
Literature Report 2013-03-19

Huang, W.-X. checker: Cai, X.-F.

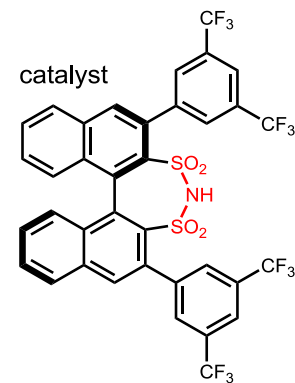
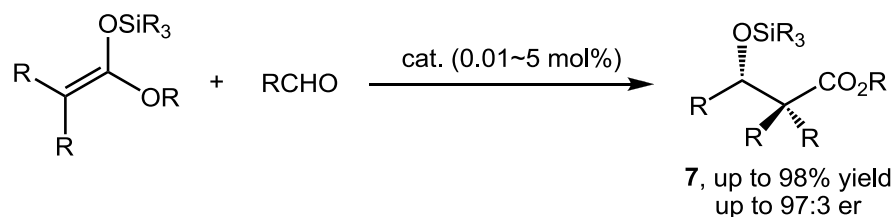
Asymmetric Synthesis of α -Branched Nitriles

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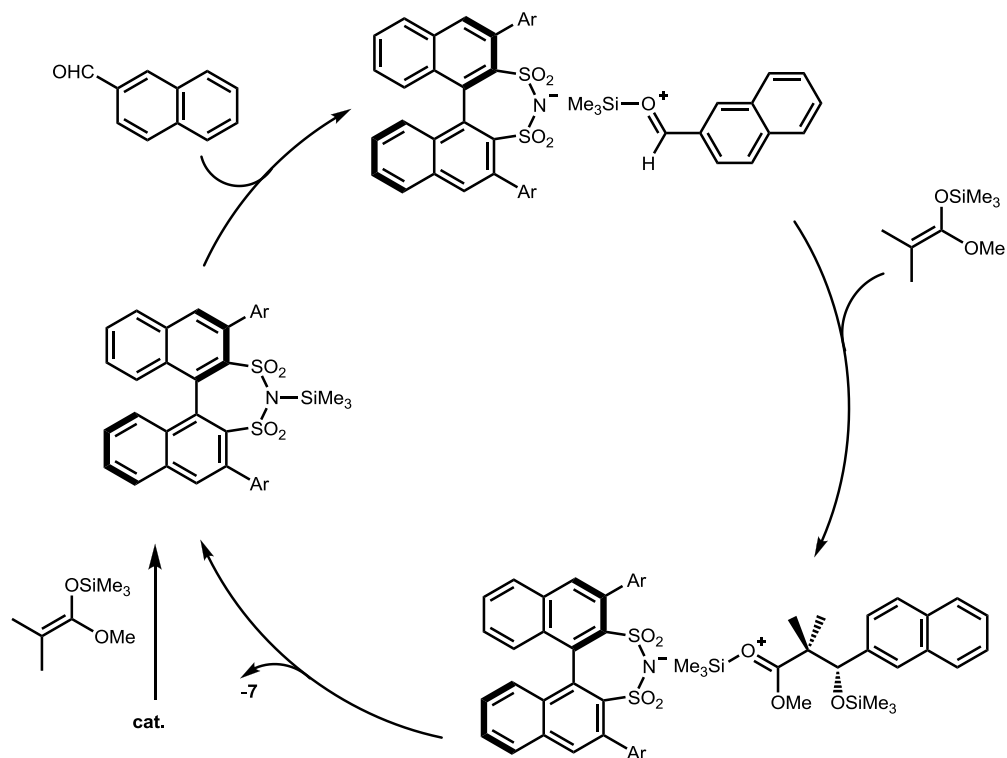
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1. Asymmetric Synthesis of α -Branched Nitriles via Protonation

Scheme 1

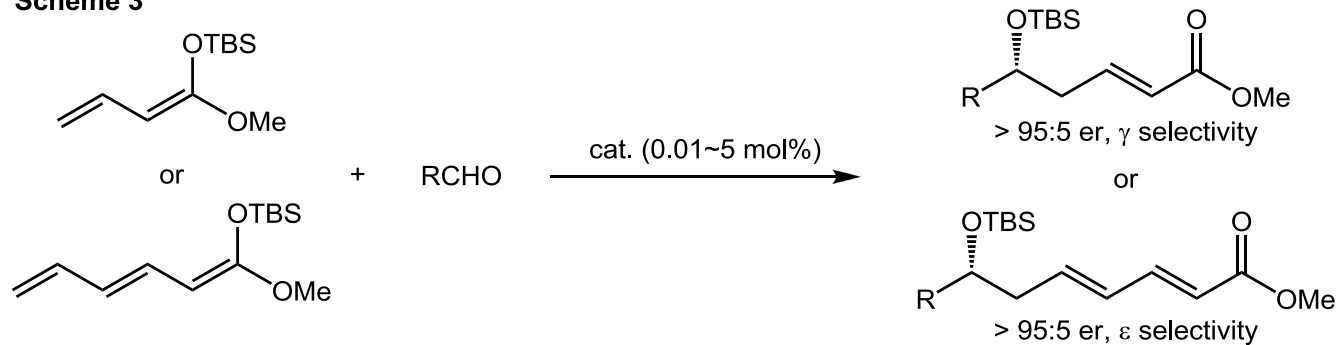


Scheme 2



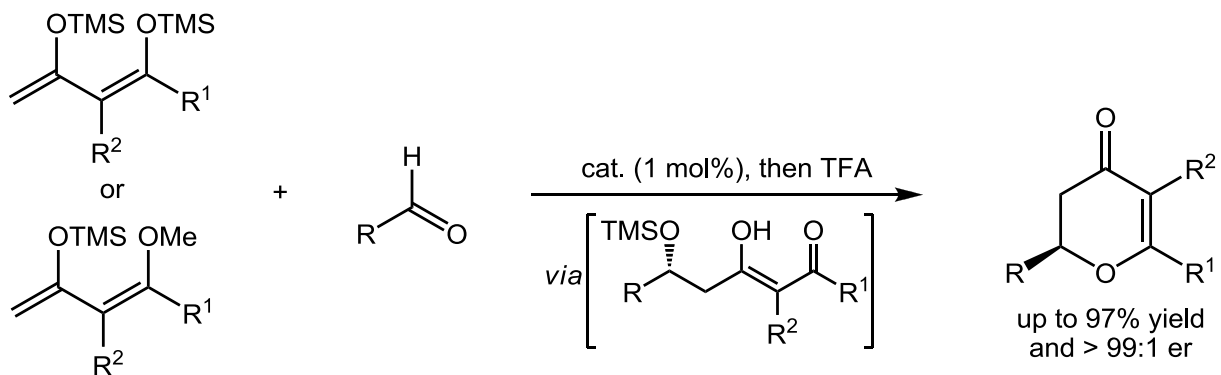
List, B. *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 4363-4366.

Scheme 3



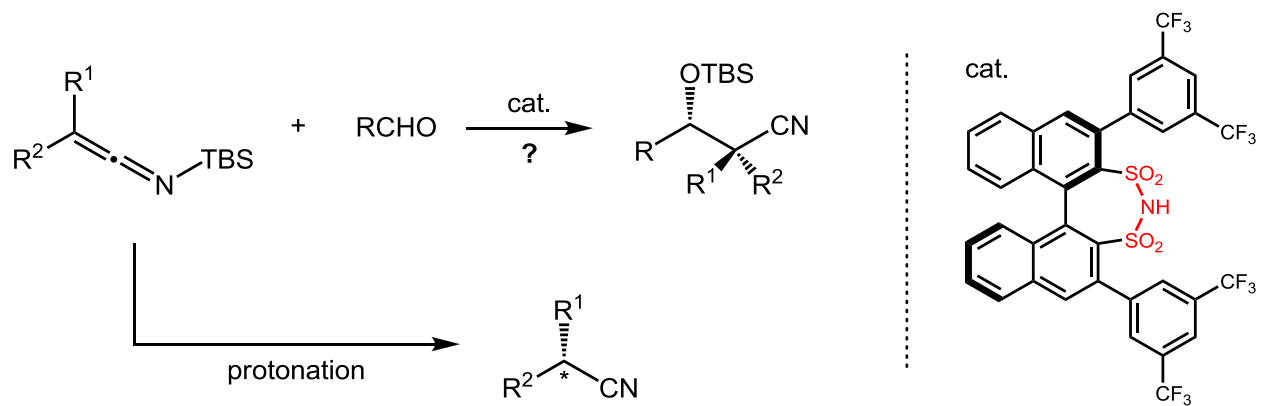
List, B. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 754-758.

Scheme 4



List, B. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 8859-8863.

Scheme 5



Scheme 6

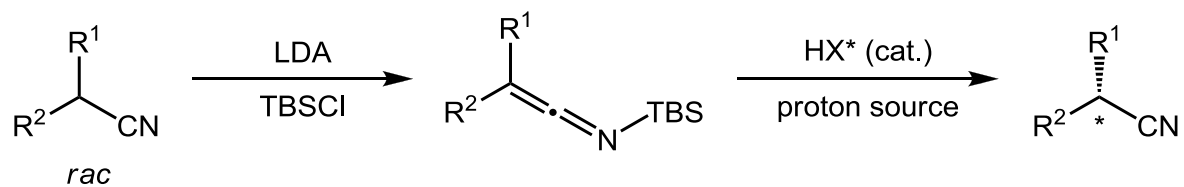
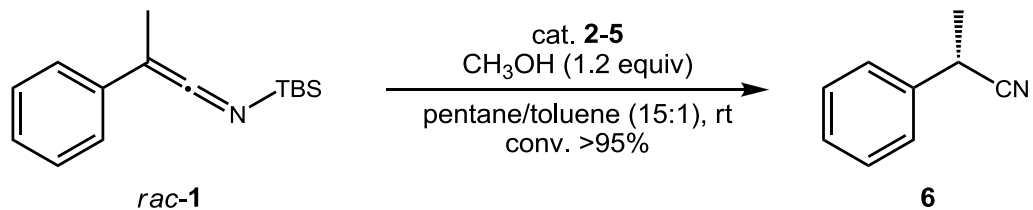
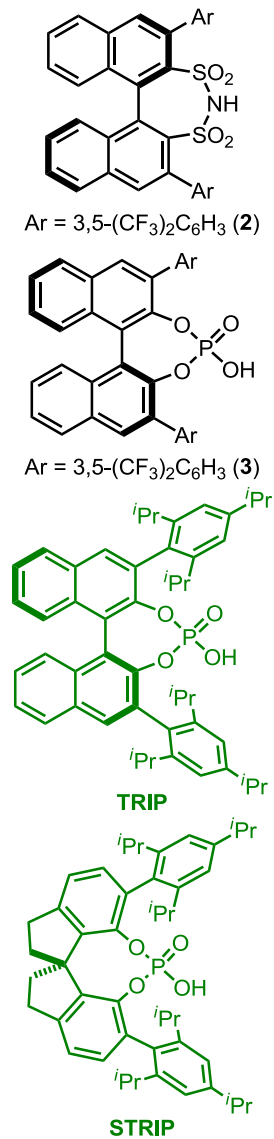


Table 1

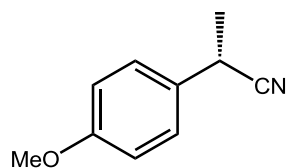
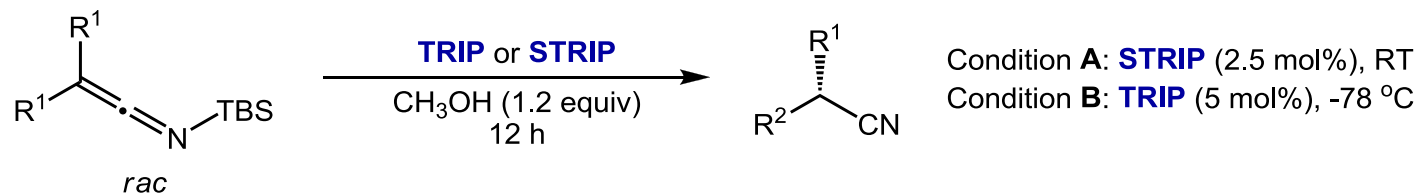


entry	cat (mol%)	t (h)	er
1	2 (5.0)	2	60:40
2	3 (5.0)	6	53:47
5	TRIP (5.0)	6	92:8
6 ^a	TRIP (5.0)	12	96:4
7 ^a	TRIP (2.5)	24	64:36
8	STRIP (5.0)	6	96:4
9	STRIP (2.5)	12	96:4

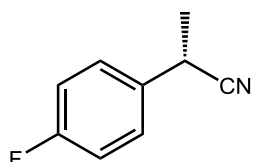
^aReactions were performed at $-78\text{ }^\circ\text{C}$.



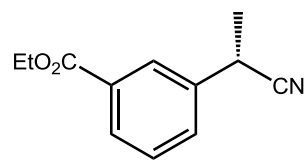
List, B. *et al.* *J. Am. Chem. Soc.* **2013**, 135, 2100–2103.

Table 2

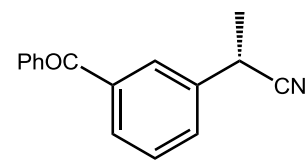
A: 82%, 95:5 er



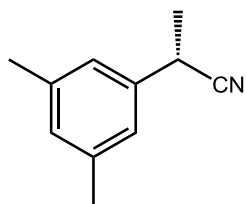
A: 85%, 97:3 er



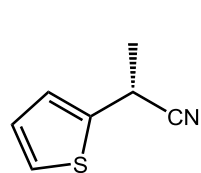
A: 92%, 90:10 er



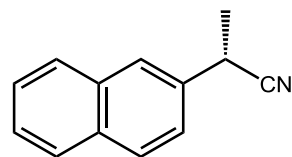
A: 87%, 91:9 er



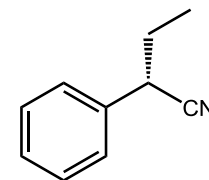
B: 94%, 97:3 er



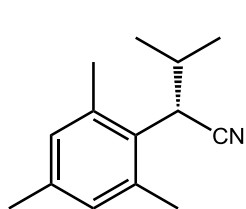
B: 82%, 97:3 er



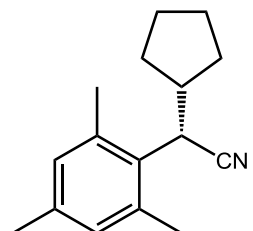
B: 97%, 94:6 er



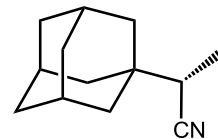
B: 90%, 93:7 er



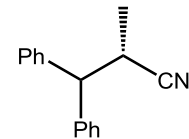
B: 97%, 98:2 er



B: 90%, 98:2 er

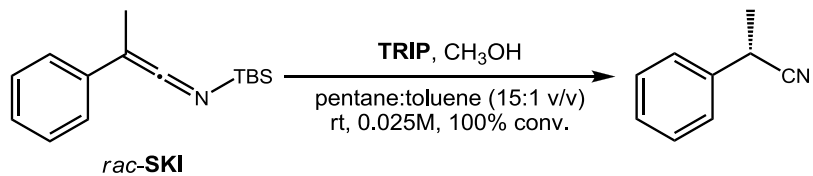


B: 94%, 85:15 er



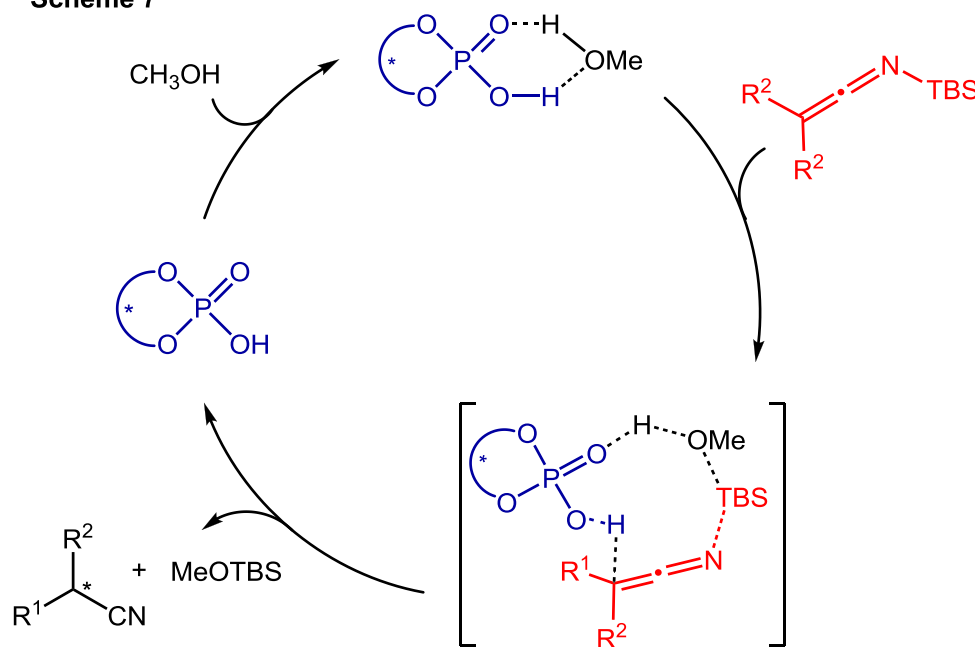
B: 91%, 57:43 er

Table 3



entry	TRIP (mol%)	CH ₃ OH	t (h)	er
1	110.0	-	6	59:41
2	5.0	1.2 eq.	6	92:8
3 ^a	5.0	1.2 eq.	36	87:13

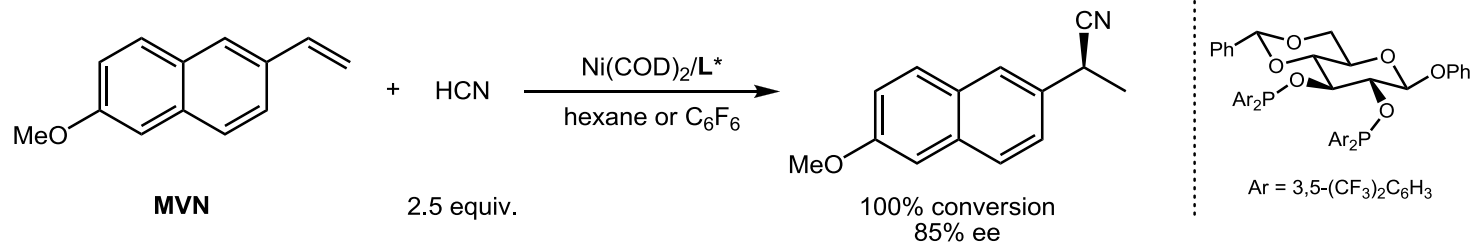
Scheme 7



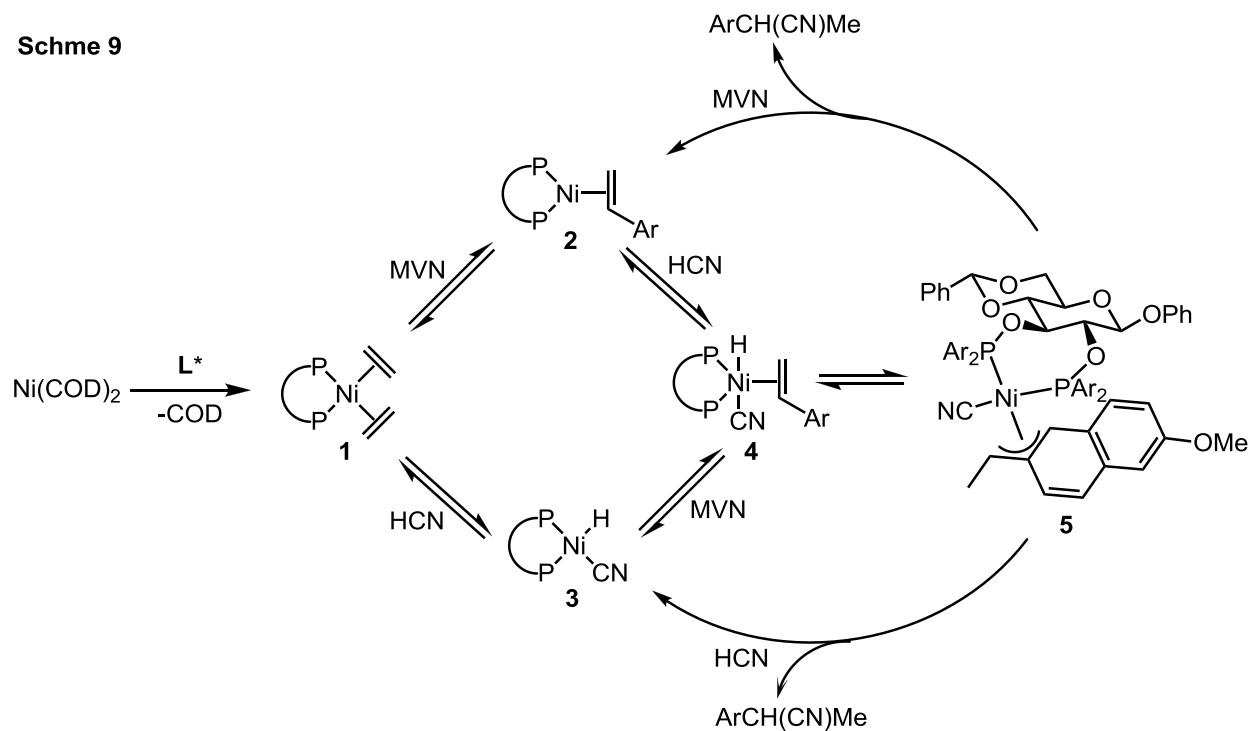
^aSKI was introduced into the reaction mixture prior (15 min) to the proton source.

2. Hydrocyanation of Vinylarenes

Scheme 8



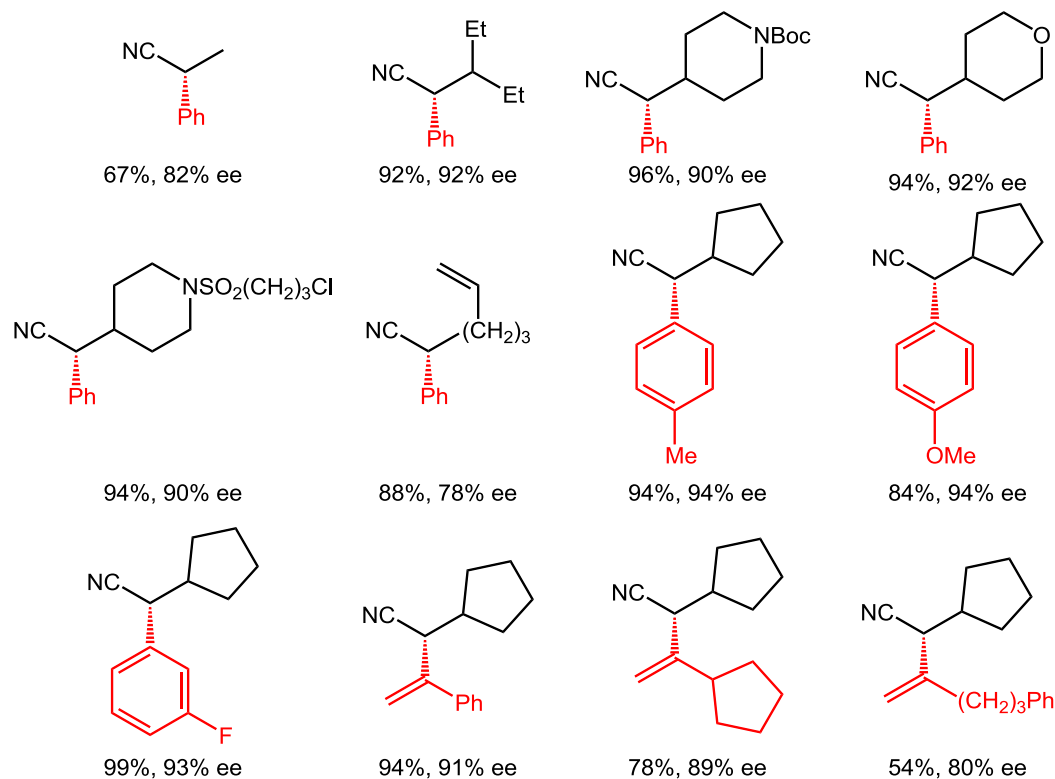
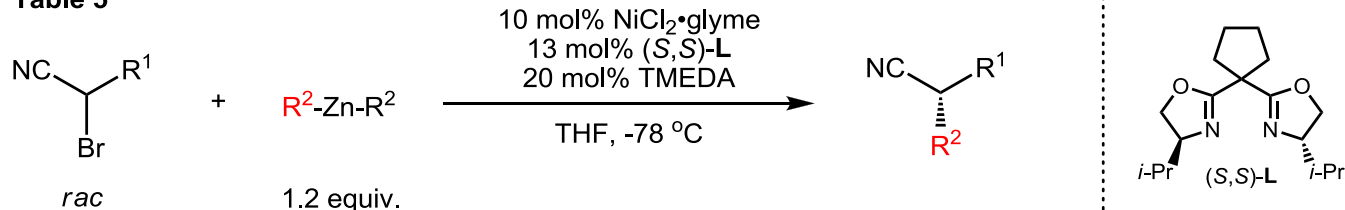
Scheme 9



RajanBabu, T. V.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, 116, 9869-9882.

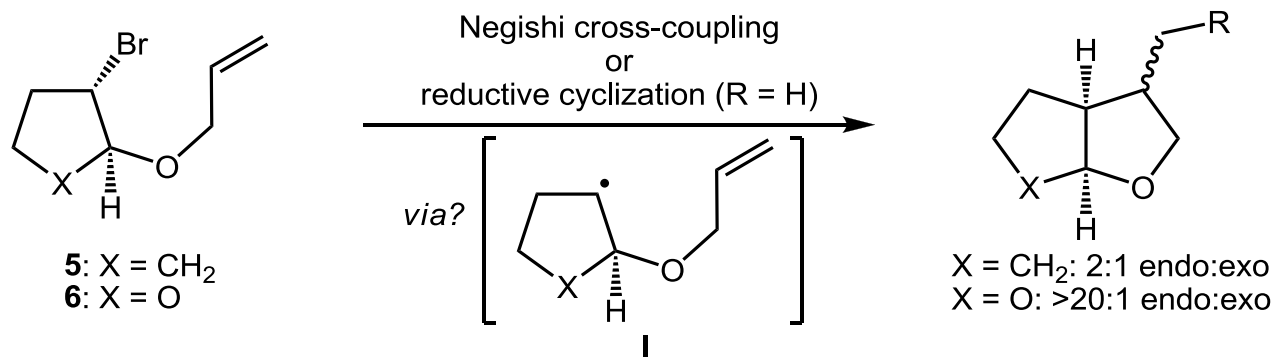
3. Negishi Cross-Couplings

Table 5

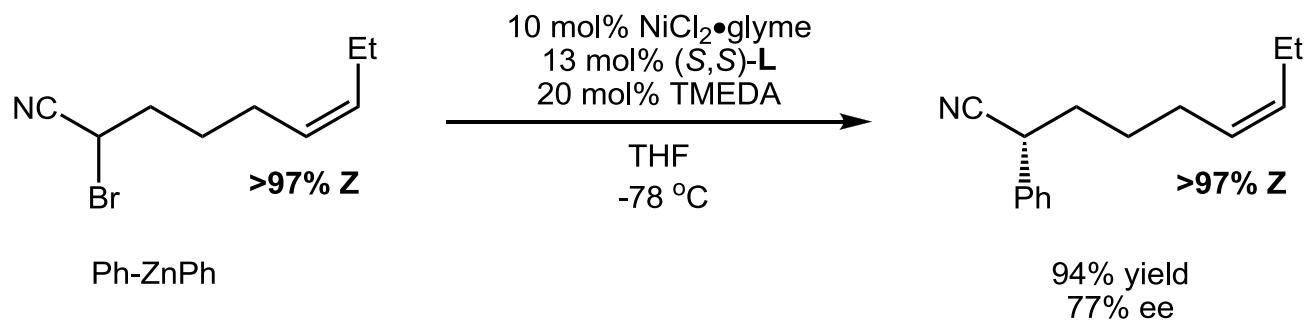


Fu, G. C. *et al.* *J. Am. Chem. Soc.* **2012**, *134*, 9102-9105.

Scheme 10

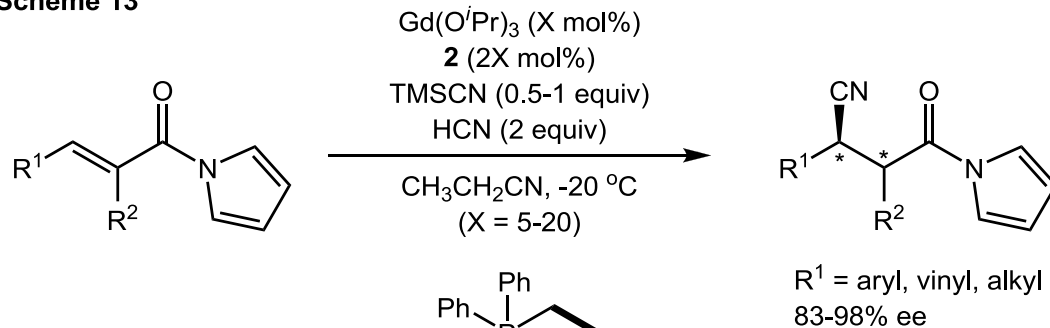


Scheme 11

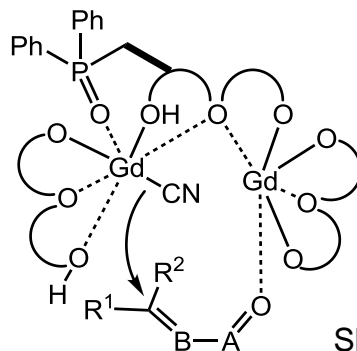


4. Conjugate Cyanations

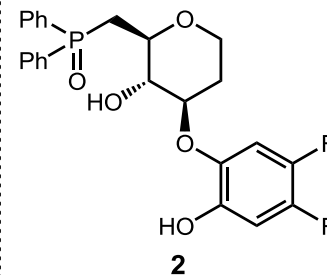
Scheme 13



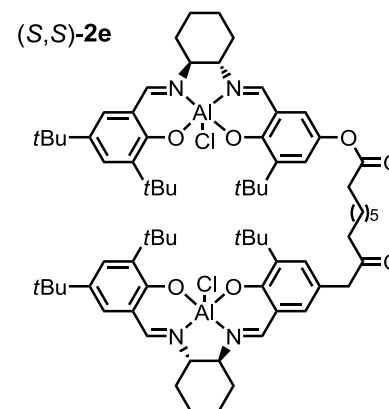
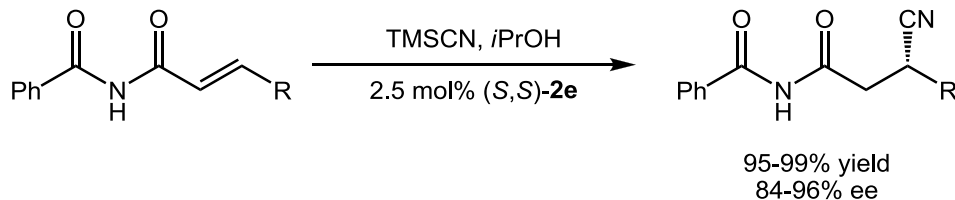
hypothesis for the transition-state model



Shibasaki, M. *et al. J. Am. Chem. Soc.* **2005**, *127*, 514-515.

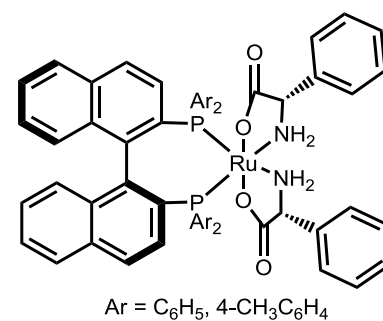
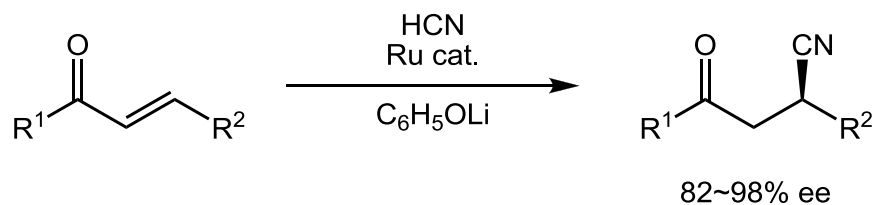


Scheme 12

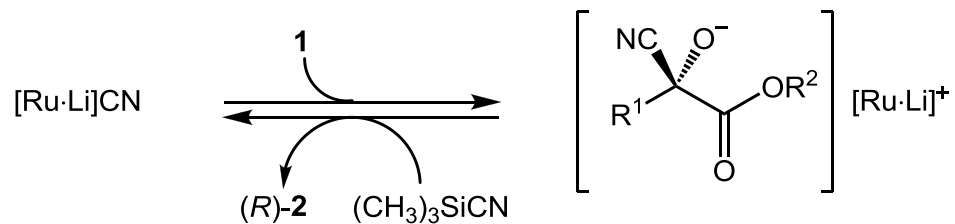
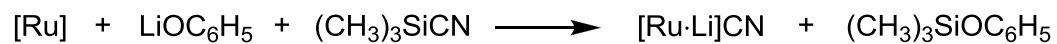


Jacobsen, E. N. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 1762-1765.

Scheme 14

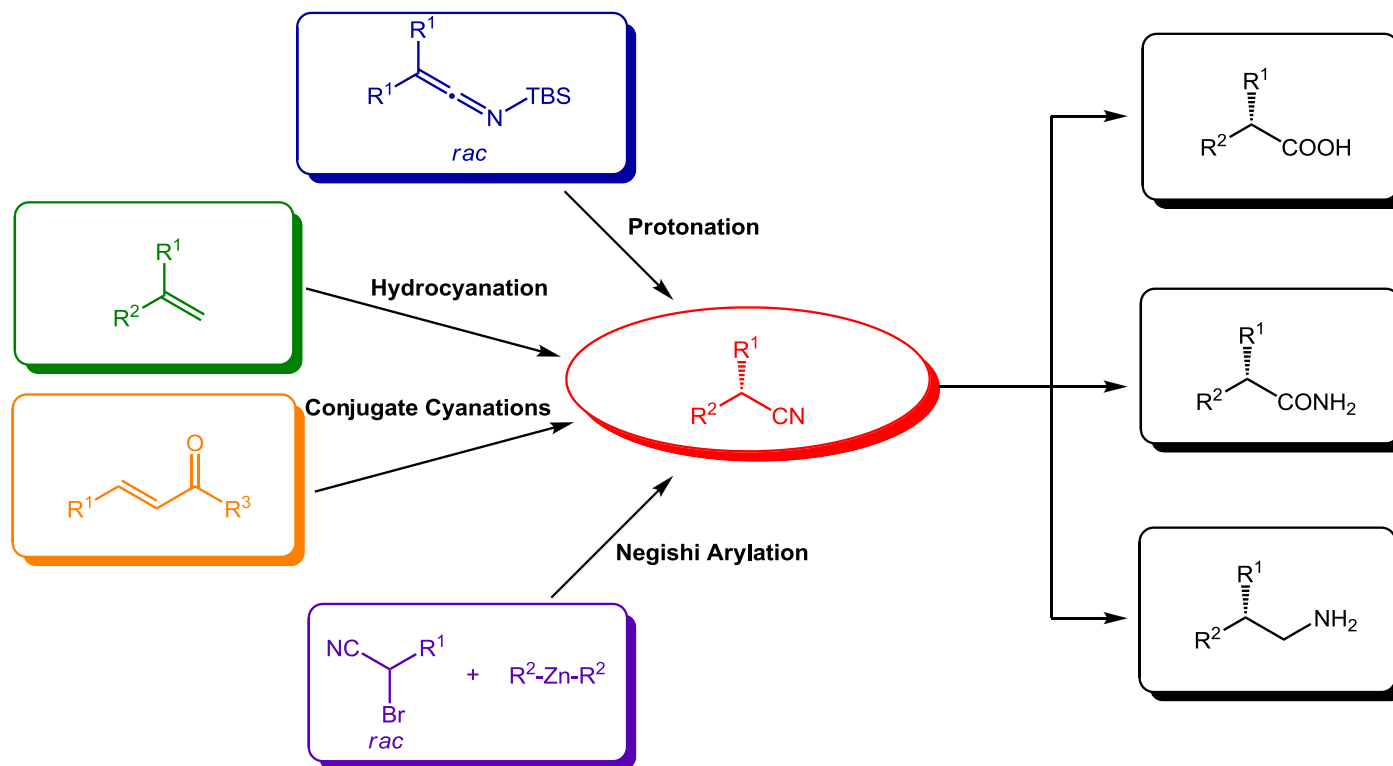


Ohkuma, T. *et al. Angew. Chem. Int. Ed.* **2011**, 50, 5541-5544.



Ohkuma, T. *et al. Eur. J. Org. Chem.* **2010**, 1455-1459.

5. Summary



The nitrile functional group is a pharmacophore in biologically active compounds and a versatile precursor of other functionalities such as carboxylic acids, ketones, aldehydes, and amines. Enantiopure α -alkyl- α -arylnitriles are particularly important as the corresponding carboxylic acids have extensively been used as nonsteroidal anti-inflammatory drugs. While few catalytic asymmetric syntheses of α -branched nitriles have been reported, including olefin hydrocyanations, conjugate cyanations, and Negishi cross-couplings, a mild, organocatalytic approach may constitute an attractive and complementary alternative. Herein we describe an efficient catalytic and enantioselective protonation of silyl ketene imines (SKIs), which are readily available from racemic nitriles. Our method offers a straightforward entry to enantioenriched secondary nitriles under mild reaction conditions.

In summary, we have described an unprecedented catalytic asymmetric protonation of silyl ketene imines providing an easy access to highly enantioenriched α -branched nitriles. The reaction is catalyzed by either chiral phosphoric acids **STRIP** or commercially available **TRIP**. The use of methanol as the stoichiometric proton source adds to the potential practical value of our method. Several functionalized α -alkyl- α -arylnitriles with varying substituents at both aryl and alkyl chains were obtained in good yields and with excellent enantioselectivity. A gram scale experiment has been performed to illustrate practical aspects, and a mechanism has been suggested.

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