C-H Functionalization of Amines through Cooperative Action of Chiral and Achiral Lewis Acids

Reporter: Bo Wu
Checker: Yang Zhao
Date: 2020/12/14

Chan, J. Z.; Wasa, M. *et al*. *J. Am. Chem. Soc.* **2020***, 142,* 16493

Contents

CV of Prof. Masayuki Wasa

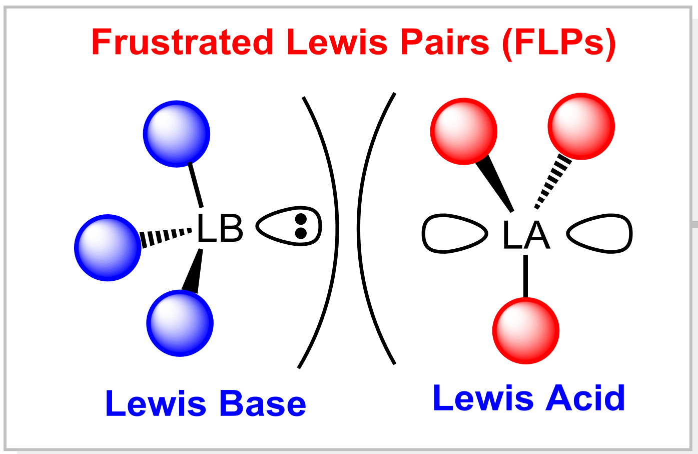
Background:

- **2013** Ph. D., The Scripps Research Institute (with Prof. Jin-Quan Yu)
- **2013-2015** JSPS Postdoctoral Fellow, Harvard University (with Prof. Eric N. Jacobsen)
- **2015-present** Assistant Professor of Chemistry, Boston College

Research Interests:

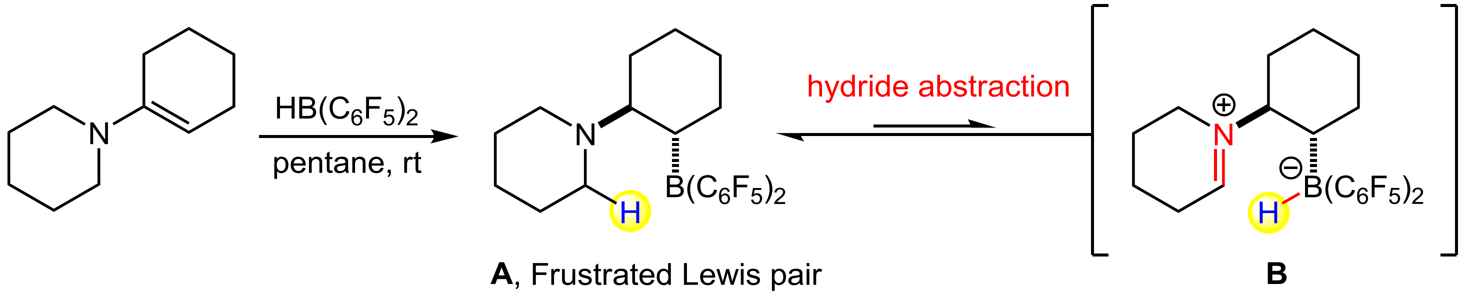
✓ Development of polyfunctional Lewis pair catalysis for practical synthetic transformations with applications in drug discovery and development, and alternative energy.

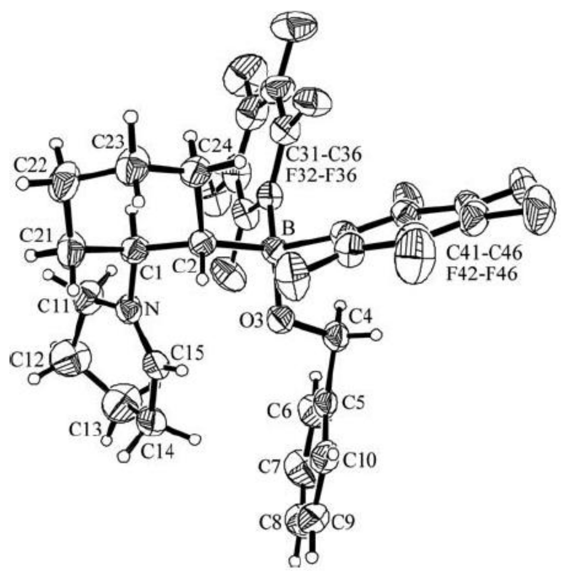
Frustrated Lewis Pairs (FLPs)

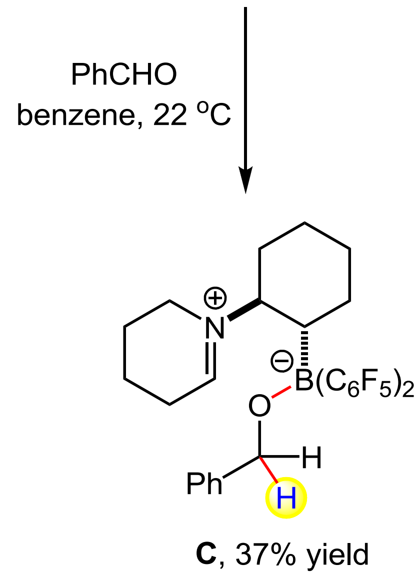


- Small Molecule Activation
- Catalytic Hydrogenation
- Polymerization

Intramolecular Hydride Transfer within FLPs

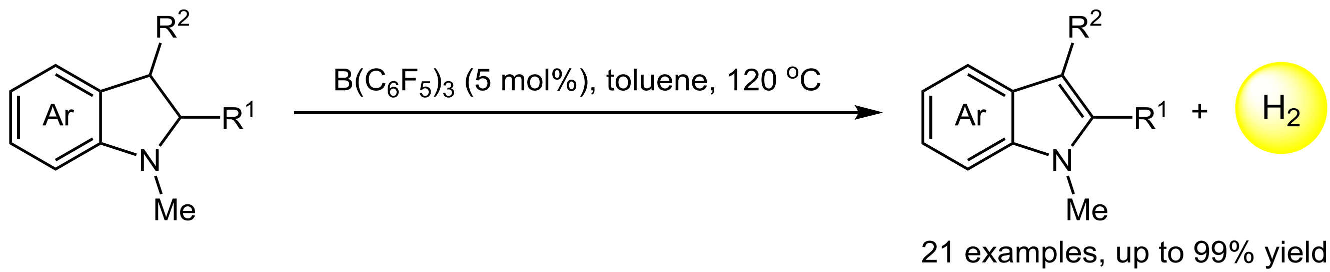




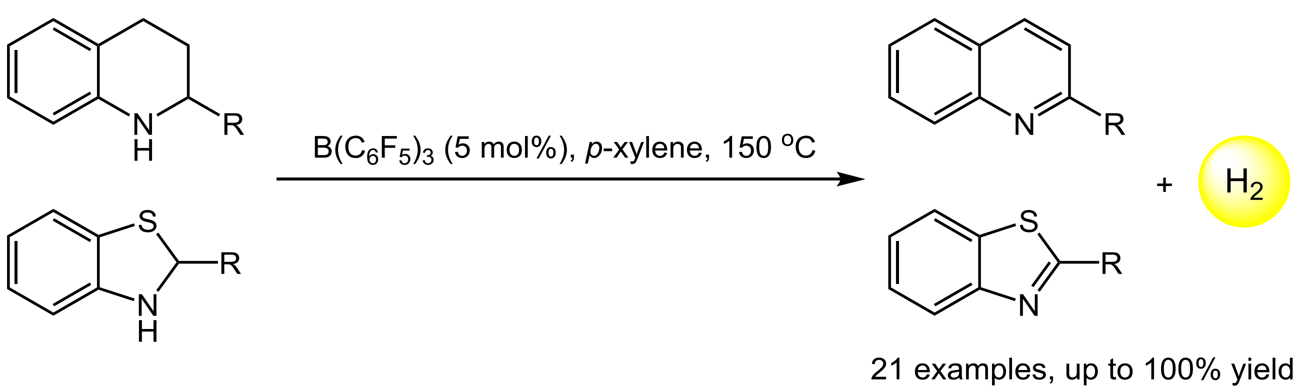


Erker, G. *et al*. *Chem. Sci.* **2011**, *2*, 1842

Dehydrogenation of *N*-Heterocycles

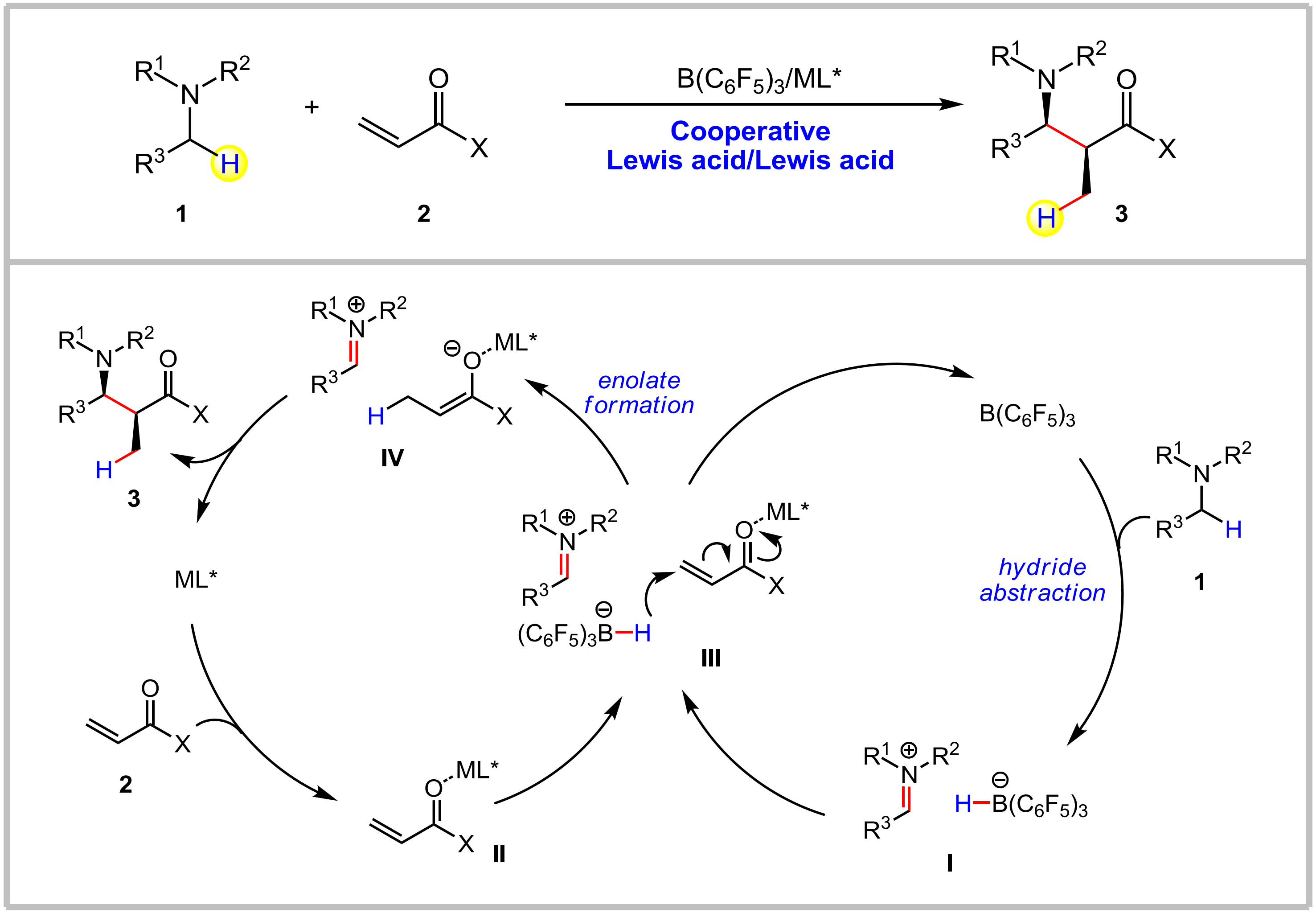


Paradies, J. *et al*. *Angew. Chem. Int. Ed.* **2016**, *55*, 12219



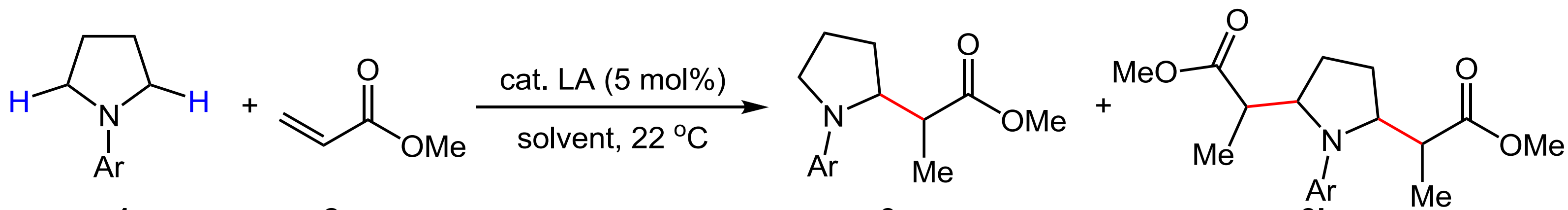
Kanai, M. *et al*. *Angew. Chem. Int. Ed.* **2016**, *55*, 12224

Enantioselective C-H Functionalization of Amines



Wasa, M. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 10593

C-H Functionalization of Amines

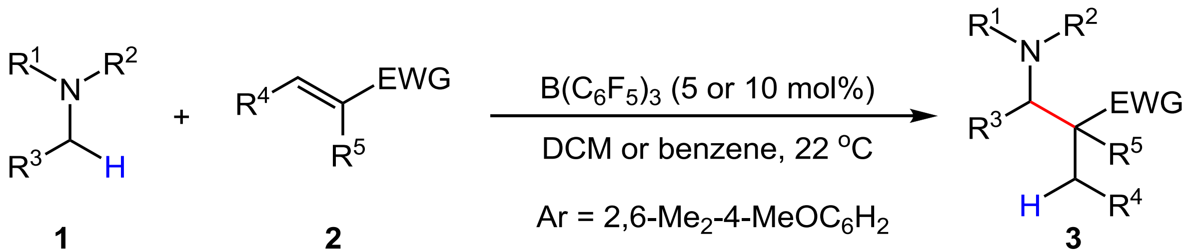


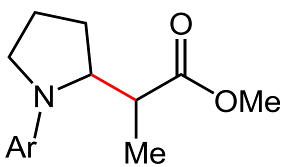
1a **2a** **3a** **3b**

Ar = 2,6-Me_2-4-$MeOC_6H_2$

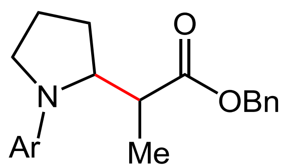
Entry	LA	Solvent	Time (h)	Yield of **3a** (%) *anti*/*syn*	Yield of **3b** (%)
1	$B(C_6F_5)_3$	DCM	12	>95, 2.3:1	<5
2	$B(C_6F_5)_3$	Et_2O	12	94, 2.3:1	<5
3	$B(C_6F_5)_3$	Toluene	12	81, 2.4:1	5
4	**$B(C_6F_5)_3$**	**Benzene**	**0.5**	**>95, 2.4:1**	**<5**
5	none	Benzene	12	0	0
6	$BF_3 \cdot OEt_2$	Benzene	12	0	0
7	BPh_3	Benzene	12	0	0

Substrate Scope

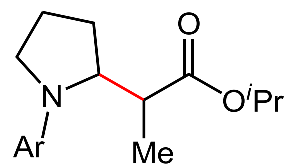




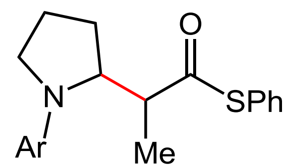
3a: 97% yield
2.3:1 *anti:syn*



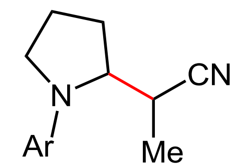
3c: 91% yield
2.5:1 *anti:syn*



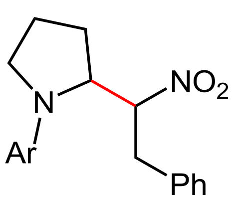
3d: 78% yield
2.1:1 *anti:syn*



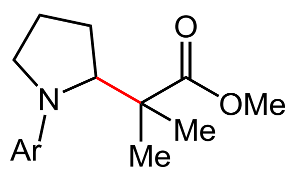
3e: 53% yield
1.8:1 *anti:syn*



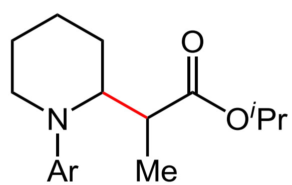
3f: 50% yield
1.3:1 *anti:syn*



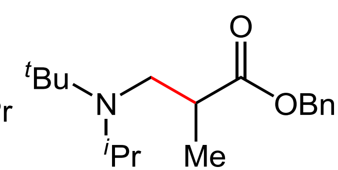
3g: 84% yield
1.2:1 *anti:syn*



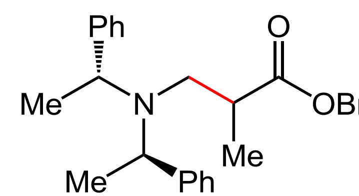
3h: 97% yield



3i: 63% yield
10:1 *anti:syn*

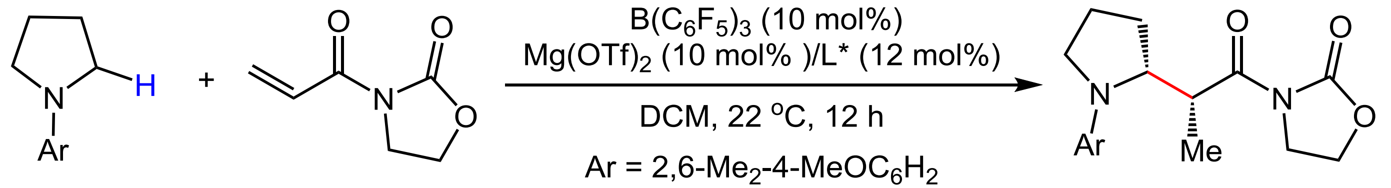


3j: 85% yield

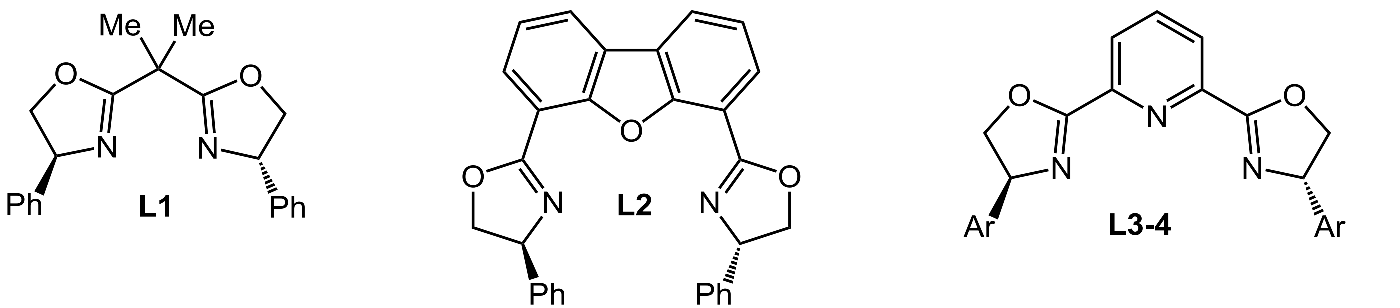


3k: 91% yield
(*R,S*)/(*R,R*) = 1.5:1

Enantioselective C-H Functionalization of Amines

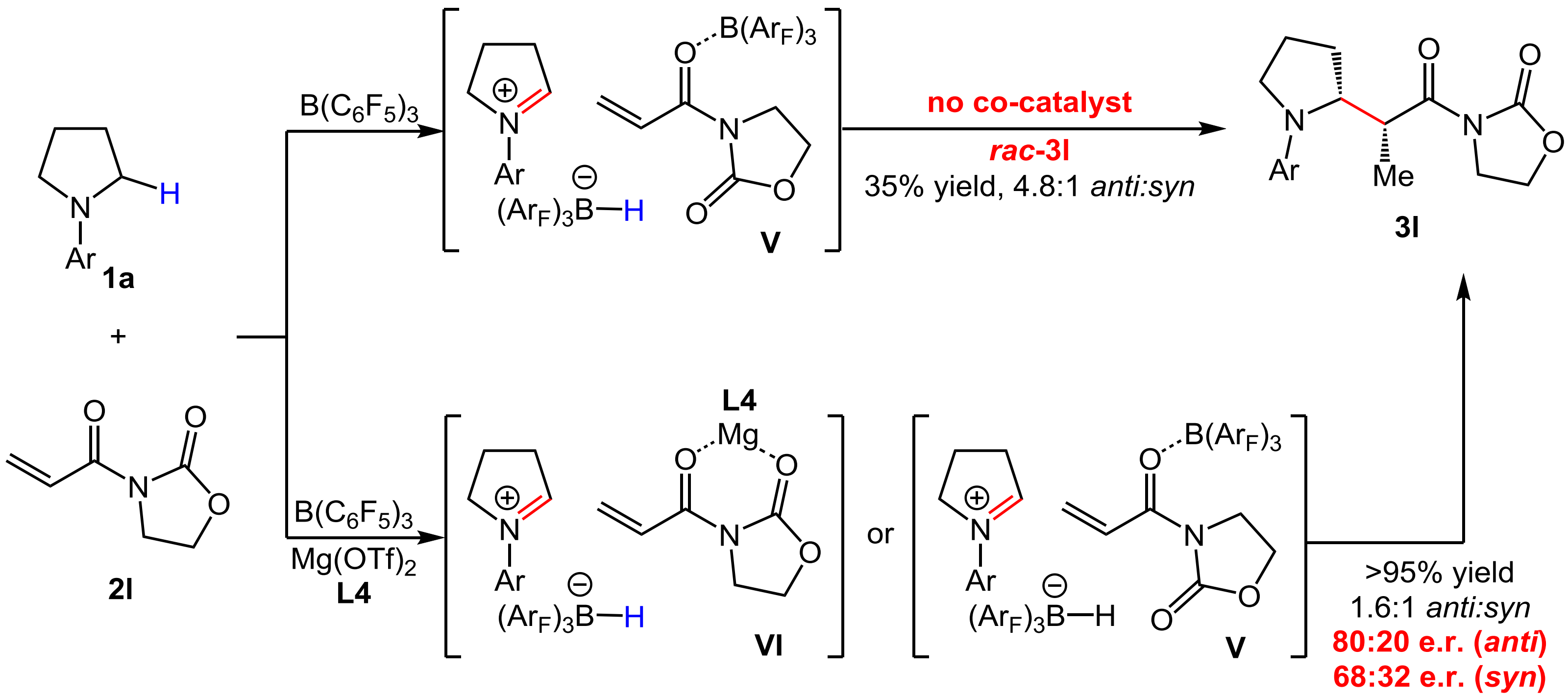


1a **2l** **3l**

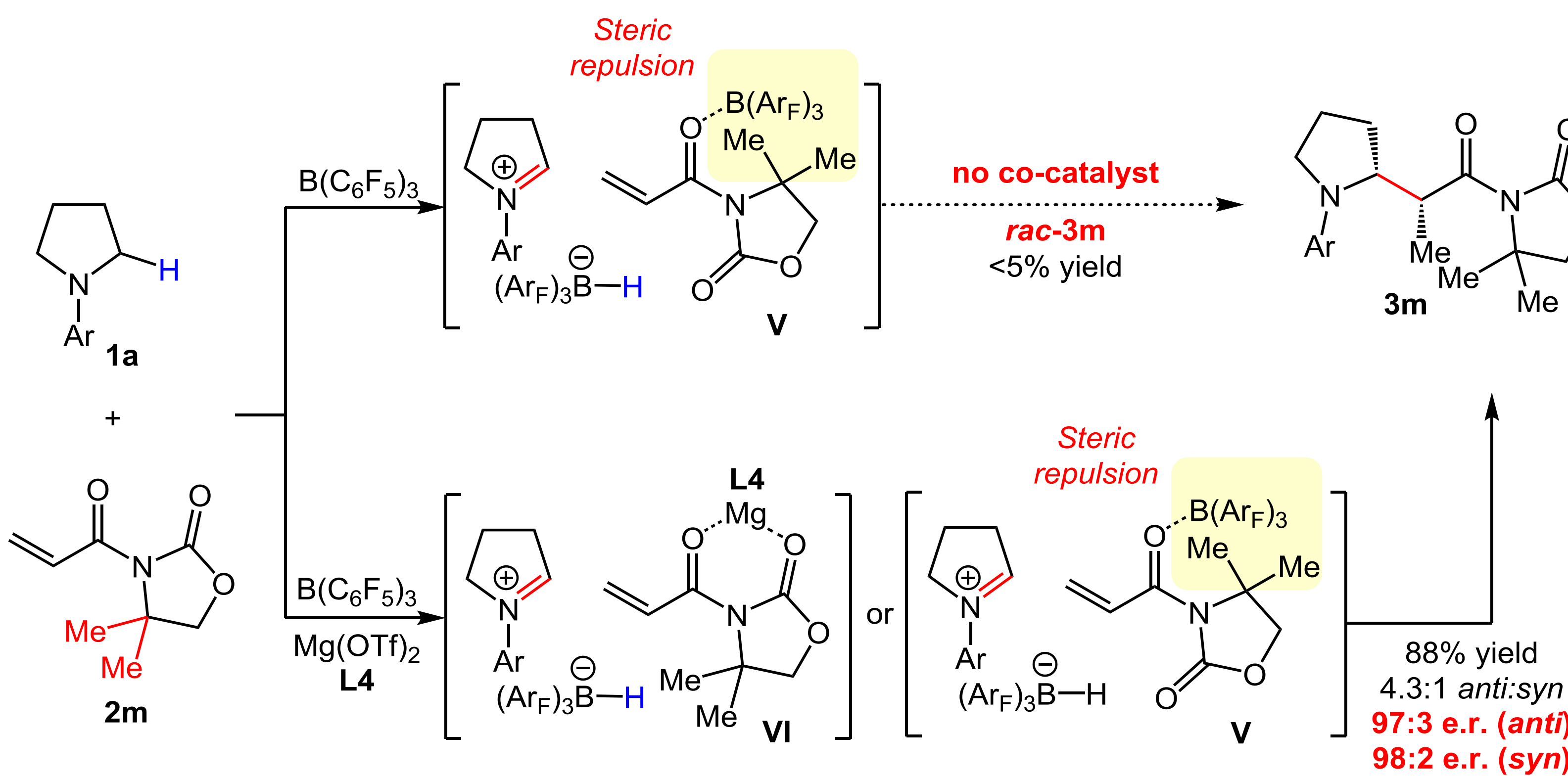


L1	L2	L3	L4
		L3: Ar = Ph	**L4**: Ar = 3-ClC$_6$H$_4$
7% yield	<5% yield	35% yield	>95% yield
1.3:1 *anti:syn*	2.0:1 *anti:syn*	1.1:1 *anti:syn*	1.6:1 *anti:syn*
56:44 e.r. (*anti*)	50:50 e.r. (*anti*)	71:29 e.r. (*anti*)	80:20 e.r. (*anti*)
52:48 e.r. (*syn*)	50:50 e.r. (*syn*)	80:20 e.r. (*syn*)	68:32 e.r. (*syn*)

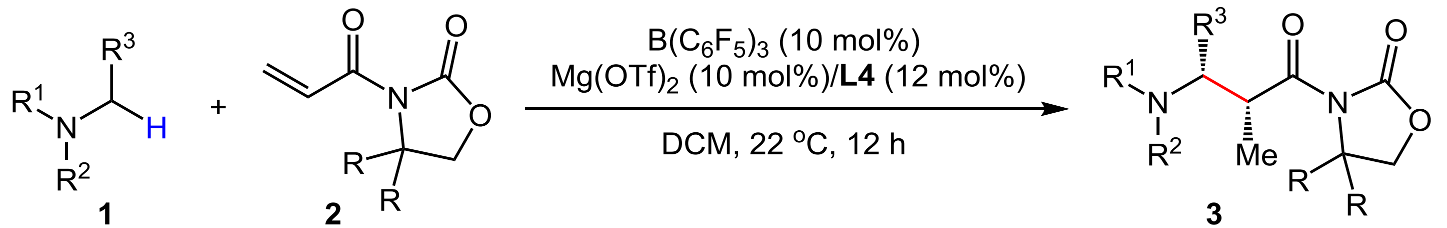
Enantioselective C-H Functionalization of Amines

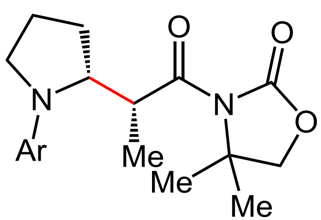


Enantioselective C-H Functionalization of Amines



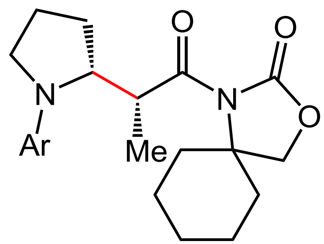
Substrate Scope





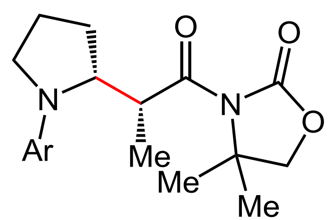
Ar = 2,6-Me$_2$-4-MeOC$_6$H$_2$

3m: 88% yield
anti:syn: 4.3:1
anti: 97:3 e.r.
syn: 98:2 e.r.



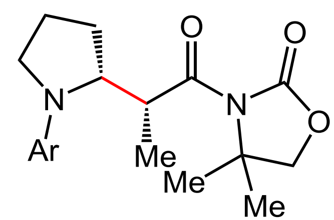
Ar = 2,6-Me$_2$-4-MeOC$_6$H$_2$

3n: 79% yield
anti:syn: 5.6:1
anti: 95:5 e.r.
syn: 98:2 e.r.



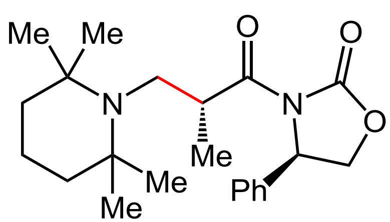
Ar = 2,6-Me$_2$C$_6$H$_3$

3o-*anti*
56% yield, 89:11 e.r.
3o-*syn*
15% yield, 93:7 e.r.

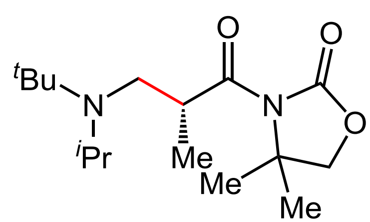


Ar = 2,6-Me$_2$-4^{t}BuC$_6$H$_2$

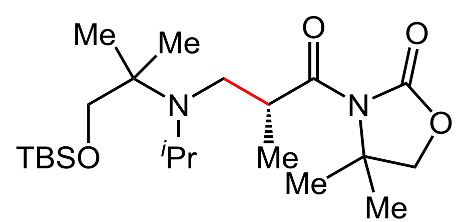
3p-*anti*
57% yield, 91:9 e.r.
3p-*syn*
13% yield, 98:2 e.r.



3r-major: 47% yield, >99:1 e.r.
3r-minor: 24% yield, >99:1 e.r.

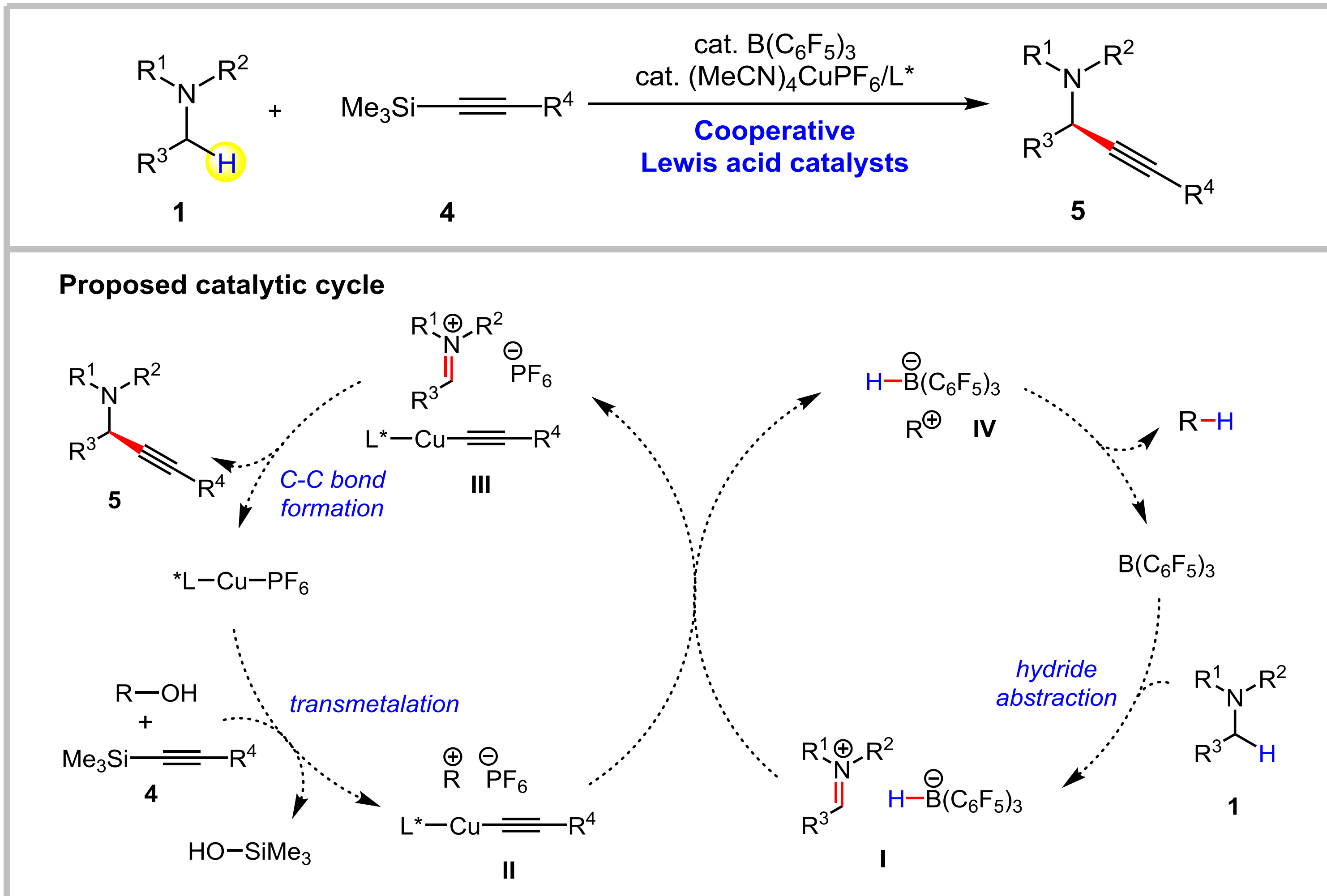


3s: 52% yield
88:12 e.r.



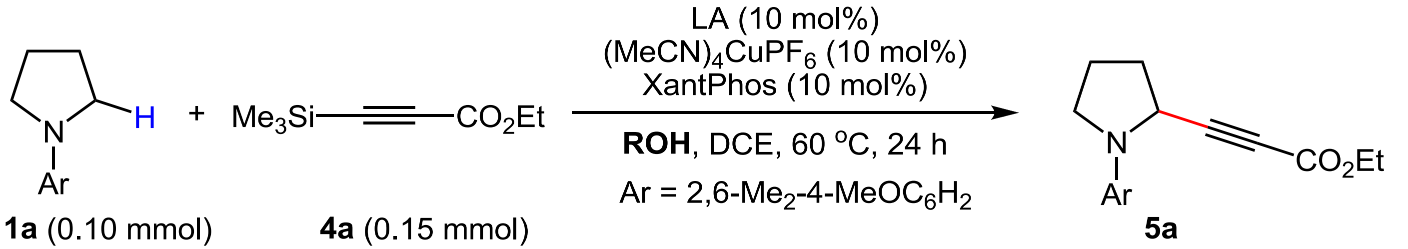
3t: 46% yield
96:4 e.r.

Enantioselective C-H Functionalization of Amines



Wasa, M. *et al. J. Am. Chem. Soc.* **2020**, *142*, 16493

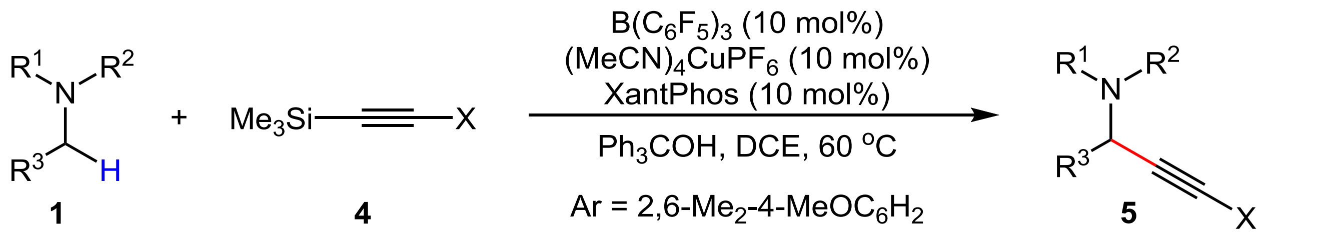
C-H Functionalization of Amines

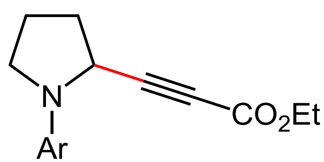


Entry	LA	ROH (x mmol)	Yield of **5a** (%)
1	$B(C_6F_5)_3$	none	7
2	$B(C_6F_5)_3$	^{i}PrOH (0.20)	0
3	$B(C_6F_5)_3$	^{t}BuOH (0.20)	17
4	$B(C_6F_5)_3$	Ph_3COH (0.20)	52
5	$B(C_6F_5)_3$	Ph_3COH (0.10)	83
6[a]	**$B(C_6F_5)_3$**	**Ph_3COH (0.10)**	**90**
7	none	Ph_3COH (0.10)	0
8	BPh_3	Ph_3COH (0.10)	0

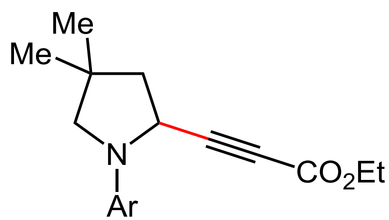
[a] 12 h

Substrate Scope

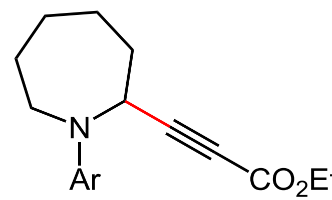




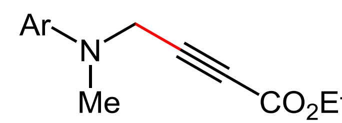
5a: 90% yield



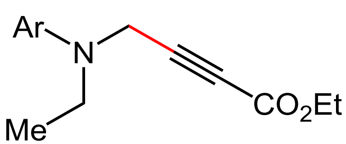
5b: 77% yield



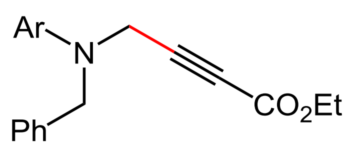
5c: 77% yield



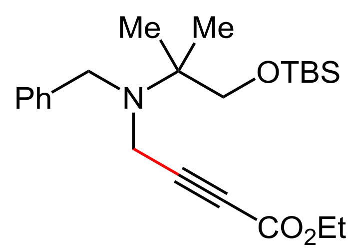
5d: 90% yield



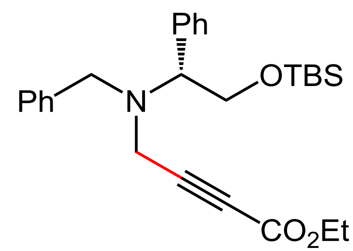
5e: 42% yield



5f: 70% yield



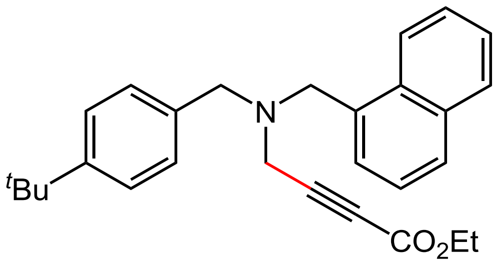
5g: 76% yield[a]



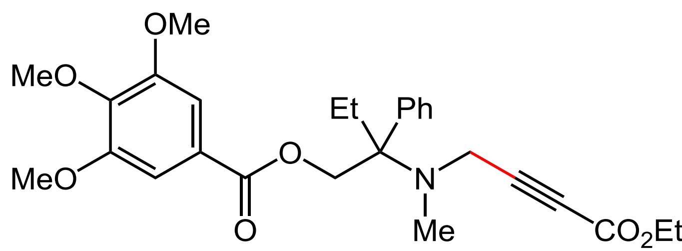
5h: 86% yield[a]

[a] Dppe (10 mol %), Ph_3COH (2.0 equiv.), 80 ^oC.

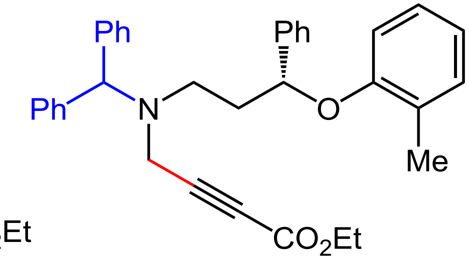
Substrate Scope



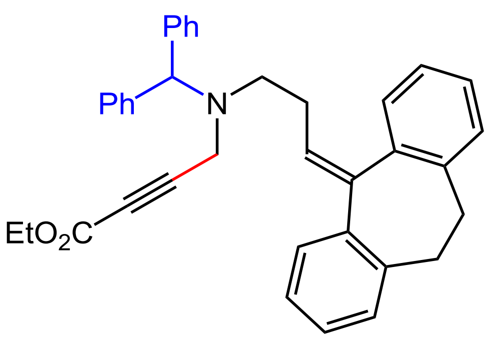
5i: 76% yield[a]
butenafine derivative



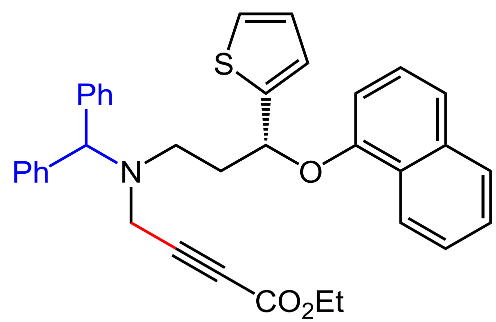
5j: 71% yield[a]
trimebutine derivative



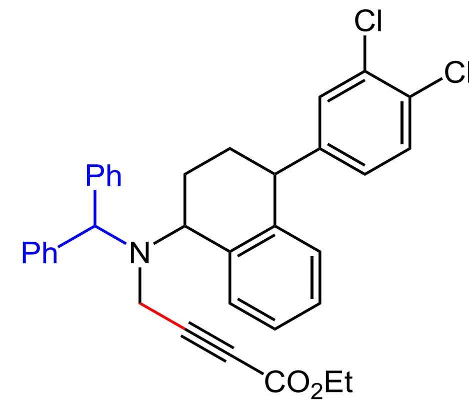
5k: 56% yield[a]
atomoxetine derivative



5l: 74% yield[a]
nortriptyline derivative



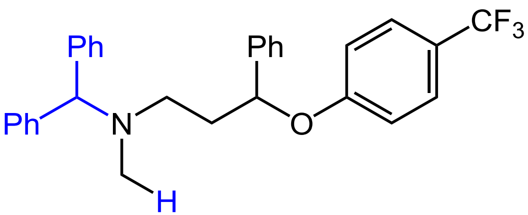
5m: 68% yield[a]
duloxetine derivative



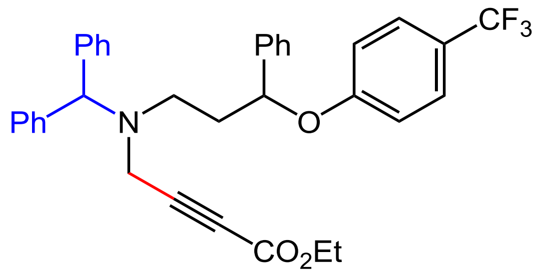
5n: 67% yield[a]
sertraline derivative

[a] Dppe (10 mol %), Ph_3COH (2.0 equiv.), 80 ^oC.

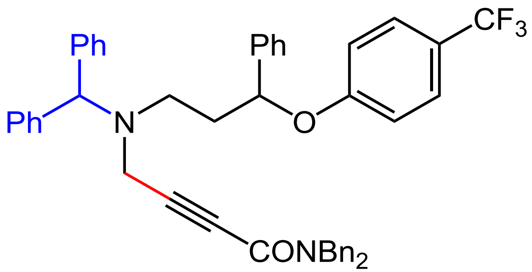
Substrate Scope



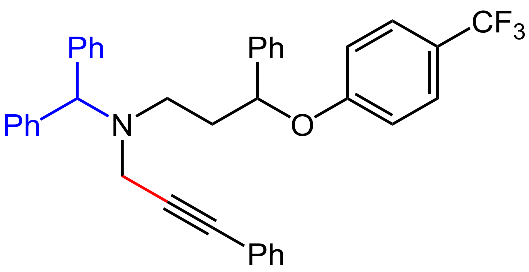
1o *N*-Bzh fluoxetine



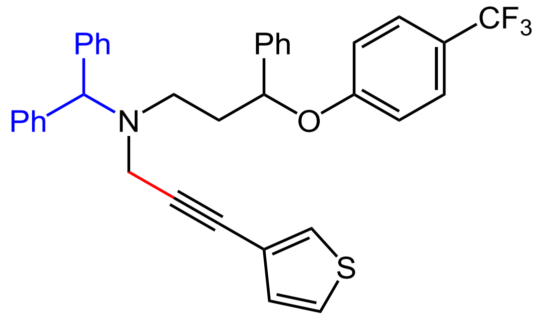
5oa: 82% yield[a]



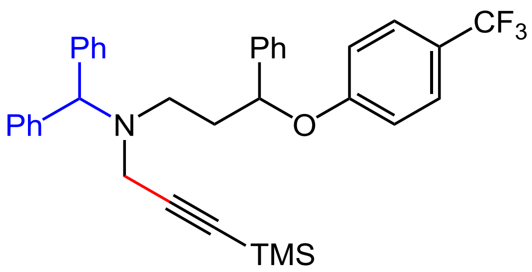
5ob: 80% yield[a]



5oc: 75% yield[a]



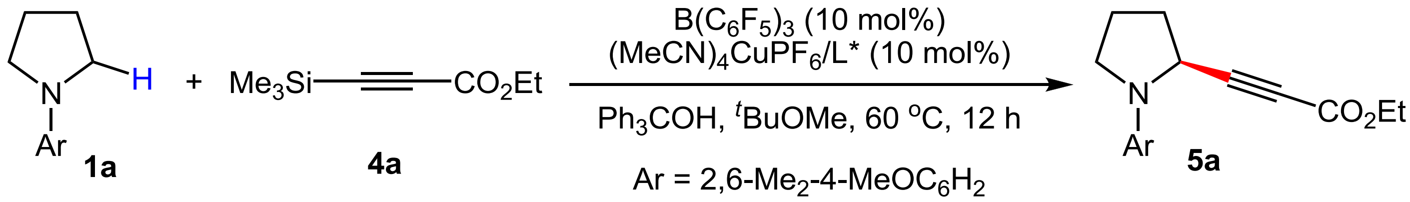
5od: 74% yield[a]

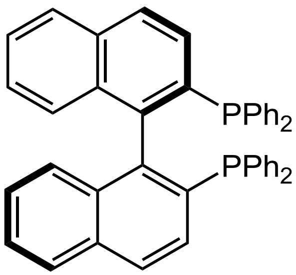


5oe: 87% yield[a]

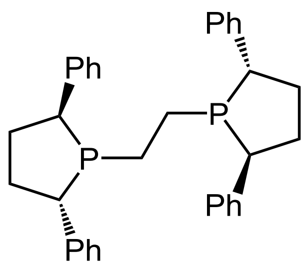
[a] Dppe (10 mol %), Ph_3COH (2.0 equiv.), 80 ^{o}C.

Enantioselective C-H Functionalization of Amines

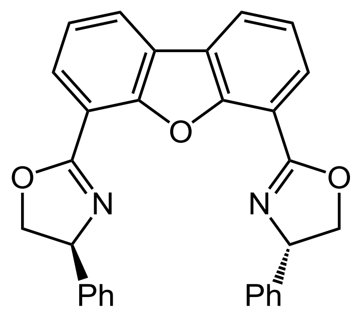




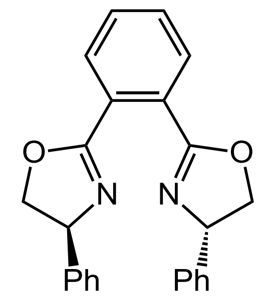
L1: 61% yield, 49:51 e.r.



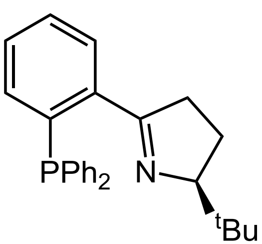
L2: 70% yield, 45:55 e.r.



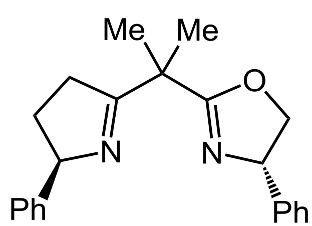
L3: 6% yield, 72:28 e.r.



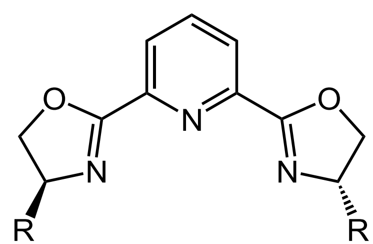
L4: 29% yield, 66:34 e.r.



L5: 15% yield, 41:59 e.r.

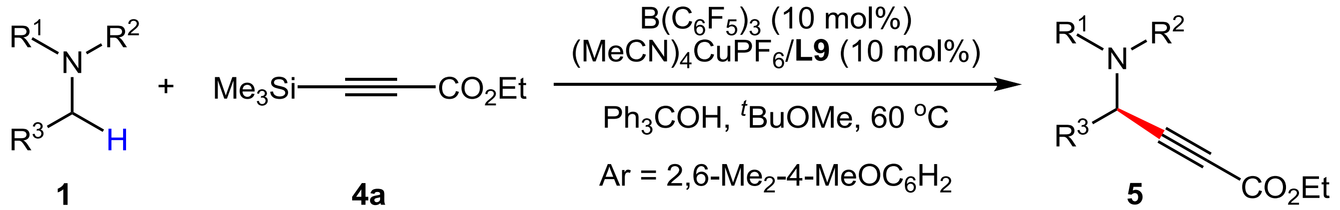


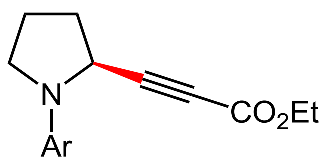
L6: 53% yield, 48:52 e.r.



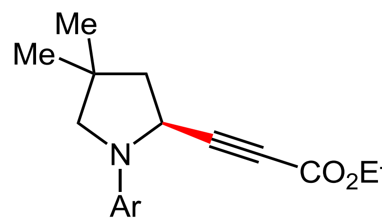
L7: R = ^tBu
81% yield, 52:48 e.r.
L8: R = Ph
84% yield, 82:18 e.r.
L9: R = 3,5-$Me_2C_6H_3$
75% yield, 95:5 e.r.

Substrate Scope

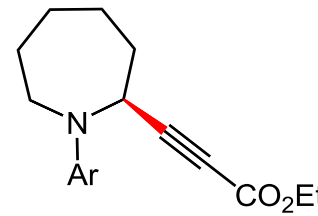




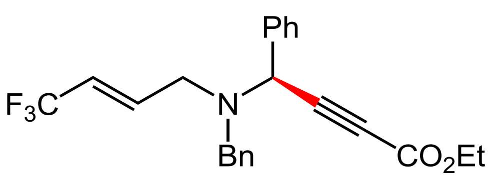
5a: 75% yield, 95:5 e.r.



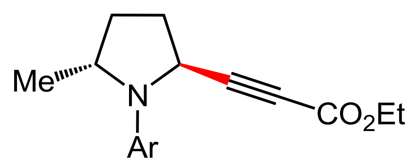
5b: 69% yield, 93:7 e.r.



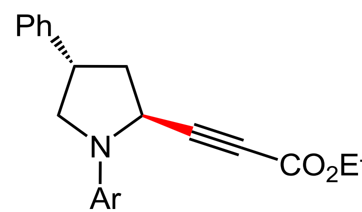
5c: 64% yield, 95:5 e.r.



5p: 64% yield, 84:16 e.r.

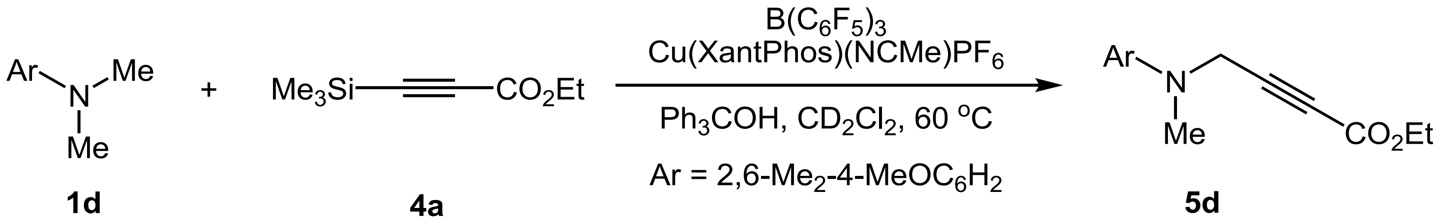


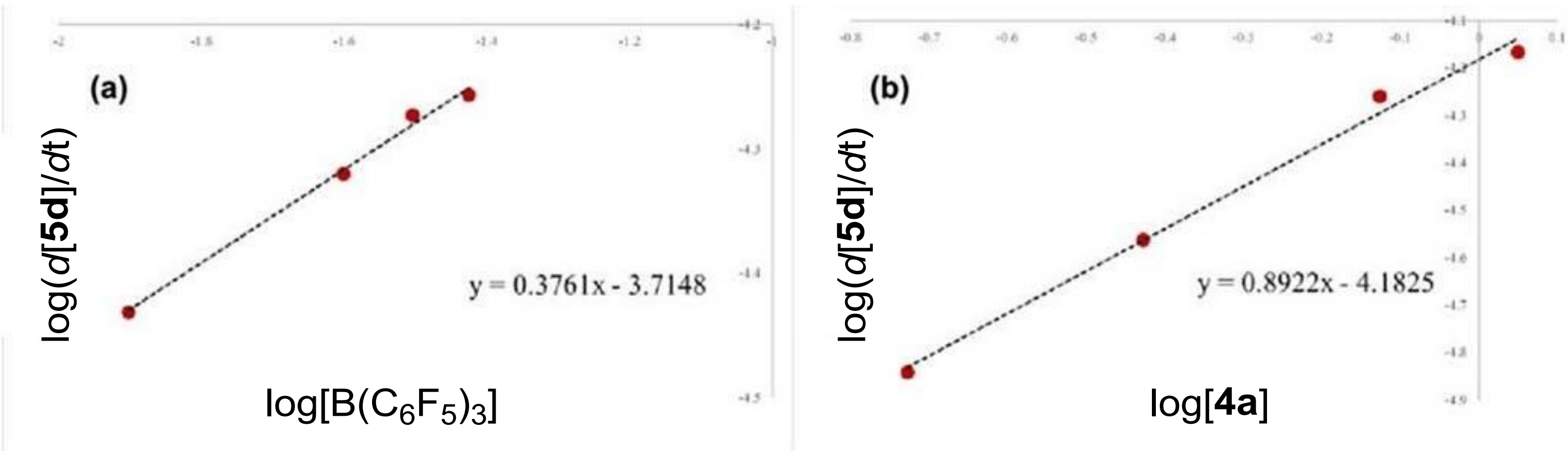
5q: 66% yield
6.3:1 (*trans:cis*)
83:17 e.r. (*trans*)



5r: 68% yield
10.1:1 (*trans:cis*)
88:12 e.r. (*trans*)

Kinetic Studies

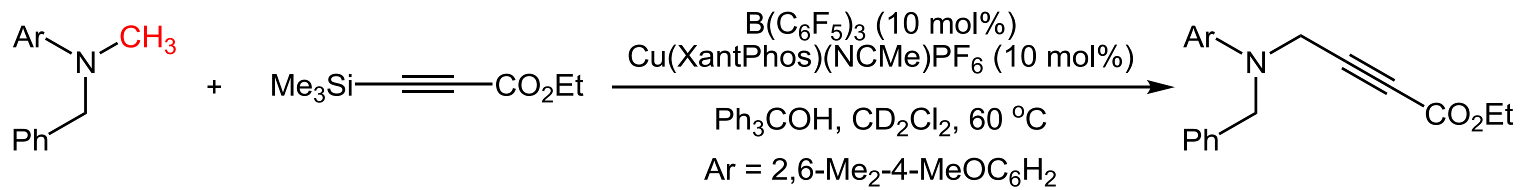




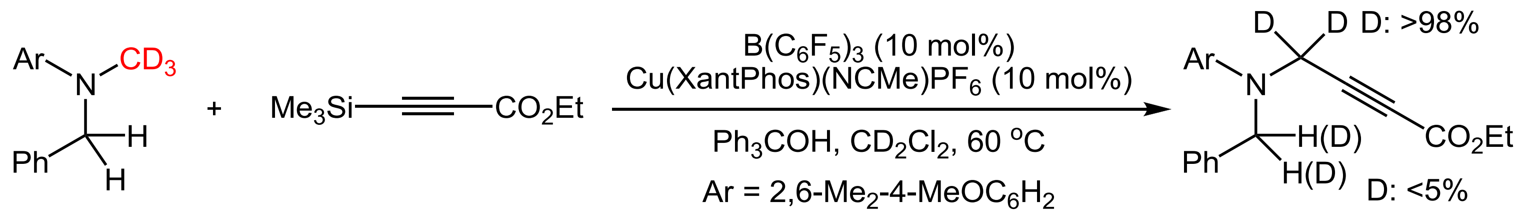
The reaction of 1d and 4a to afford propargylamine 5d was found to be 0.5-order in $B(C_6F_5)_3$ and 1.0-order in alkyne.

These data imply that C-H bond cleavage through $B(C_6F_5)_3$ catalyzed hydride abstraction occurs after the turnover-limiting step.

Kinetic Isotope Effect Studies



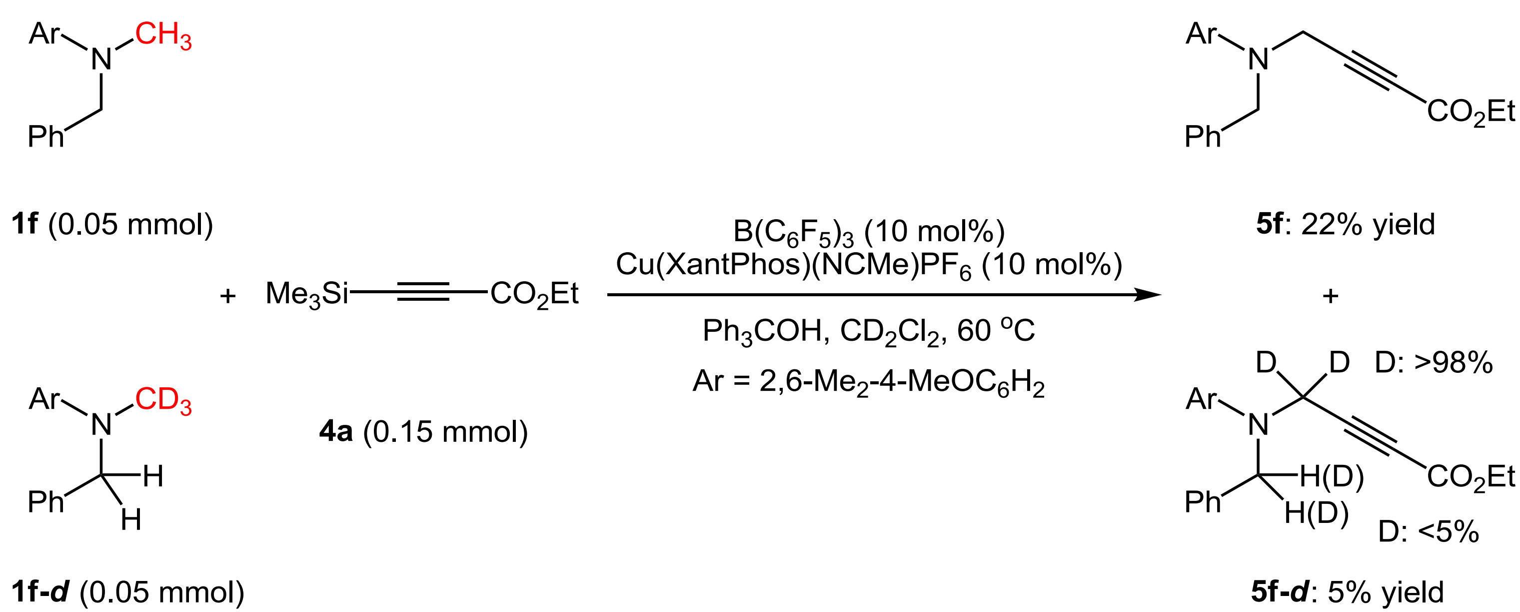
1f (0.10 mmol) **4a** (0.15 mmol) **5f**



1f-*d* (0.10 mmol) **4a** (0.15 mmol) **5f-*d***

$$k_H/k_D = 1.02 \pm 0.02$$

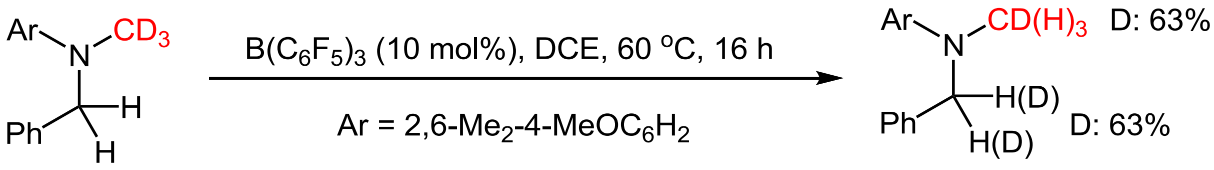
Kinetic Isotope Effect Studies



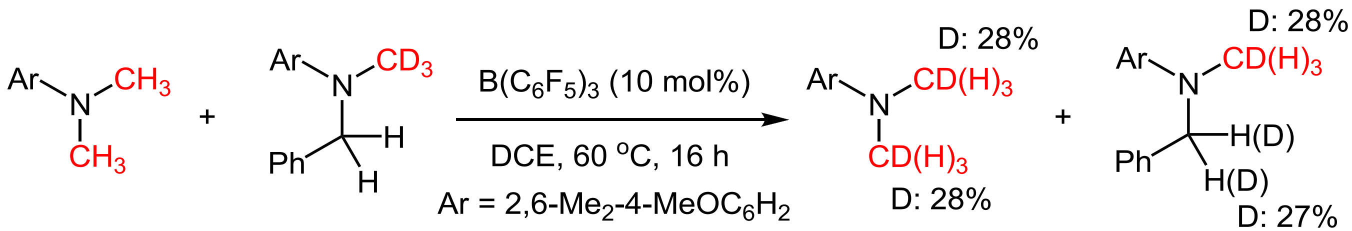
$k_H/k_D = 4.4$

These data imply that the turnover-limiting step is before the $(F_5C_6)_3B$-catalyzed hydride abstraction and that the C-H bond cleavage step isirreversible.

Isotope Experiments



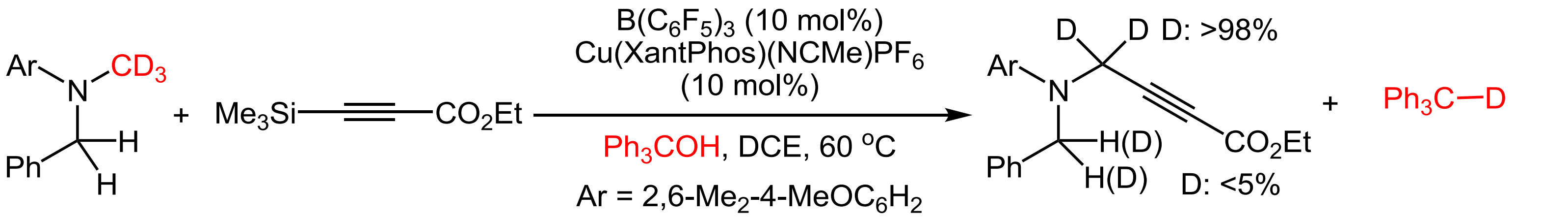
1f-*d* (0.10 mmol) **6f-*d***: >95% yield



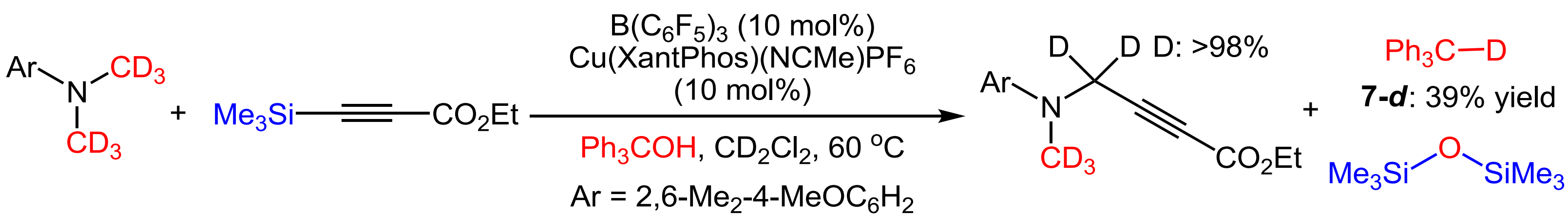
1d (0.10 mmol) **1f-*d*** (0.10 mmol) **6d-*d***: >95% yield **6f-*d***: >95% yield

C-H bond cleavage step is irreversible

Structure Determination of Products

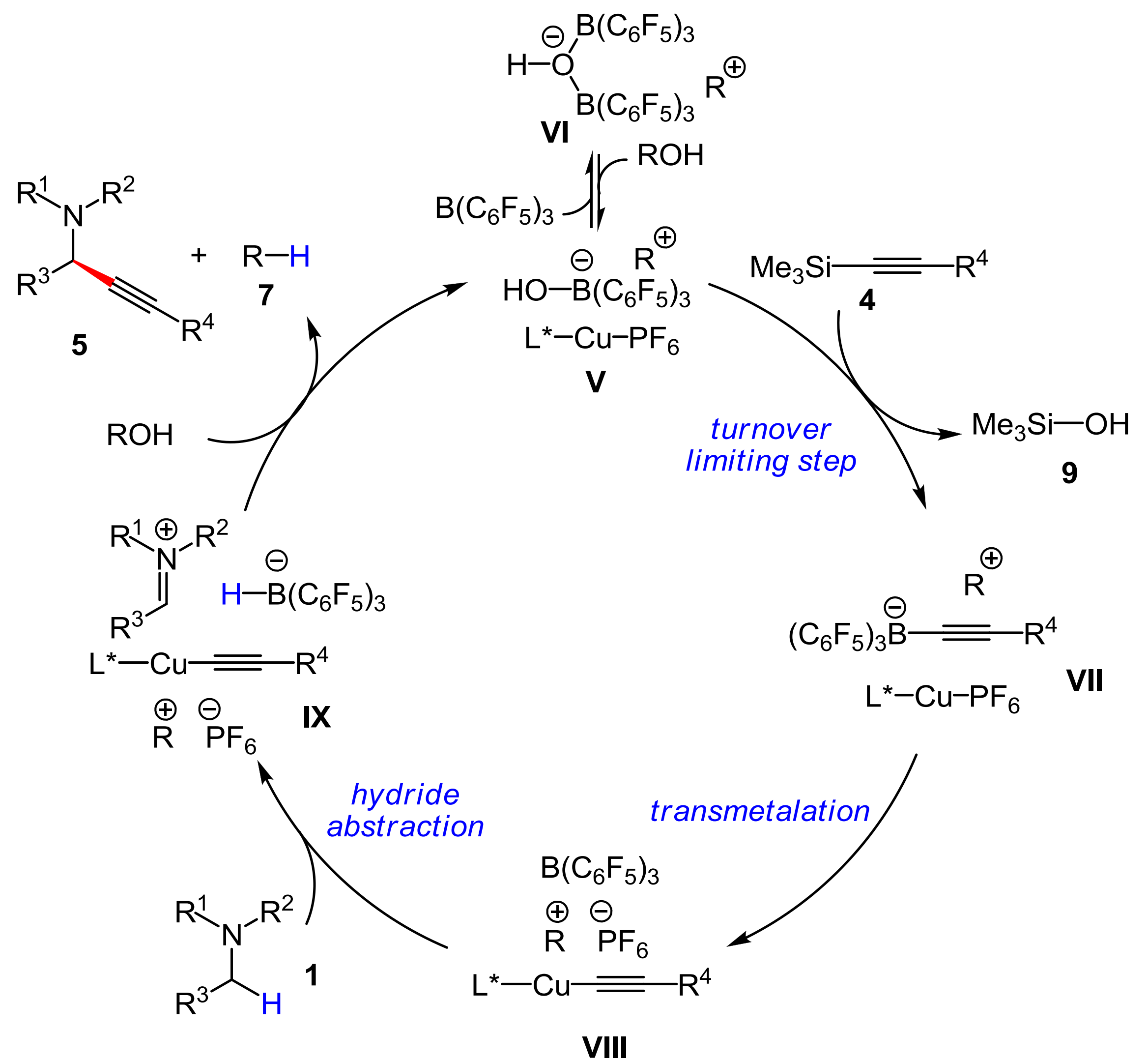


1f-*d* (0.10 mmol) **4a** (0.15 mmol) **5f-*d***: 31% yield **7-*d***: 24% yield

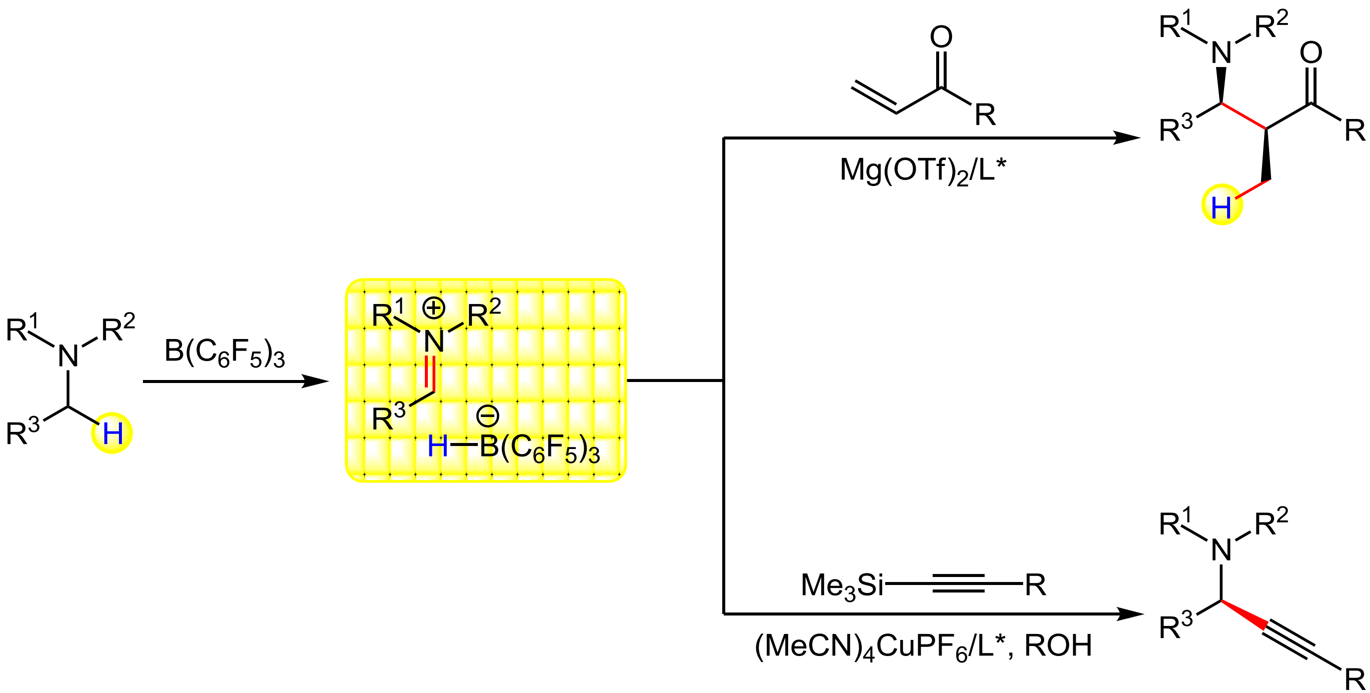


1d-*d* (0.10 mmol) **4a** (0.15 mmol) **5d-*d***: 37% yield **8**: 14% yield

Mechanism of Catalytic Process



Summary



Wasa, M. *et al*. *J. Am. Chem. Soc.* **2018**, *140*, 10593;
J. Am. Chem. Soc. **2020**, *142*, 16493.

The First Paragraph

Writing Strategy

The importance of propargylamines

↓

Methods for the preparation of chiral propargylamines

↓

The advantages of direct conversion of alkylamines to propargylamines

The First Paragraph

Propargylamines are prevalent in pharmaceuticals and are commonly used as intermediates in the synthesis of bioactive amines. Enantiomerically enriched propargylamines have been prepared by the addition of an alkynylmetal compound to an imine. An attractive alternative would entail the conversion of an α-amino $C(sp^3)$-H bond into an α-C-alkynyl bond. One way to accomplish this would be through in situ generation of an iminium ion intermediate formed from the corresponding amine under oxidative conditions. An illustrative case is enantioselective Cu-PyBOX-catalyzed coupling of a benzylic α-amino C-H bond of *N*-phenyl tetrahydroisoquinoline **1a** with ethynylbenzene **2a** to afford propargylamine **3a**.

The First Paragraph

Still, development of a nonprecious transition metal- and oxidant-free catalytic C-H functionalization process represents a compelling research objective. Particularly noteworthy would be the direct conversion of α-C−H bonds contained in bioactive *N*-alkylamines into α-C-alkynyl bonds, because these entities constitute over 50% of the top-selling drugs; the resulting derivatives of these pharmaceuticals possessing the alkyne unit can serve as modifiable intermediates for late-stage structural diversification that could lead to new leads and/or more effective therapeutics.

The Last Paragraph

Writing Strategy

Summary of this work

↓

Significance of this work

The Last Paragraph

In summary, we developed an efficient and diastereo- and enantioselective method for the activation of α-amino C-H bonds to generate propargylamines. We find that by using a blend of $B(C_6F_5)_3$ and an organocopper complex, it is possible to generate an iminium from a *N*-alkylamine, and a L_nCu-alkynyl complex from an alkynyl-silane. The catalyst system tolerates a wide variety of Lewis acid-sensitive functional groups and is therefore applicable to the late-stage transformation of a complex (and bioactive) trialkyl amine molecule to its derived propargylamine. Mechanistic investigations indicate that the turnover-limiting step occurs prior to $(F_5C_6)_3B$-catalyzed C-H abstraction and that $(F_5C_6)_3B$ catalyzed C-H abstraction is an irreversible process under the reaction conditions for alkyne incorporation.

The Last Paragraph

The principles outlined here demonstrate that the proper combination of an achiral organoborane and a chiral organometallic catalyst can be used for chemo- and enantioselective C-H bond activation, providing a rational framework for the further development of processes involving the late-stage stereoselective α-functionalization of bioactive amines. Studies aimed at achieving these objectives are currently underway.

Representative Examples

An attractive alternative would entail the conversion of an α-amino C(sp3)−H bond into an α-C-alkynyl bond. (阐述合成方法)

Still, development of a nonprecious transition metal- and oxidant-free catalytic C-H functionalization process represents a compelling research objective. (引出方法的重要性)

To begin, we set out to identify a suitable combination of catalysts. (条件优化)

An assortment of cyclic and acyclic *N*-alkylanilines may be used in reaction with 3-(trimethylsilyl)propiolate to generate the corres-ponding propargylamines. (底物拓展)

We designed and performed studies aimed at shedding light on the mechanism of the catalytic process. (机理研究)

Acknowledgement

Thanks
for your attention