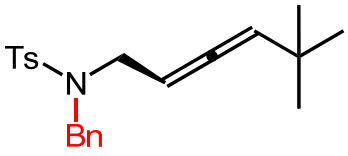




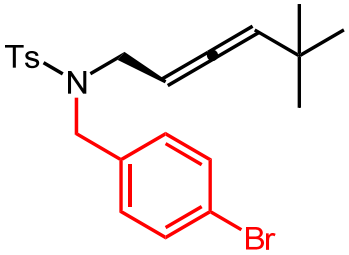
84%, 94% ee



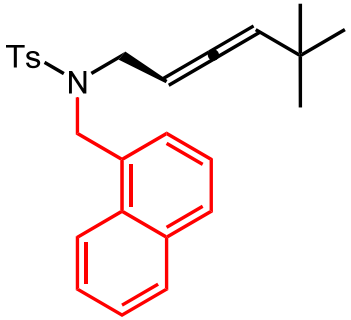
82%, 97% ee



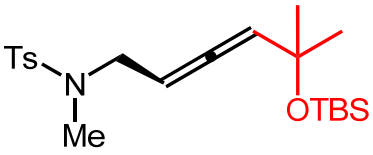
78%, 93% ee



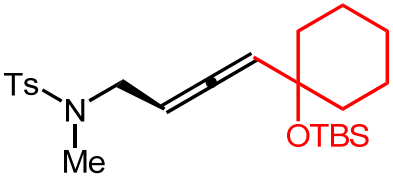
85%, 92% ee



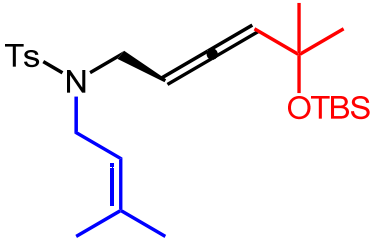
76%, 91% ee



91%, 93% ee

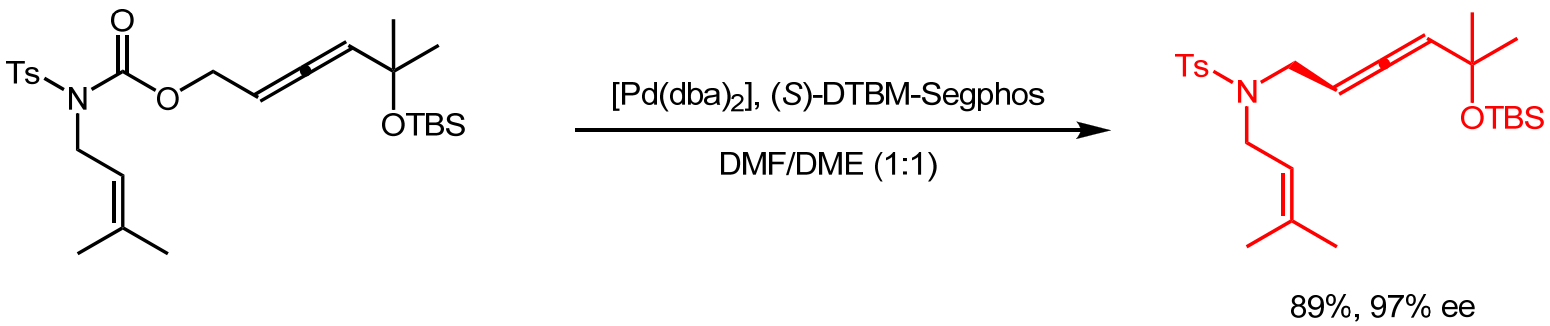


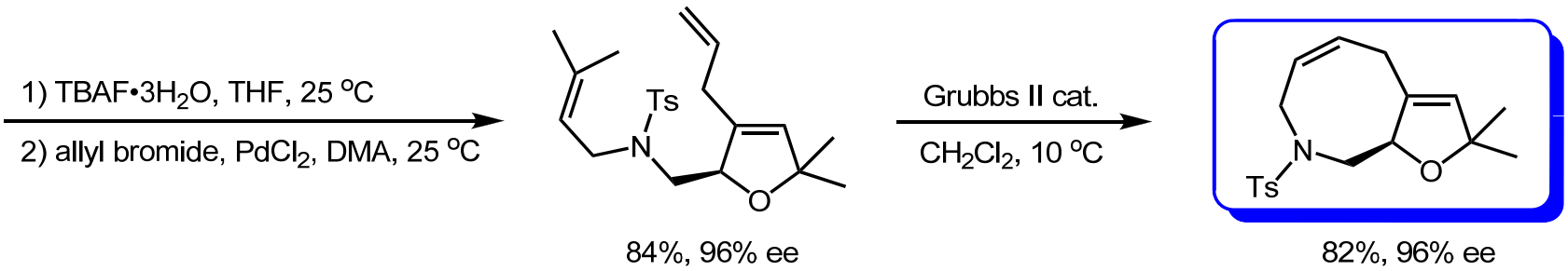
90%, 93% ee



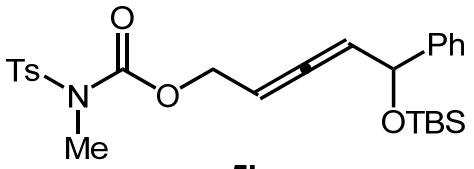
88%, 97% ee

Synthesis of 2,5-Dihydrofuran Derivatives





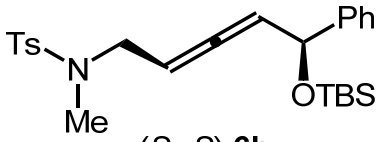
Enantioselective Decarboxylative Amination



5b

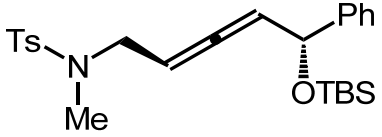
$[Pd(dba)_2]$, (*S*)-DTBM-Segphos

DMF/DME (1:1)

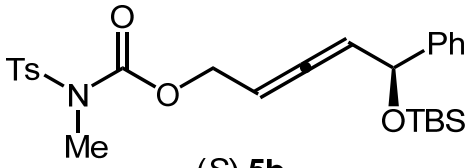


(S_a,*S*)-**6b**
94% de, 98% ee

+



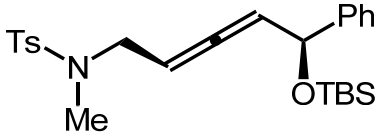
(S_a,*R*)-**6b**
98% de, 94% ee



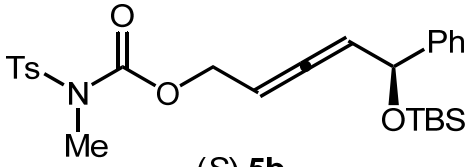
(*S*)-**5b**
96% ee

$[Pd(dba)_2]$, (*S*)-DTBM-Segphos

DMF/DME (1:1)



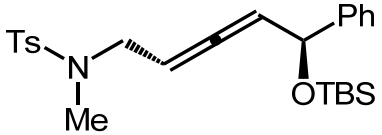
(S_a,*S*)-**6b**
93% de, >99% ee



(*S*)-**5b**
96% ee

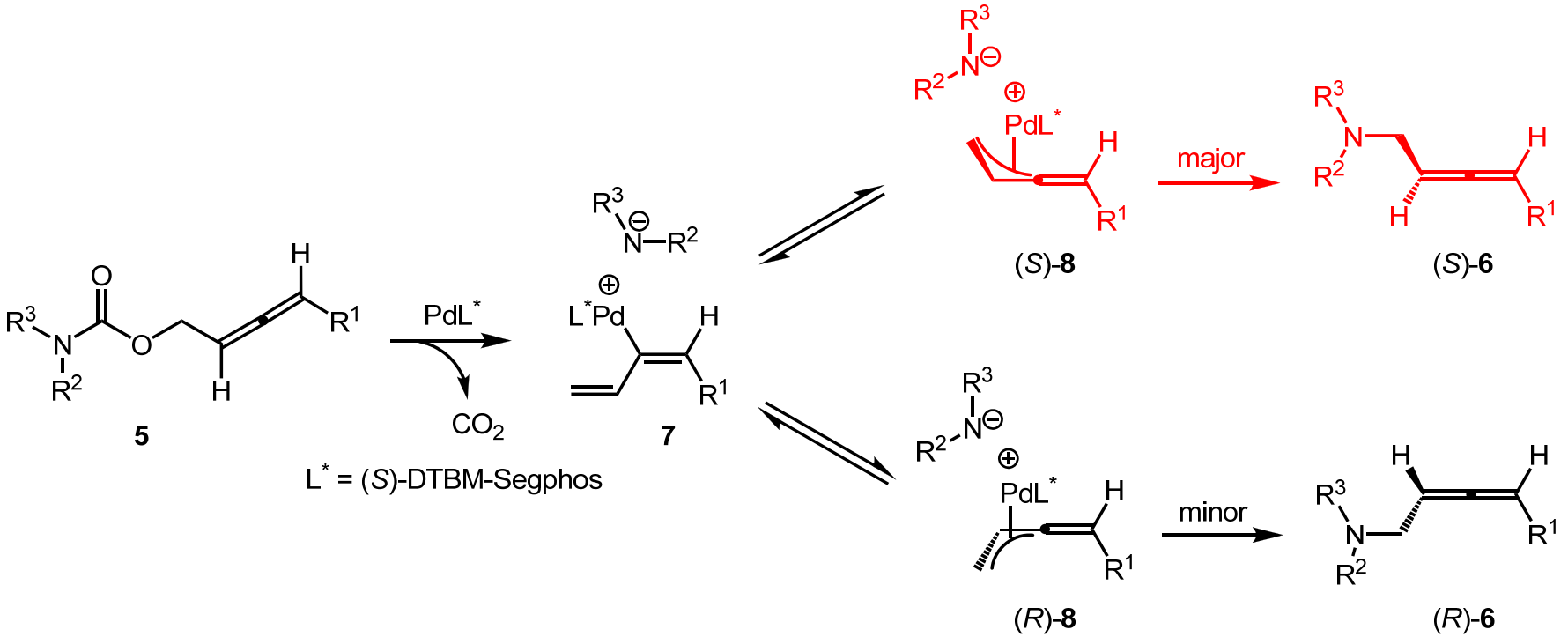
$[Pd(dba)_2]$, (*R*)-DTBM-Segphos

DMF/DME (1:1)



(R_a,*S*)-**6b**
97% de, 99% ee

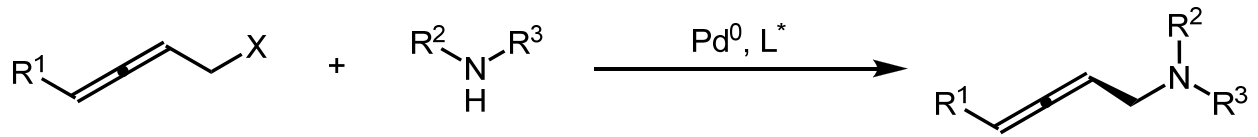
Proposed Mechanism



Summary

Intermolecular Reaction

Trost & Imada

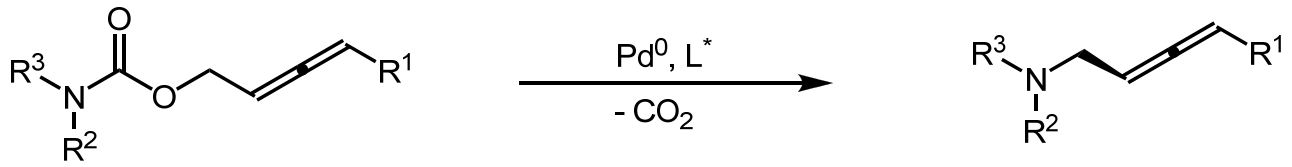


X = OAc or $OPO(OEt)_2$

up to 98% yield
76-97% ee

Decarboxylative Coupling

Ma



up to 93% yield
91-99% ee

Naturally occurring biomolecules that display chirality are enantiomerically enriched and different enantiomers show different biological activities. Thus, the development of new enantioselective approaches for chiral compounds are still of great interest. Allenes are now an important class of compounds and versatile intermediates in organic synthesis. Thus, efficient methodologies for synthesizing allenes is of current interest for organic chemists. The synthesis of axially chiral allenes are particularly important because of their efficient chirality transfer and their existence as core structures in natural products and pharmaceuticals. Typically, the synthesis of axially chiral allenes relies on the resolution of racemic allenic precursors and the chirality transfer of chiral propargyl alcohols or propargyl amine derivatives. However, most of these procedures require stoichiometric amounts of enantiomerically enriched chiral compounds, and are thus inefficient. Recently, asymmetric catalysis for the synthesis of chiral allenes has attracted much attention. Trost et al. and Imada et al. have independently reported the asymmetric synthesis of allenyl amines with 76-91% ee by using intermolecular reactions. Interestingly, in two reported examples, 95 or 97 % of ee has been realized. Herein, we disclose a different protocol for the construction of axially chiral allenyl amines, bearing an extra hydroxy group or C=C bond, by the decarboxylative amination of allenyl N-tosylcarbamates; the products are obtained in 91-99% ee.

In conclusion, a novel intramolecular decarboxylative amination protocol for the synthesis of axially chiral allenes containing synthetically attractive functionalities has been developed with excellent enantioselectivities and good yields. The synthetic utility of optically active allenyl amines involving axial-to-central chirality transfer and the extra functionalities, such as an alcohol and C=C bond, should make this protocol of particular value in organic and medicinal chemistry. Further studies to expand the scope of this reaction and application of the chiral products are ongoing in our laboratory.