Highly Enantioselective Aza-Michael Reaction between Alkyl Amines and β-Trifluoromethyl β-Aryl Nitroolefins

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Date: 12/01/2016

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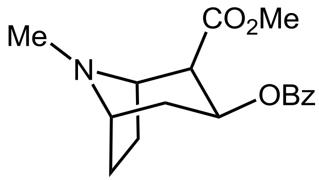
Shenzhen Graduate School

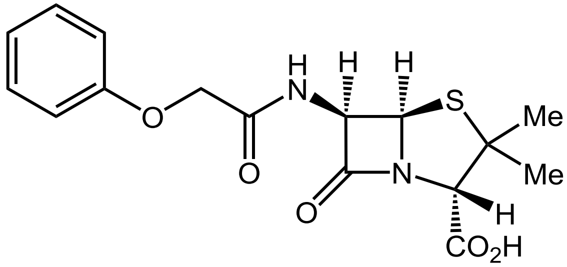
Huang, Y. *et al*. *Angew*. *Chem*. *Int. Ed.* **2015**, *54*, 15414–15418.

Contents

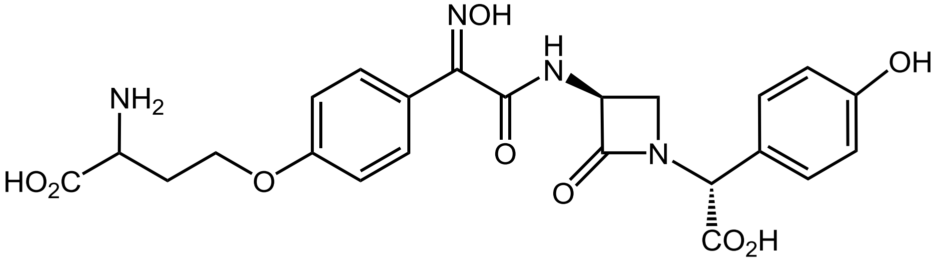
➢ Introduction



(-)-Cocaine

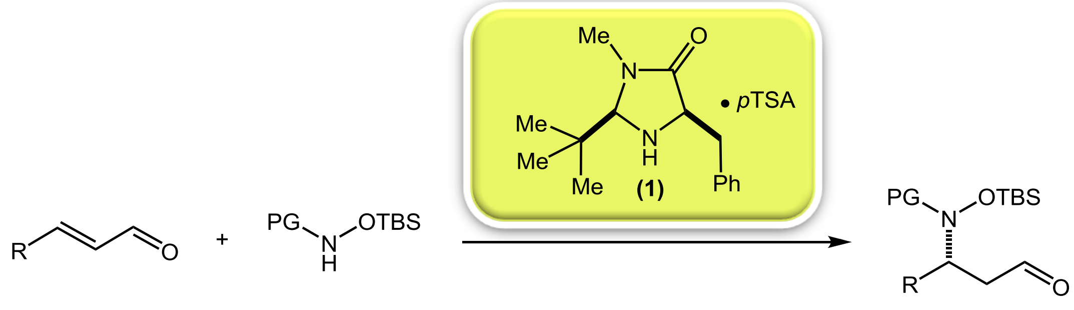


Penicillin V

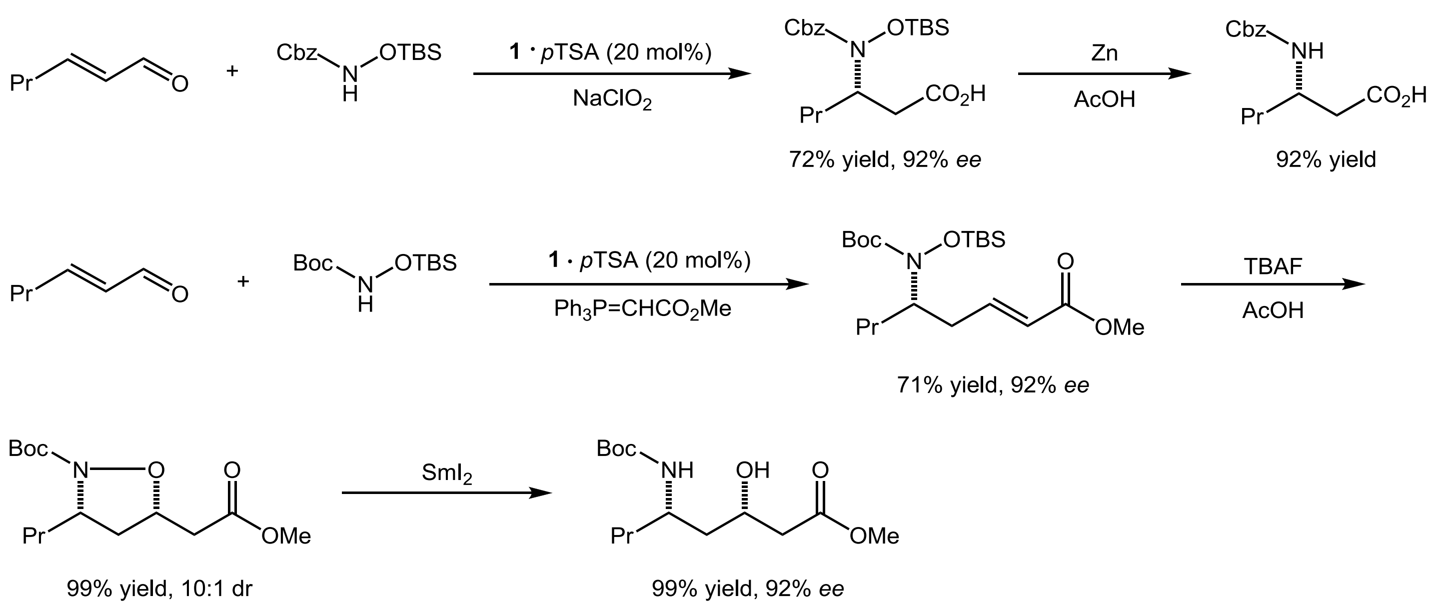


(-)-Nocardicin A

Enantioselective aza-Michael reaction with secondary-amine catalysis

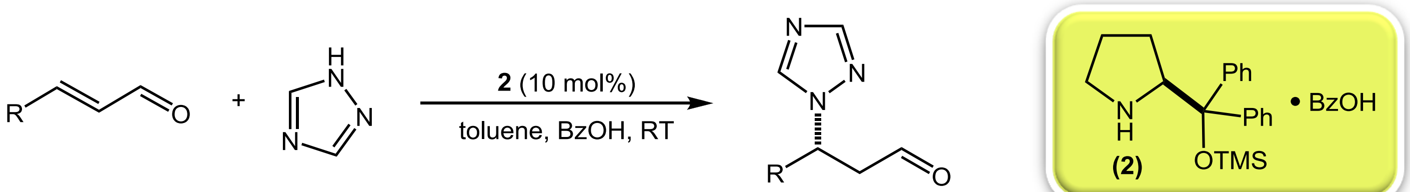


secondary-amine catalysis
9 examples
up to 95% yield, 97% *ee*

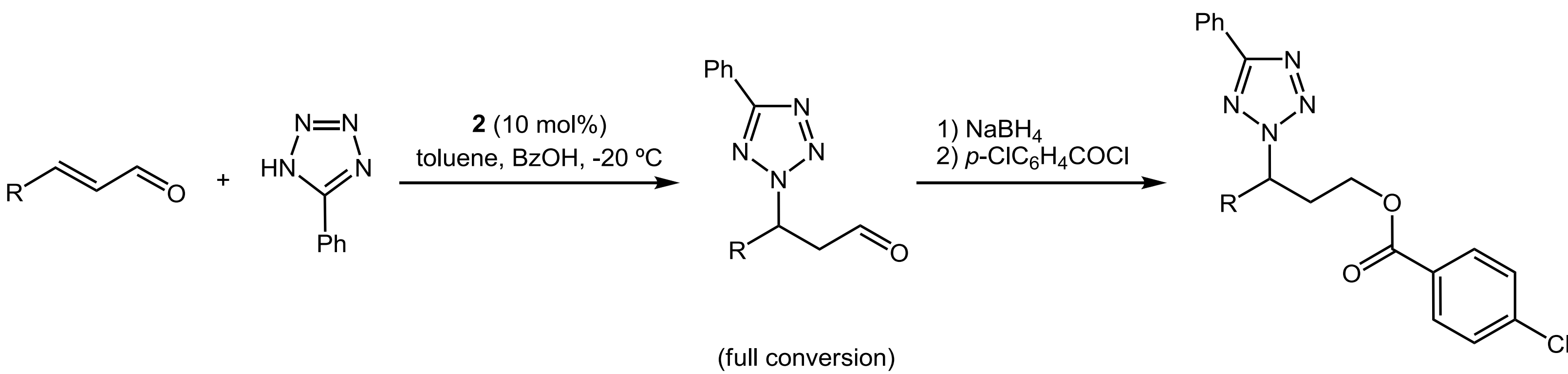


MacMillan, D. W. C. *et al. J. Am. Chem. Soc*. **2006**, *128*, 9328-9329

➤ Enantioselective aza-Michael reaction with secondary-amine catalysis



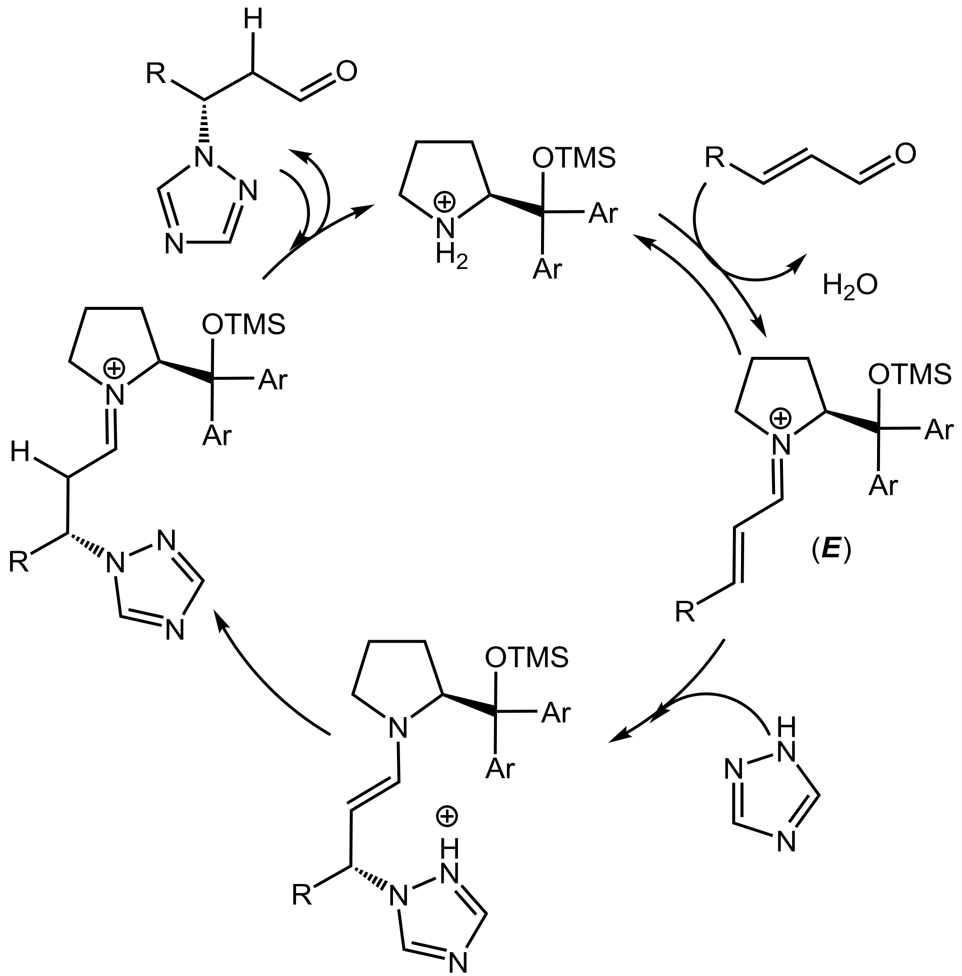
6 examples
up to 87% yield, 94% *ee*



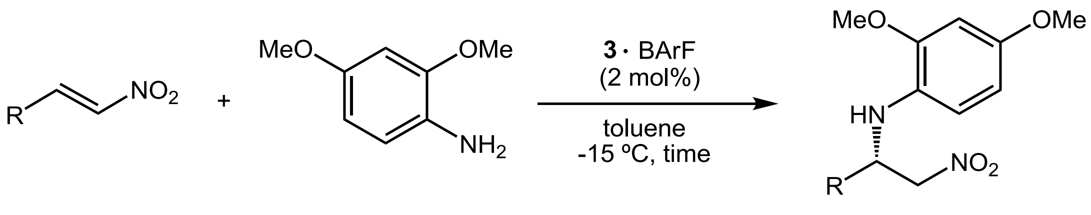
4 examples
45-66% yield, 85-92% *ee*

Jørgensen, K. A. *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 1983-1987

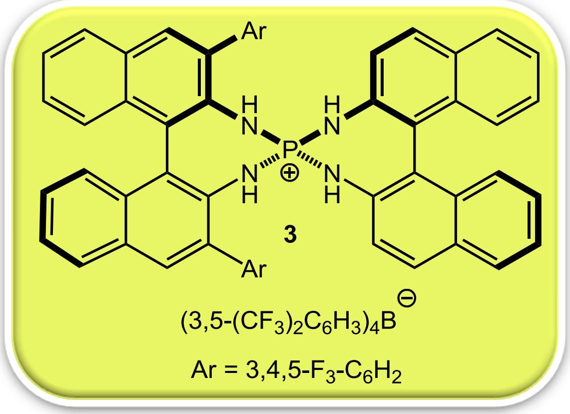
➢ Proposed catalytic cycle for aza-Michael reaction



➢ Enantioselective aza-Michael reaction with Brønsted acid catalysis

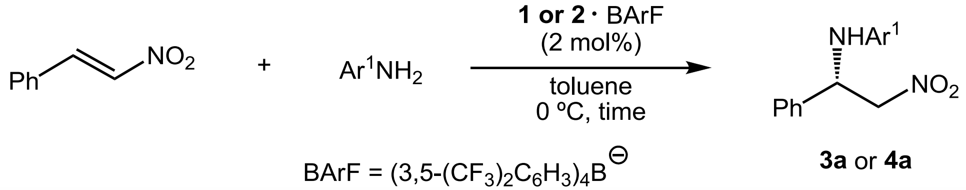


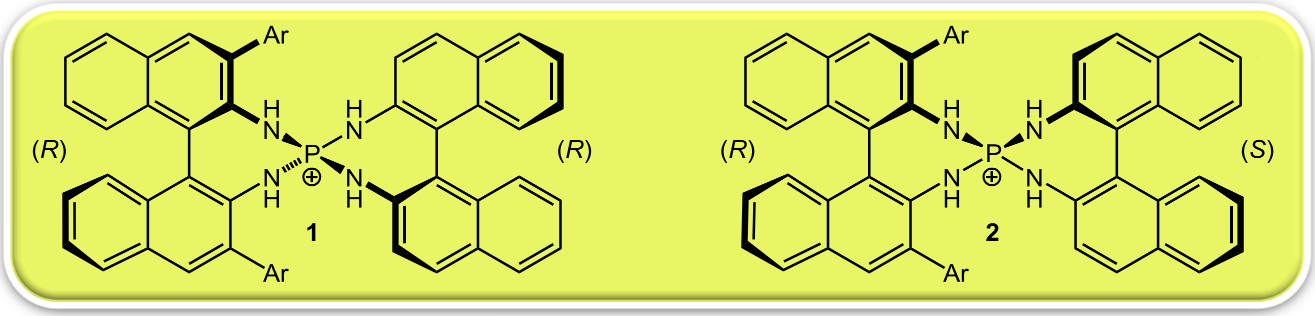
12 examples
up to 99% yield, 97% *ee*



Ooi, T. *et al. J. Am. Chem. Soc.* **2009**, *131*, 7242-7243

➢ Effect of the structure of the arylamine and catalyst

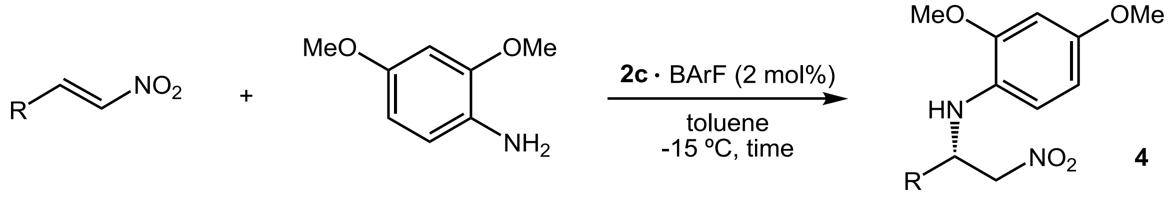




Entry	Catalyst (Ar)	Ar^1	Time [h]	Yield [%]	Ee [%]	Prod.
1	**1a (H)**	4-MeO-C_6H_4	23	37	19	**3a**
2	**1a (H)**	2,4-$(MeO)_2$-C_6H_3	23	42	41	**4a**
3	**1b (Ph)**	2,4-$(MeO)_2$-C_6H_3	23	86	61	**4a**
4	**2b (Ph)**	2,4-$(MeO)_2$-C_6H_3	27	87	83	**4a**
5	**2c (3,4,5-F_3-C_6H_2)**	2,4-$(MeO)_2$-C_6H_3	11	98	94	**4a**
6[a]	**2c (3,4,5-F_3-C_6H_2)**	2,4-$(MeO)_2$-C_6H_3	12	98	95	**4a**

[a] Reaction was conducted at -15 ºC.

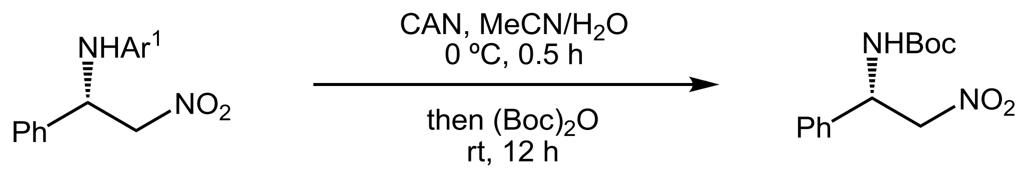
➢ Scope of nitroolefins



Entry	R	Time [h]	Yield [%]	Ee [%]	Prod.
1	4-F-C_6H_4	12	98	94	**4b**
2	4-Cl-C_6H_4	4	99	95	**4c**
3	4-Br-C_6H_4	4	99	94	**4d**
4	4-Me-C_6H_4	12	99	97	**4e**
5	3-MeO-C_6H_4	4	99	93	**4f**
6	3-Br-C_6H_4	9	99	93	**4g**
7	2-F-C_6H_4	12	99	92	**4h**
8	1-naphthyl	19	99	91	**4i**
9	2-naphthyl	19	99	95	**4j**
10	3-furyl	24	89	94	**4k**
11[a]	Me_2CHCH_2	7	98	89	**4l**
12[a,b]	$Me(CH_2)_4$	0.5	93	87	**4m**

[a] Diisopropyl ether was used as solvent instead of toluene .
[b] Reaction was performed at room temperature.

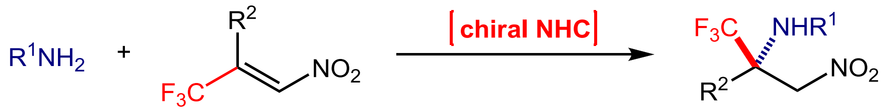
➢ Deprotection-Reprotection process



4a (95% *ee*)
Ar^1 = 2,4-$(MeO)_2$-C_6H_3

5
77% (95% *ee*)

➤ Enantioselective aza-Michael reaction with noncovalent catalysis



noncovalent catalysis
CF_3-substituted tertiary stereocenter
up to 99% yield, 98% *ee*

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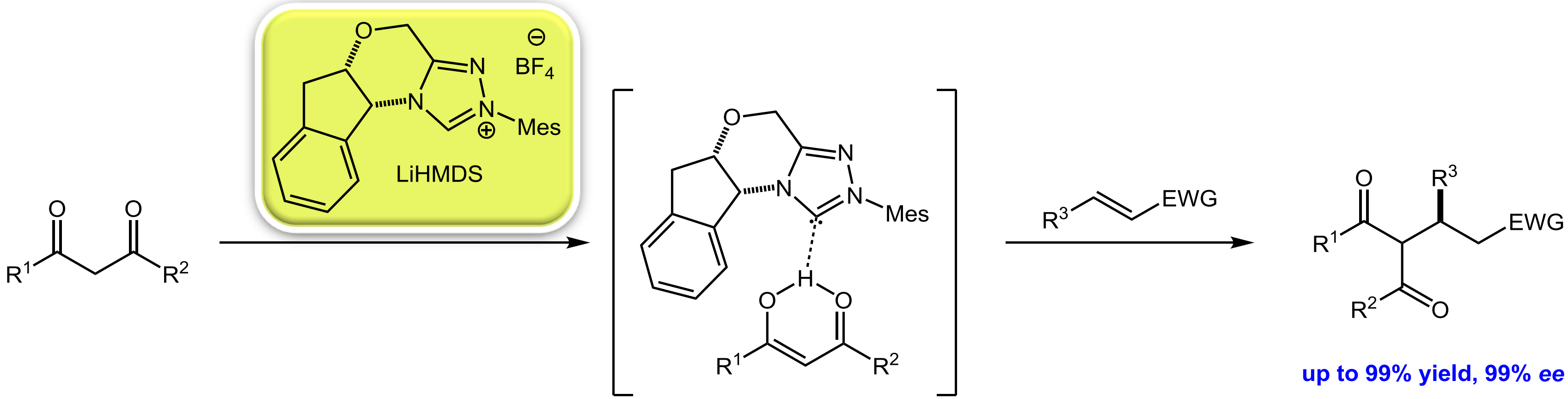
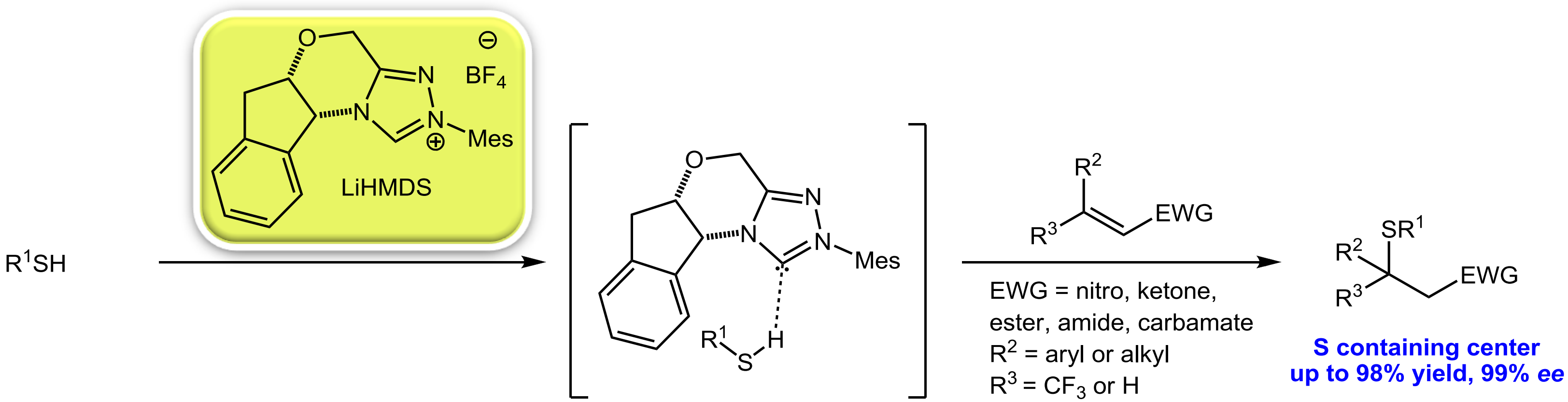
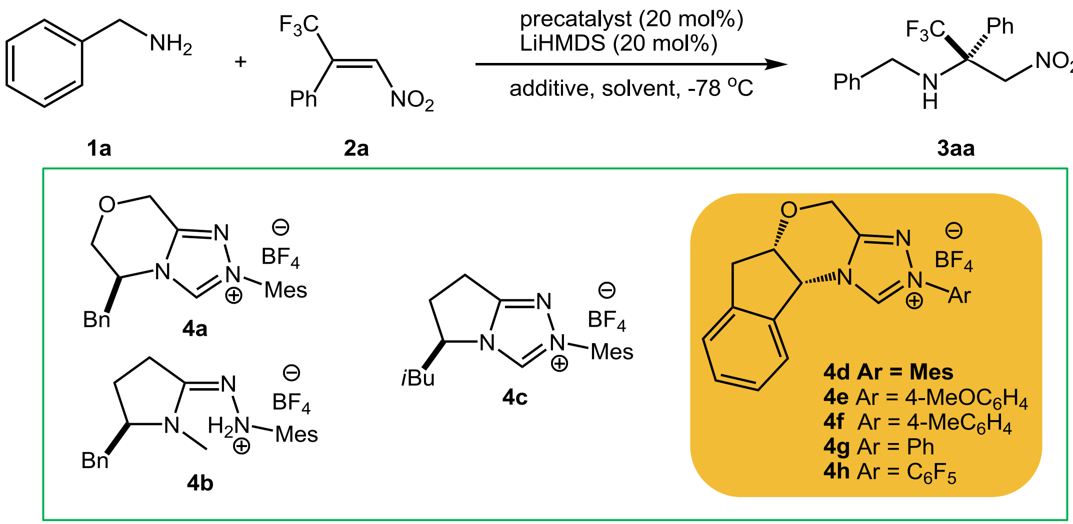
➢ NHCs as non-covalent chiral catalysts for asymmetric reaction





Huang, Y. *et al. Nat. Commun.* **2014**, *5*, 3437-3444
Huang, Y. *et al. Chem. Sci*. **2015**, *6*, 4184-4189

➢ Optimization of the reaction conditions



Entry	Catalyst	Additive	Solvent	Yield [%]	Ee [%]
1	**4a**	HFIP, 4 Å MS	toluene	88	-13
2	**4b**	HFIP, 4 Å MS	toluene	85	-16
3	**4c**	HFIP, 4 Å MS	toluene	90	2
4	**4d**	HFIP, 4 Å MS	toluene	99	91
5	**4e**	HFIP, 4 Å MS	toluene	80	51
6	**4f**	HFIP, 4 Å MS	toluene	90	28

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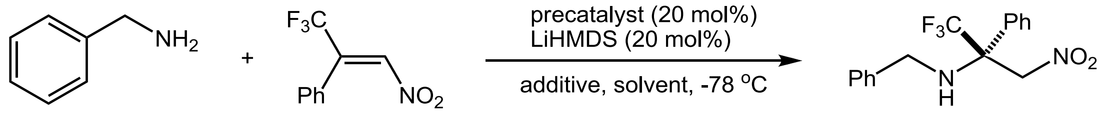
➢ Optimization of the reaction conditions

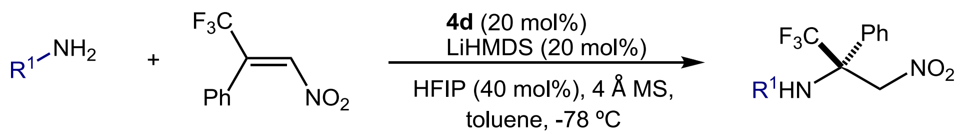


1 2a 3aa

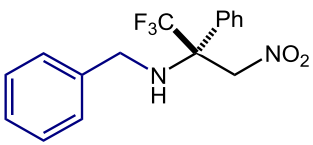
Entry	Catalyst	Additive	Solvent	Yield [%]	Ee [%]
7	**4g**	HFIP, 4 Å MS	toluene	70	7
8	**4h**	HFIP, 4 Å MS	toluene	50	0
9[a]	**4d**	HFIP, 4 Å MS	toluene	83	15
10	**4d**	HFIP, 4 Å MS	toluene	57	52
11	**4d**	HFIP, 4 Å MS	CH_2Cl_2	70	3
12	**4d**	HFIP, 4 Å MS	THF	99	0
13	**4d**	HFIP, 4 Å MS	Et_2O	70	76
14	**4d**	HFIP, 4 Å MS	MTBE	85	36
15	**4d**	4 Å MS	toluene	23	87
16	**4d**	HFIP	toluene	25	4

[a] The reaction was performed at -40 °C with 10 mol% of the catalyst.

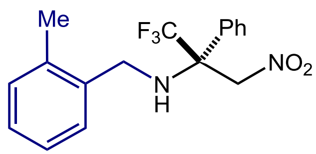
➢ Scope of the reaction with respect to the amine nucleophile



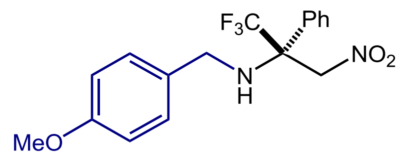
1 **2a** **3**



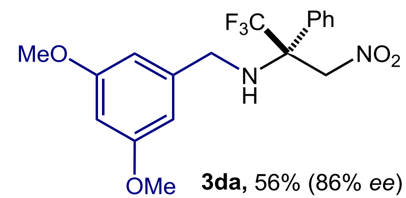
3aa, 90% (91% *ee*)



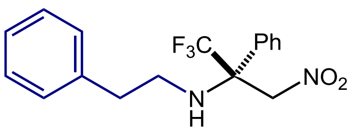
3ba, 67% (91% *ee*)



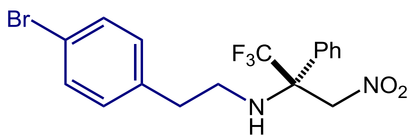
3ca, 89% (92% *ee*)



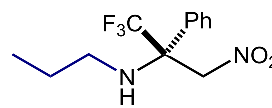
3da, 56% (86% *ee*)



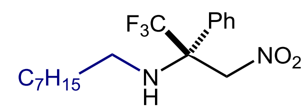
3ea, 85% (86% *ee*)



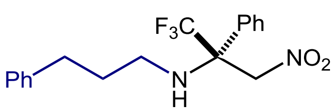
3fa, 68% (87% *ee*)



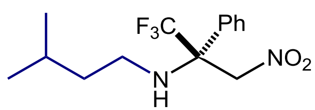
3ga, 80% (92% *ee*)



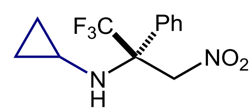
3ha, 87% (95% *ee*)



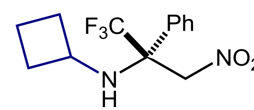
3ia, 82% (93% *ee*)



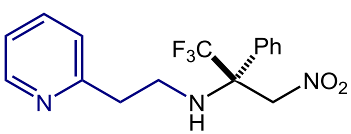
3ja, 79% (89% *ee*)



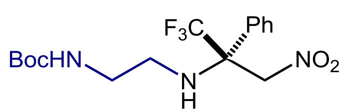
3ka, 79% (97% *ee*)



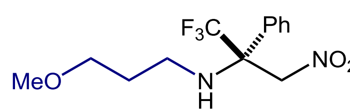
3la, 78% (94% *ee*)



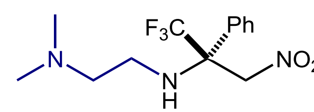
3ma, 87% (93% *ee*)



3na, 79% (91% *ee*)



3oa, 87% (87% *ee*)



3pa, 99% (91% *ee*)

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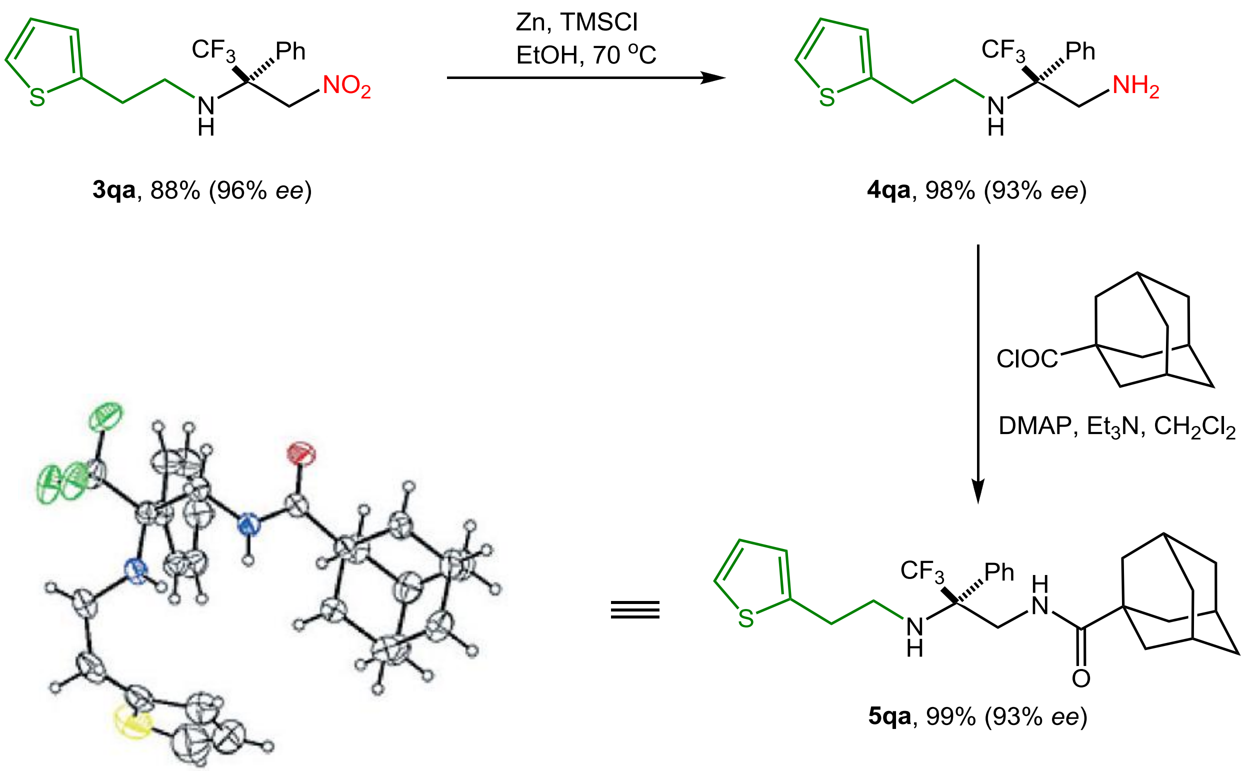
➢ The absolute configuration of product 3qa



3qa, 88% (96% *ee*)

4qa, 98% (93% *ee*)

5qa, 99% (93% *ee*)

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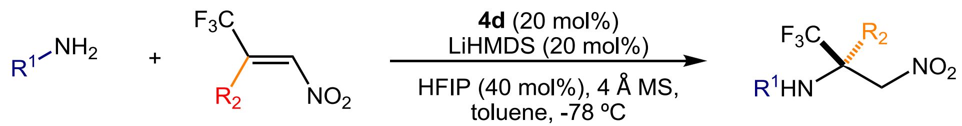
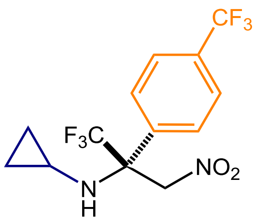
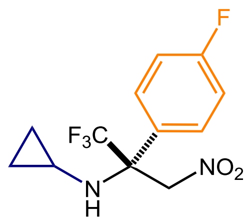
➢ Scope of the reaction with respect to the nitroalkene



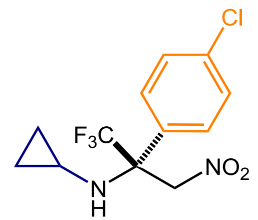
1 **2a** **3**



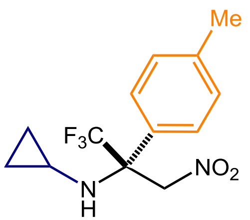
3kb, 64% (84% *ee*)



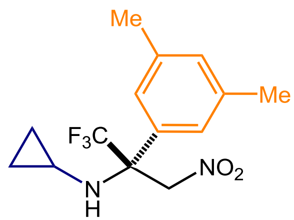
3kc, 77% (90% *ee*)



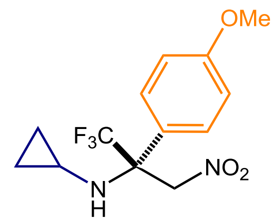
3kd, 92% (94% *ee*)



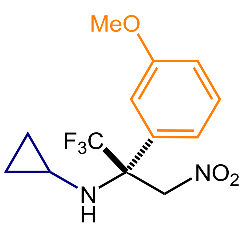
3ke, 78% (97% *ee*)



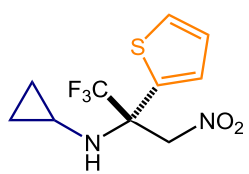
3kf, 57% (90% *ee*)



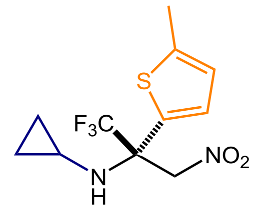
3kg, 99% (98% *ee*)



3kh, 83% (95% *ee*)



3ki, 98% (96% *ee*)



3kj, 99% (96% *ee*)

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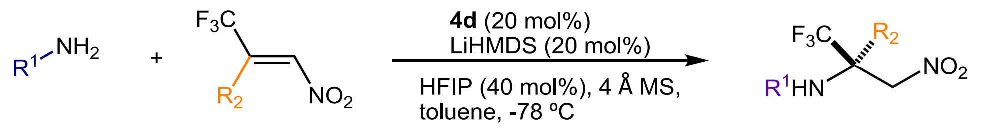
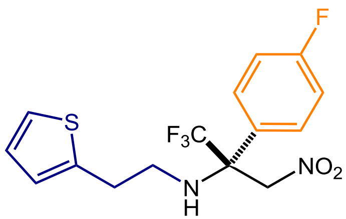
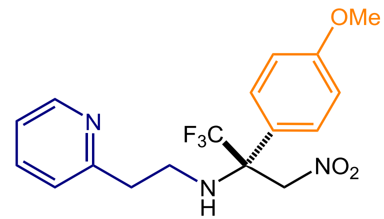
➢ Scope of the reaction with respect to the nitroalkene



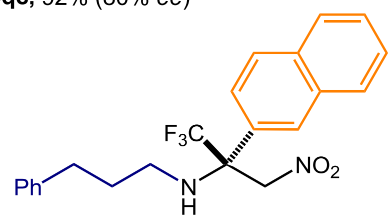
1 **2a** **3**



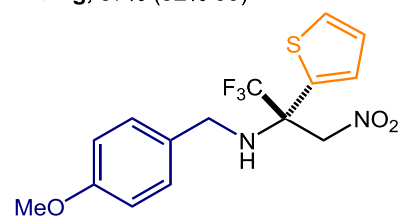
3qc, 92% (80% *ee*)



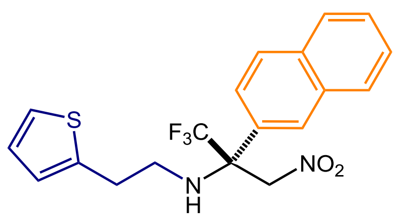
3mg, 97% (92% *ee*)



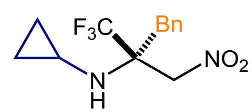
3ik, 82% (90% *ee*)



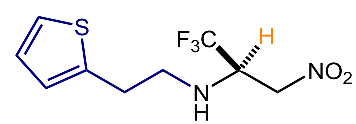
3ci, 99% (90% *ee*)



3qk, 81% (91% *ee*)



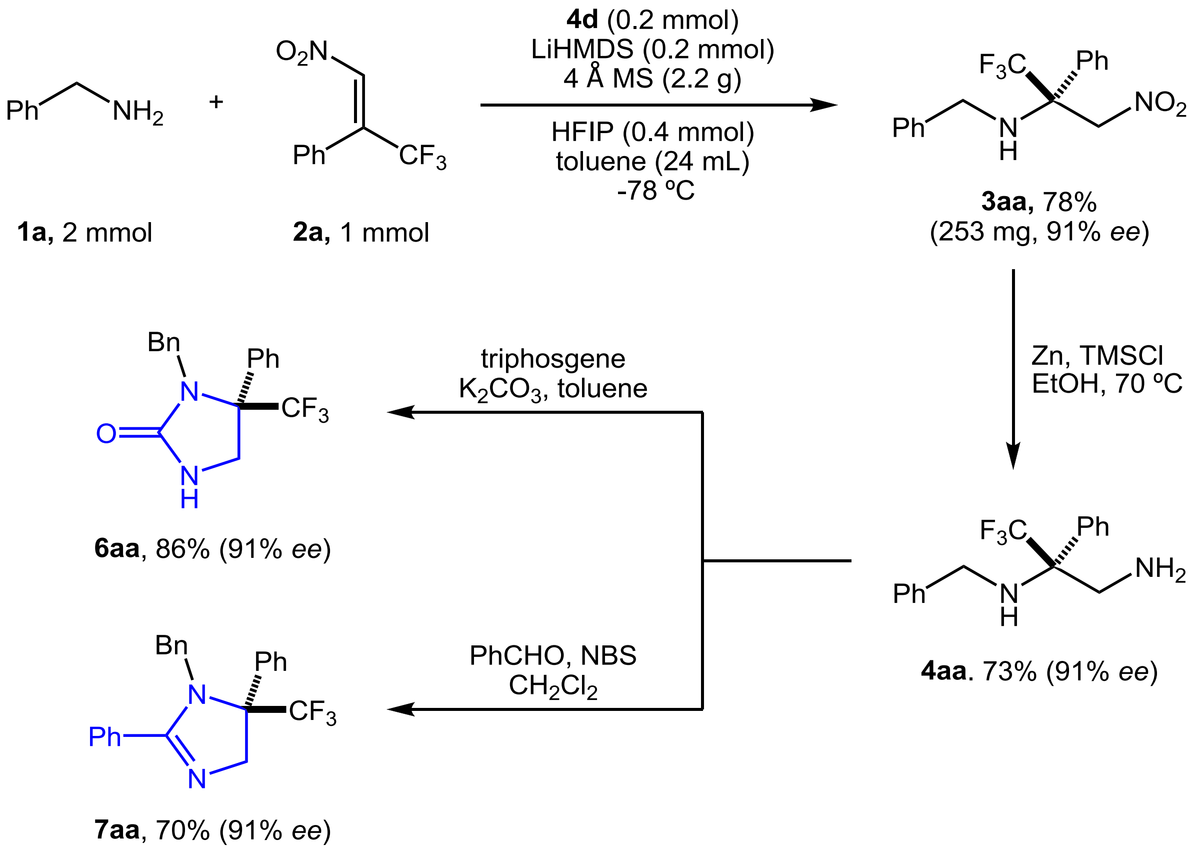
3kl, 89% (30% *ee*)



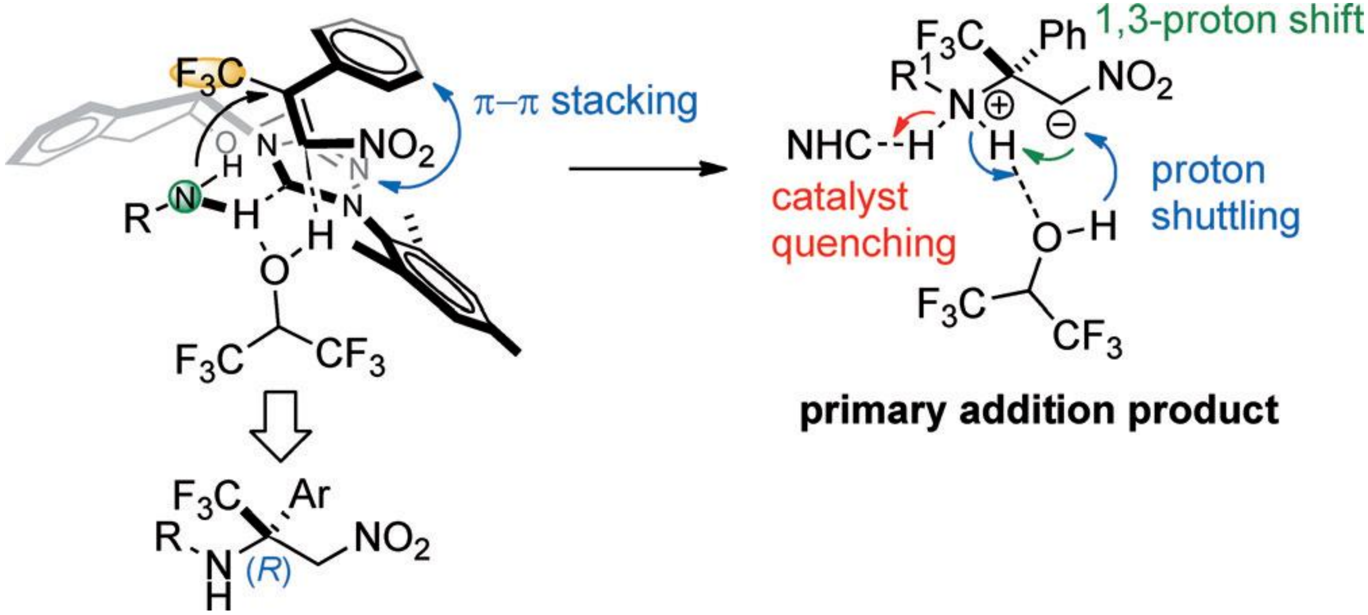
3qm, 90% (3% *ee*)

Huang, Y. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 15414-15418

➢ Synthesis of CF_3-containing chiral heterocycles

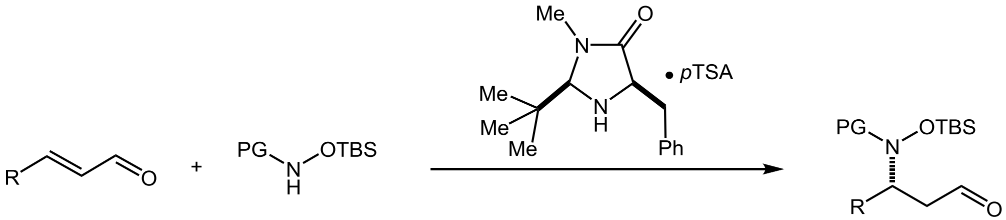


➢ Proposed transition state and proton-shuttling mechanism

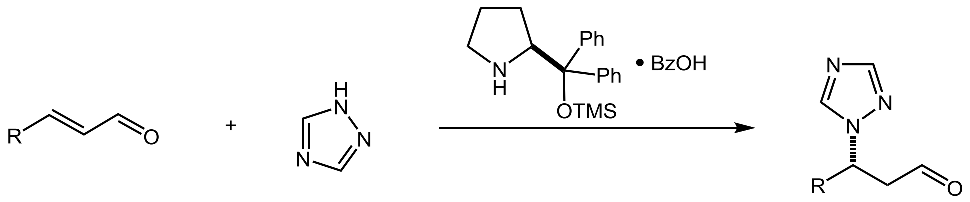


Huang, Y. *et al. Angew. Chem. Int. Ed*. **2015**, *54*, 15414-15418

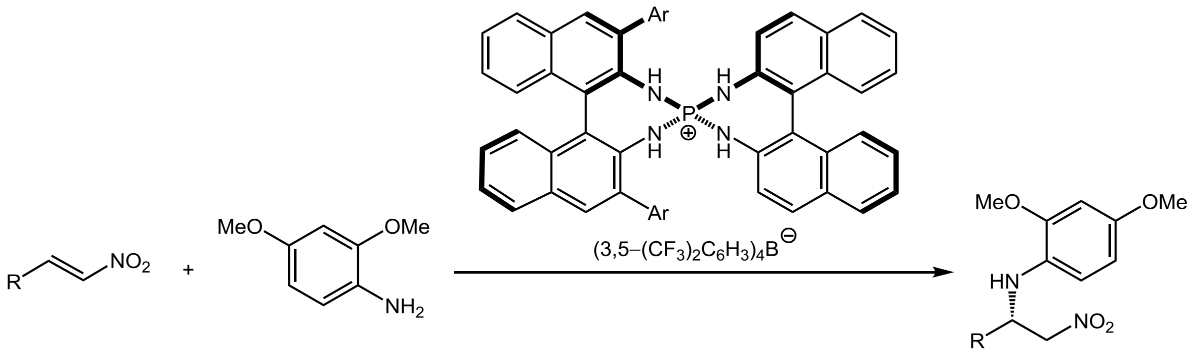
➤ Summary



secondary-amine catalysis
MacMillan and co-workers
up to 95% yield, 97% *ee*

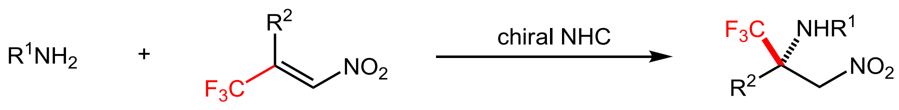


secondary-amine catalysis
Jørgensen and co-workers
up to 87% yield, 94% *ee*



Brønsted acid catalysis
Ooi and co-workers
up to 99% yield, 97% *ee*

➢ Summary



R^1 = alkyl
HOMO-raising activation
noncovalent catalysis
Huang and co-workers
CF_3-substituted tertiary stereocenter
up to 99% yield, 98% *ee*

The asymmetric aza-Michael reaction is arguably one of the most straightforward methods for the synthesis of important 1,2-difunctionalized chiral building blocks, such as 1,2-diamines. Many successful combinations of nitrogen nucleophiles and electron-deficient olefins have been reported, with either Lewis acid catalysts or organocatalysts. However, two key problems remain largely unsolved: the use of alkyl amines as the nitrogen source, and the construction of tertiary stereocenters with a nitrogen substituent. Simple alkyl amines tend to form stable complexes with Lewis acids, which not only deactivates the catalyst, but also renders the aza-Michael reaction reversible.

In the case of organocatalysis, primary and secondary amines interfere with both LUMO-lowering iminium activation (competing imine/iminium formation) and proton catalysis (acid–base neutralization). As a result, research efforts have been mostly concentrated on modulating the basicity of the donor nitrogen atom.

In summary, we have developed the first highly enantioselective aza-Michael reaction of simple aliphatic amines. 1,2-Diamine analogues with a unique CF_3-bearing tertiary stereocenter can be prepared in high yield with high enantioselectivity. The noncovalent, HOMO-raising activation of the NHC overcomes the intrinsic problem of using a basic amine in LUMO-lowering catalysis. Furthermore, an acidic proton shuttle is used to prevent catalyst quenching and retain turnover. A dual role of the NHC is proposed: activation by hydrogen bonding and π-π stacking. We expect that this generic HOMO-raising noncovalent activation mode by NHCs will find wide application in enantioselective catalysis and cascade reactions.