Transfer Hydroalumination of Alkynes

2025.5.10. Literature Seminar
M2 Sota Mochizuki

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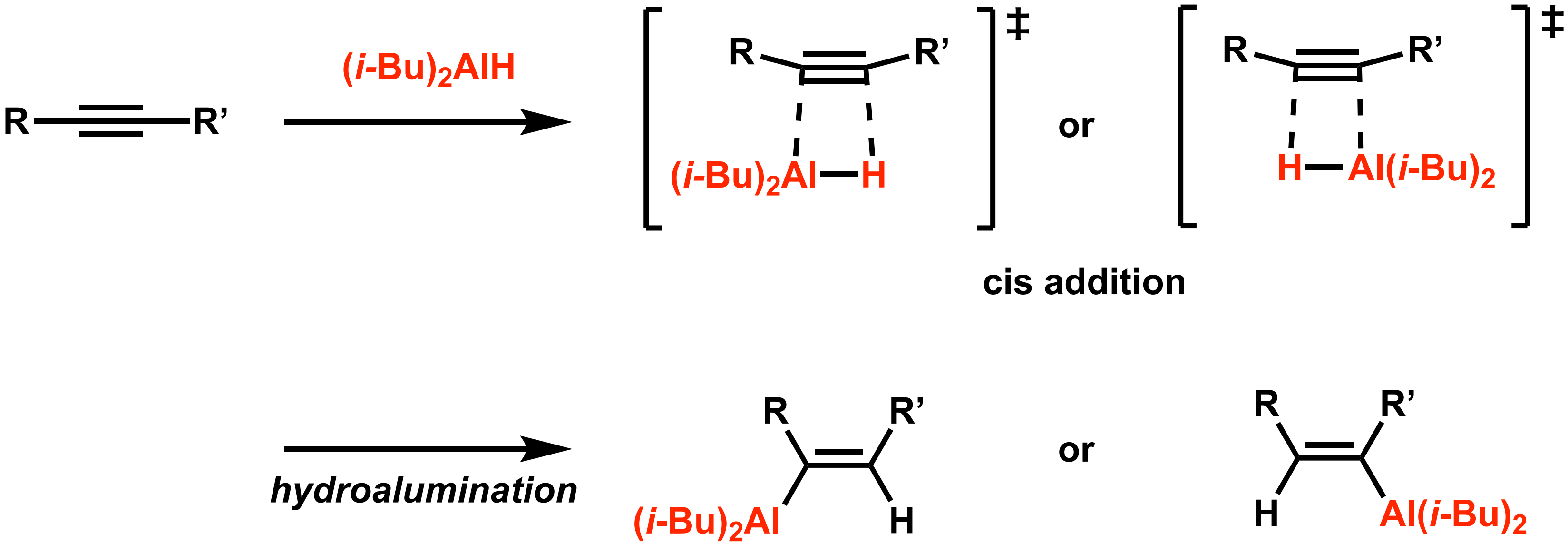
Hydroalumination of Alkynes



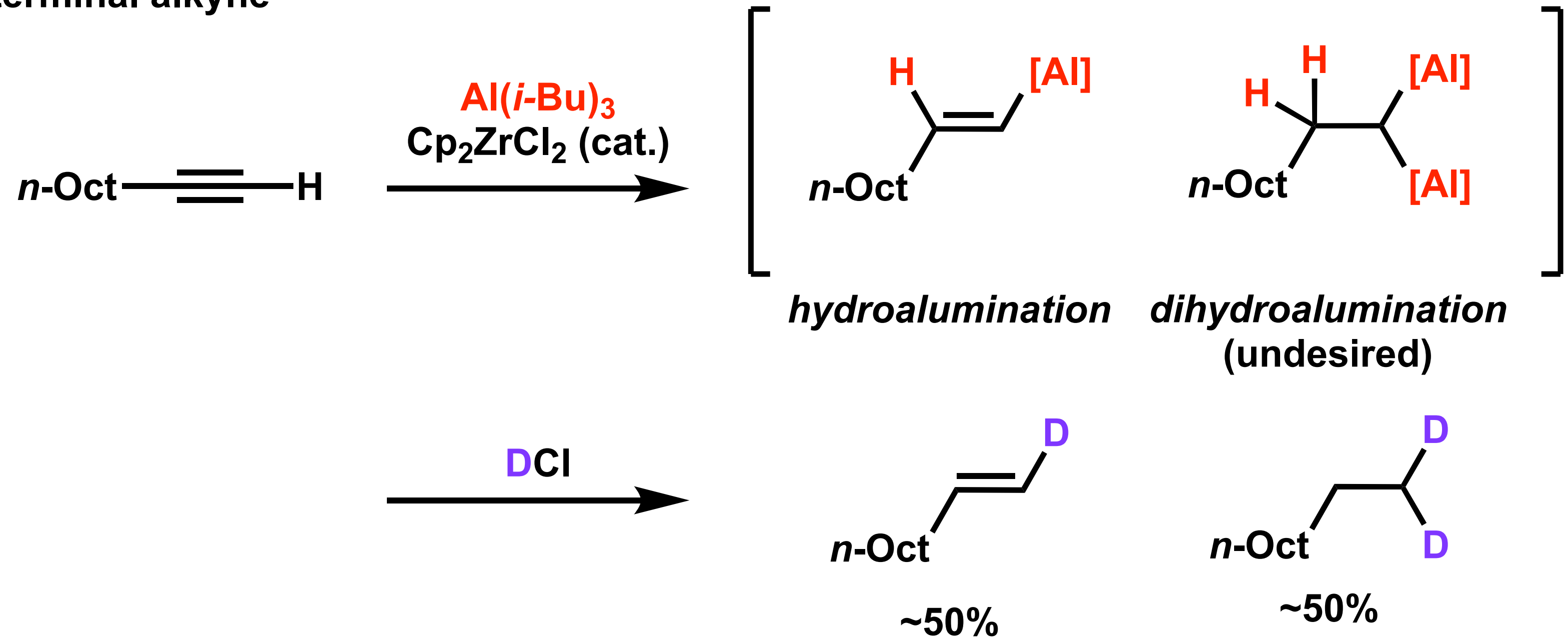
cis addition

generation of alkenyl aluminum species

regioselectivity → steric effect and electronic effect

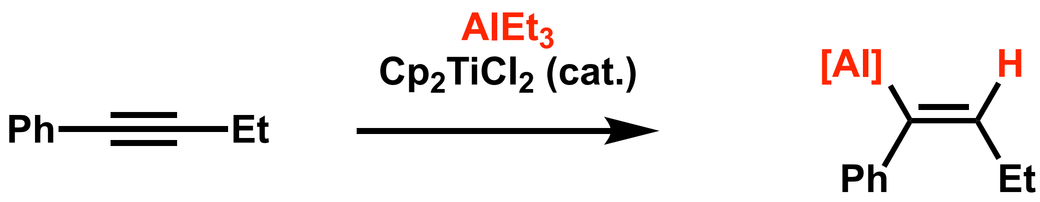
Transfer Hydroalumination: Previous Attemptions

- terminal alkyne [1)]



low chemoselectivity

- internal alkyne [2)]

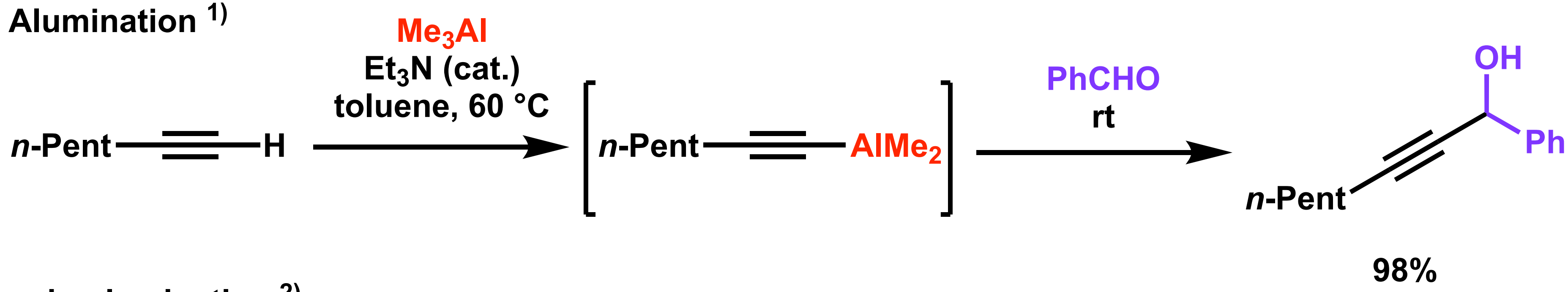


only one example

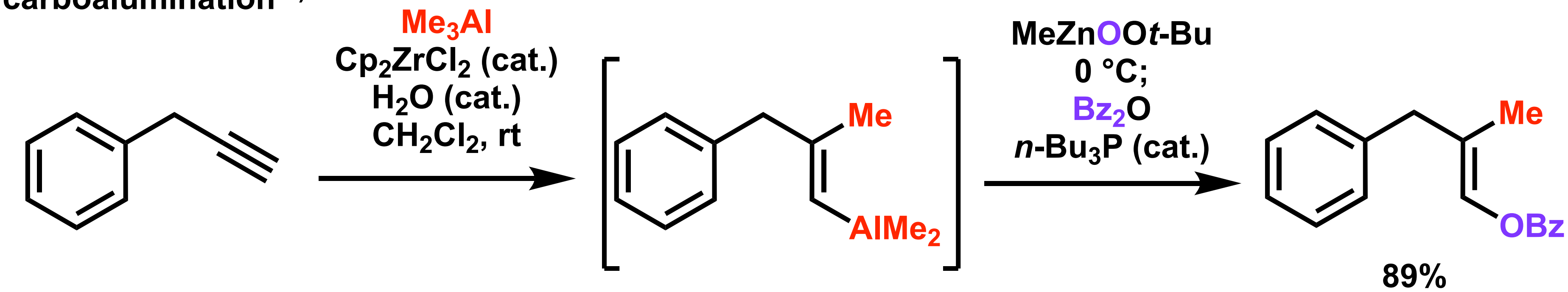
1) Negishi, E.; Kondakov, D. Y.; Choueiry, D.; Kasai, K.; Takahashi, T. *J. Org. Chem. Soc.* **1996**, *118*, 9577.
2) Ibragimov, A. G.; Ramazanov, I. R.; Khalilov, L. M.; Sultanov, R. M.; Dzhemilev, U. M. *Mendeleev Commun.* ***1996***, *6*, 231.

Possible Side Reactions in Transfer Hydroalumination

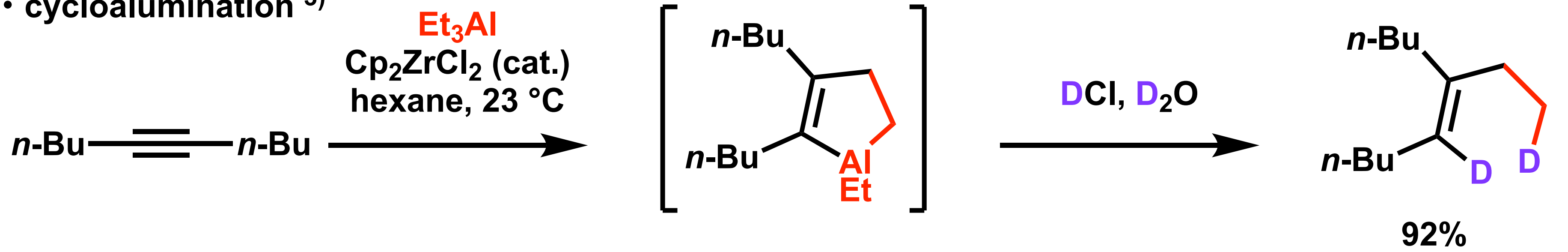
• Alumination [1)]



• carboalumination [2)]



• cycloalumination [3)]



1) Feuvrie, C.; Blanchet, J.; Bonin, M.; Micouin, L. *Org. Lett.* **2004**, 6, 2333.
2) DeBergh, J. R.; Spivey, K. M.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7828.
3) Negishi, E.; Kondakov, D. Y.; Choueiry, D.; Kasai, K.; Takahashi, T. *J. Org. Chem. Soc.* **1996**, *118*, 9577.

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1. Introduction

2. Iron-Catalyzed Transfer Hydroalumination of Alkynes
(By Zhu group) (*J. Am. Chem. Soc*. **2025**, *147*, 15545.)

Introduction of Prof. Shou-Fei Zhu

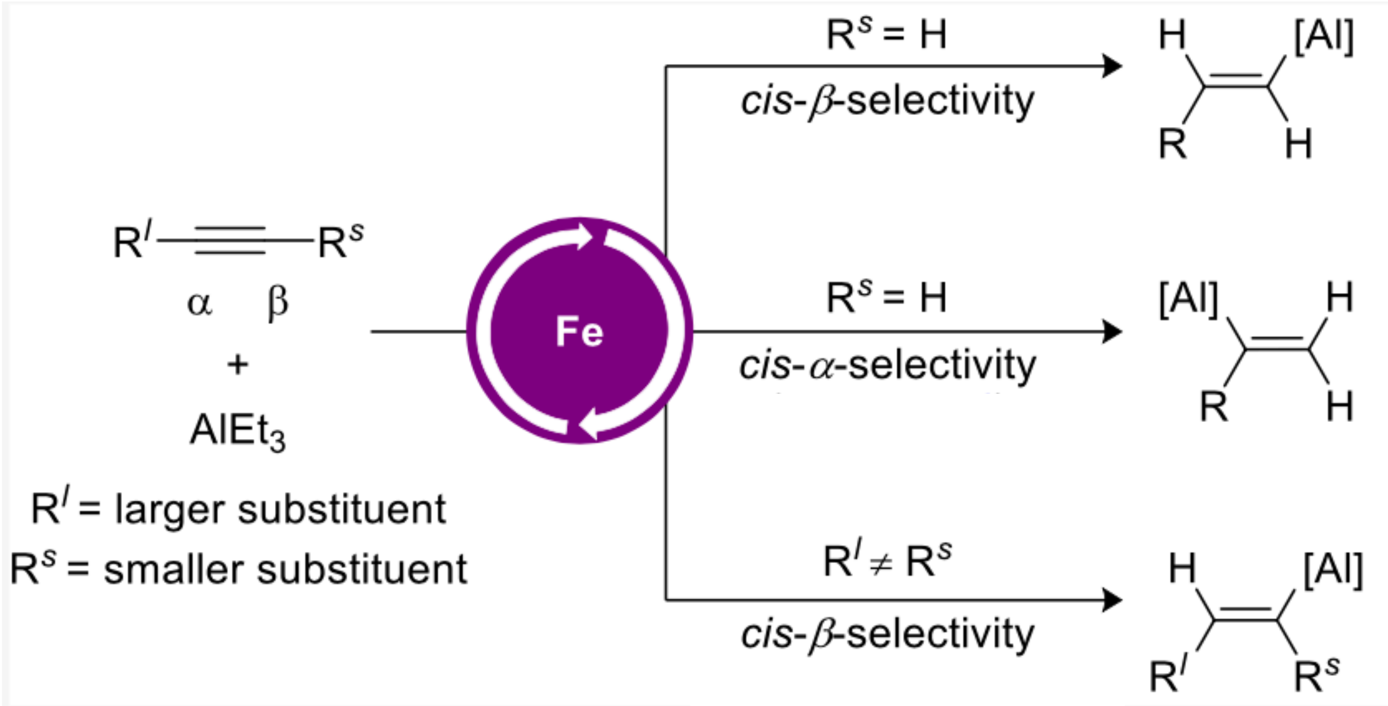
Prof. Shou-Fei Zhu

2000: B.S. @ Nankai University (Prof. Shou-He Xiang)
2005: Ph.D. @ Nankai University (Prof. Qi-Lin Zhou)
2012-2013: Postdoctoral Fellow @ University of Tokyo (Prof. Eiichi Nakamura)
2005-2008: Lecturer @ Nankai University
2008-2013: Associate Professor @ Nankai University
2013: Professor @ Nankai University

Research topics:
- **Organic synthesis**
- **Homogeneous catalysis**
- **Organometallic chemistry**

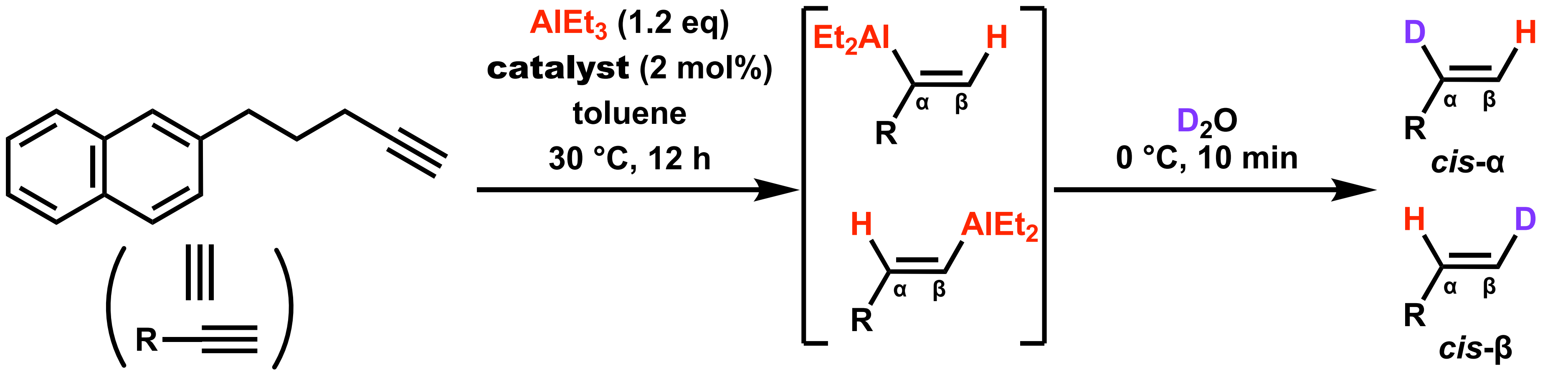
1) https://chemen.nankai.edu.cn/2021/0629/c24618a379104/page.htm

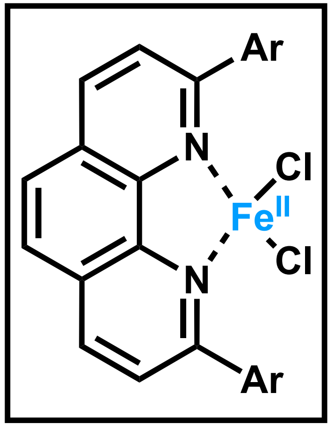
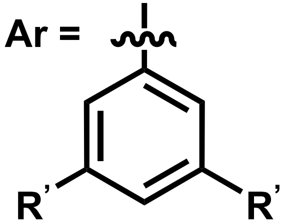
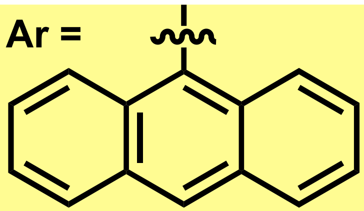
Iron-Catalyzed Transfer Hydroalumination of Alkynes



1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

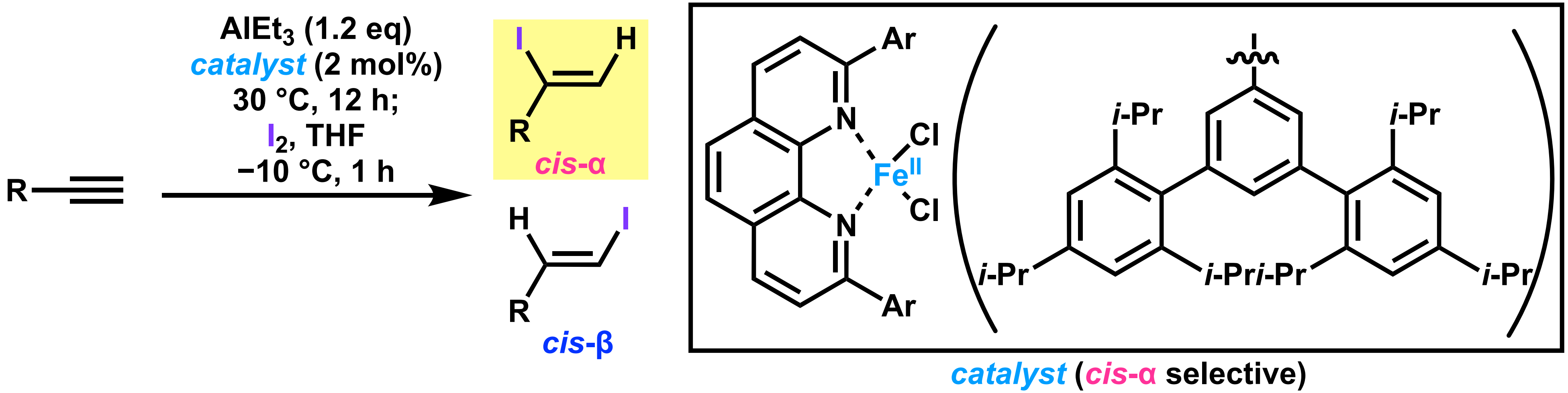
Optimization for Terminal alkynes

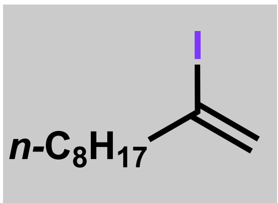


catalyst		conversion	yield (cis-α+cis-β)	r.r (cis-α / cis-β)
	Ar =  R' = 2,4,6-(i-Pr)$_3C_6H_2$	>99%	91%	> 98 : 2
	R' = 2,4,6-$Me_3C_6H_2$	>99%	73%	90 : 10
	R' = t-Bu	>99%	74%	90 : 10
	Ar = 	>99%	96%	5 : 95
Cp_2TiCl_2		66%	66%	91 : 9
Cp_2ZrCl_2		49%	not analyzed	not analyzed
$Ni(PPh_3)_2Cl_2$		80%	not analyzed	not analyzed
Ni(dppp)Cl_2		45%	not analyzed	not analyzed

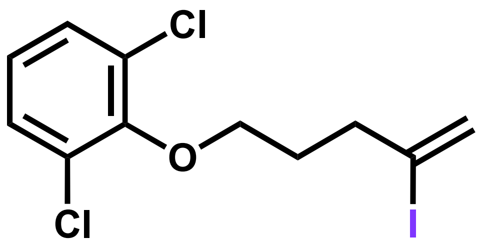
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

α-Selective Transfer hydroalumination of Terminal alkynes

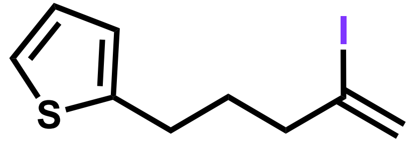




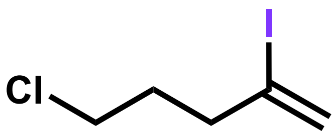
83% yield
(r.r. > 98 : 2)



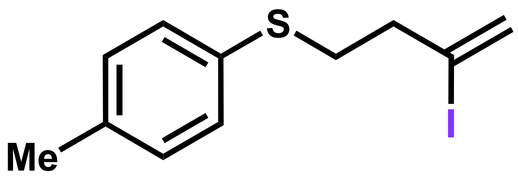
94% yield
(r.r. > 98 : 2)



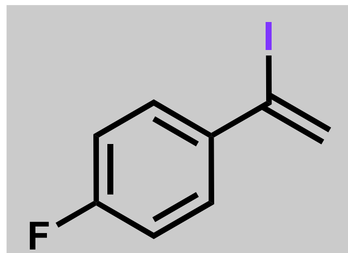
86% yield
(r.r. = 97 : 3)



58% yield
(r.r. = 98 : 2)



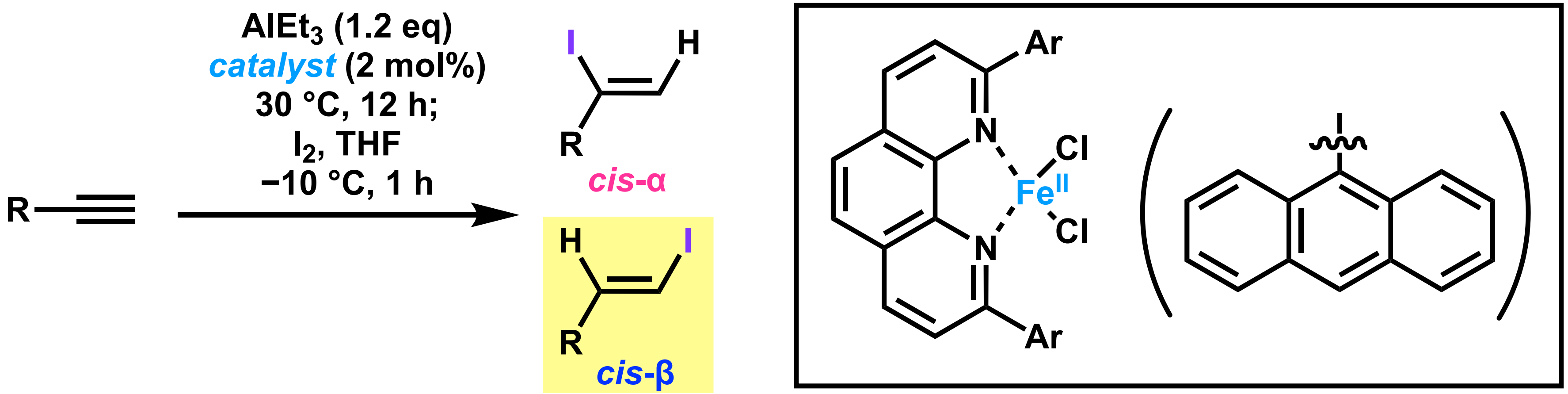
72% yield
(r.r. = 98 : 2)



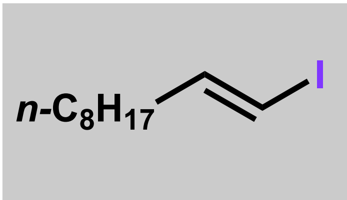
76% yield
(r.r. > 98 : 2)

1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

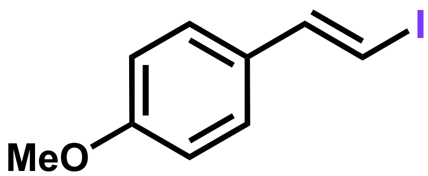
β-Selective Transfer hydroalumination of Terminal alkynes



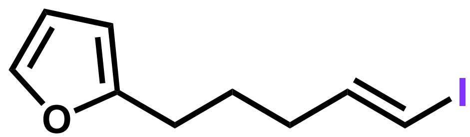
catalyst (cis-β selective)



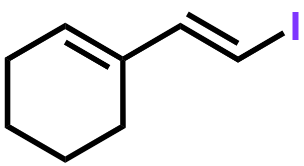
92% yield
(r.r. = 6 : 94)



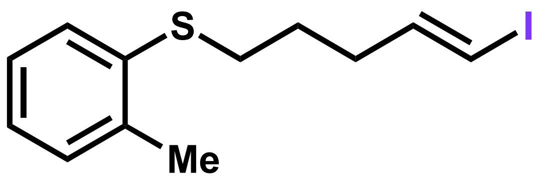
93% yield
(r.r. = 19 : 81)



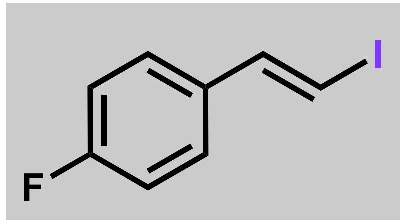
84% yield
(r.r. = 6 : 94)



92% yield
(r.r. = 6 : 94)



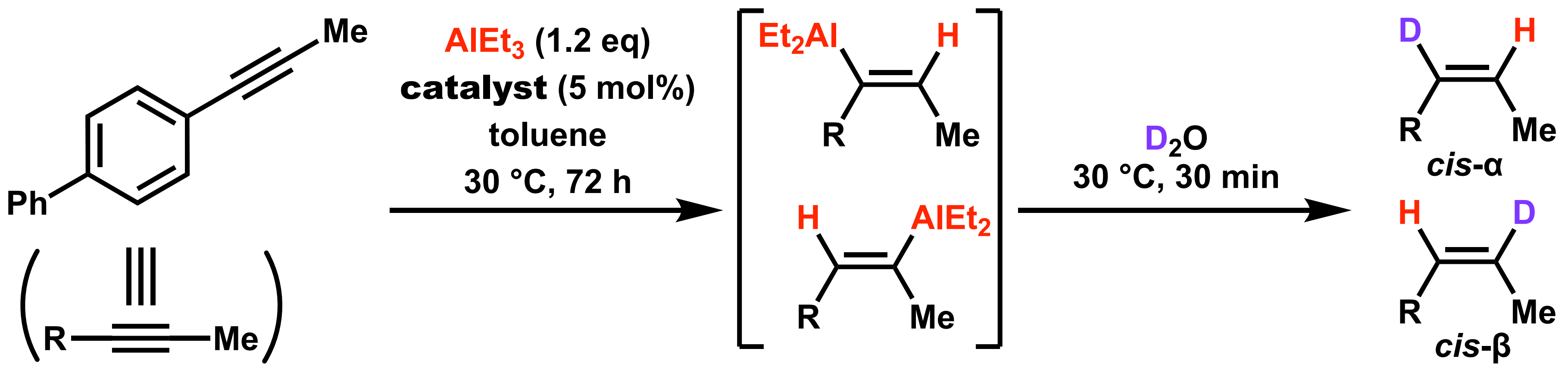
80% yield
(r.r. = 9 : 91)

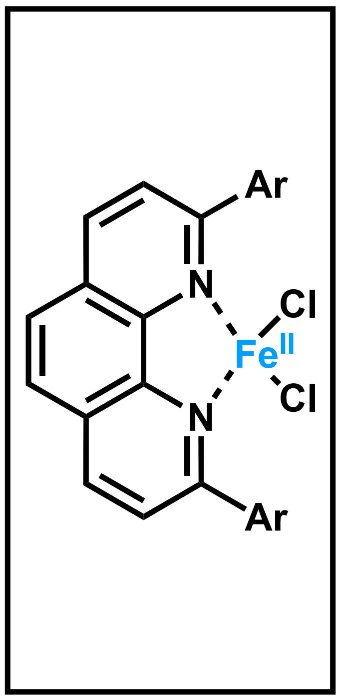
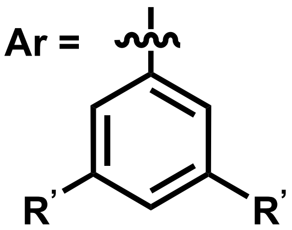
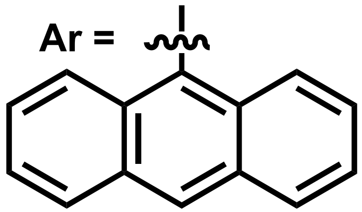
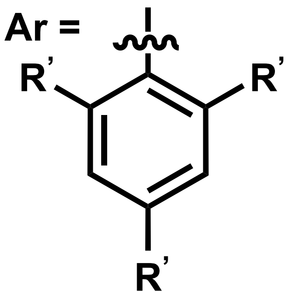


72% yield
(r.r. = 6 : 94)

1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

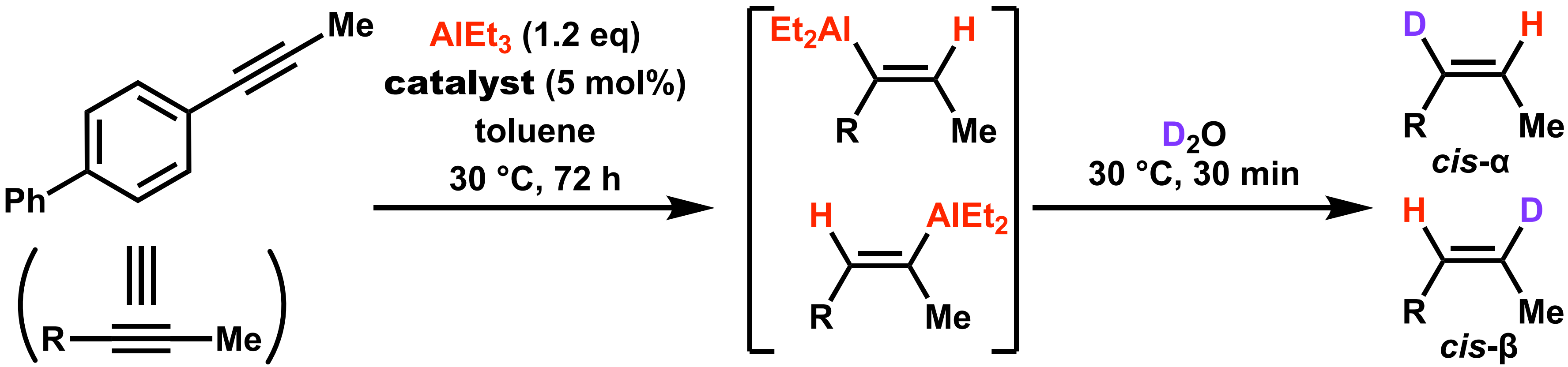
Optimization for Internal alkynes (1)

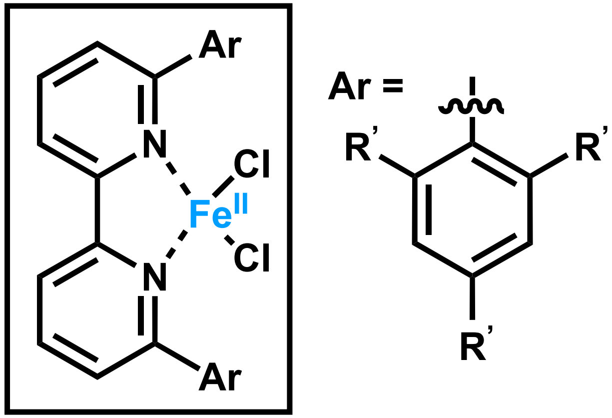


catalyst			conversion	yield (cis-α+cis-β)	r.r (cis-α / cis-β)
	Ar = 	R' = 2,4,6-(i-Pr)$_3$C$_6$H$_2$	>99%	80%	80 : 20
		R' = *t*-Bu	>99%	80%	33 : 67
	Ar = 		>99%	83%	22 : 78
	Ar = 	R' = Me	>99%	79%	10 : 90
		R' = Et	>99%	85%	15 : 85
		R' = *i*-Pr	**>99%**	**99%**	**10 : 90**

1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Optimization for Internal alkynes (2)

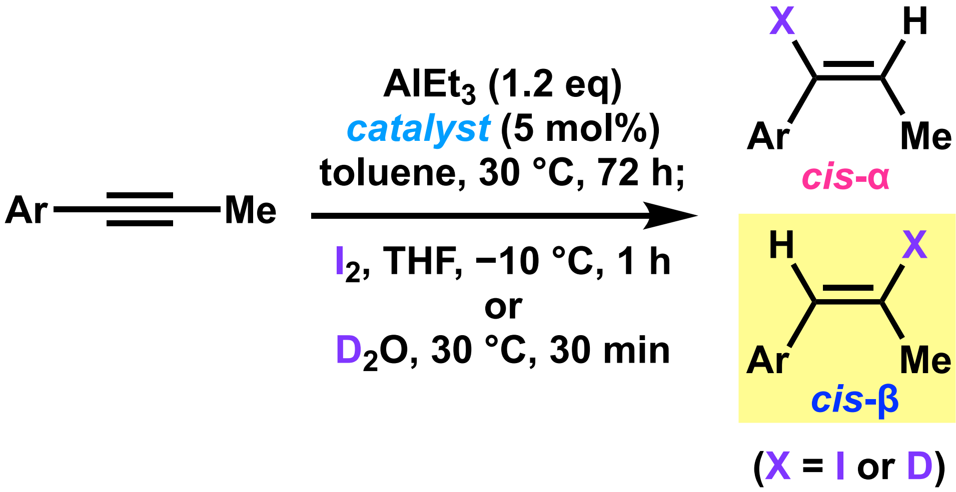


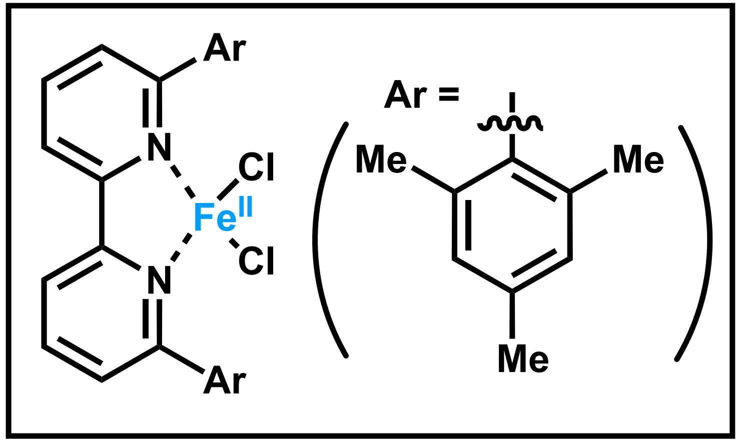


catalyst	conversion	yield (*cis*-α+*cis*-β)	r.r (*cis*-α / *cis*-β)
R' = Me	>99%	79%	6 : 94
R' = Et	>99%	85%	7 : 93
R' = *i*-Pr	87%	43%	10 : 90
Cp_2TiCl_2	>99%	99%	99 : 1
Cp_2ZrCl_2	>99%	0%	not analyzed
$Ni(PPh_3)_2Cl_2$	97%	30%	33 : 67
$Ni(dppp)Cl_2$	43%	11%	16 : 84

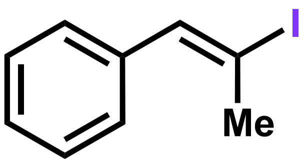
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

β-Selective Transfer Hydroalumination of Internal alkynes

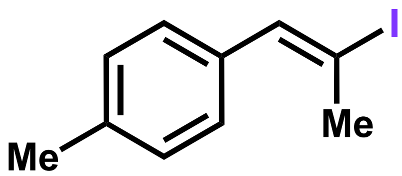




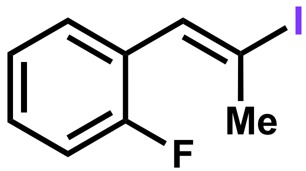
catalyst (*cis*-β selective)



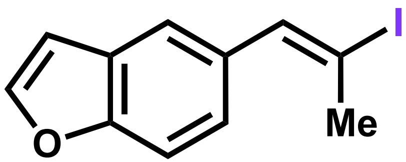
66% yield
(r.r. = 7 : 93)



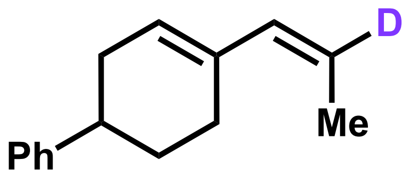
88% yield
(r.r. = 8 : 92)



99% yield
(r.r. = 8 : 92)



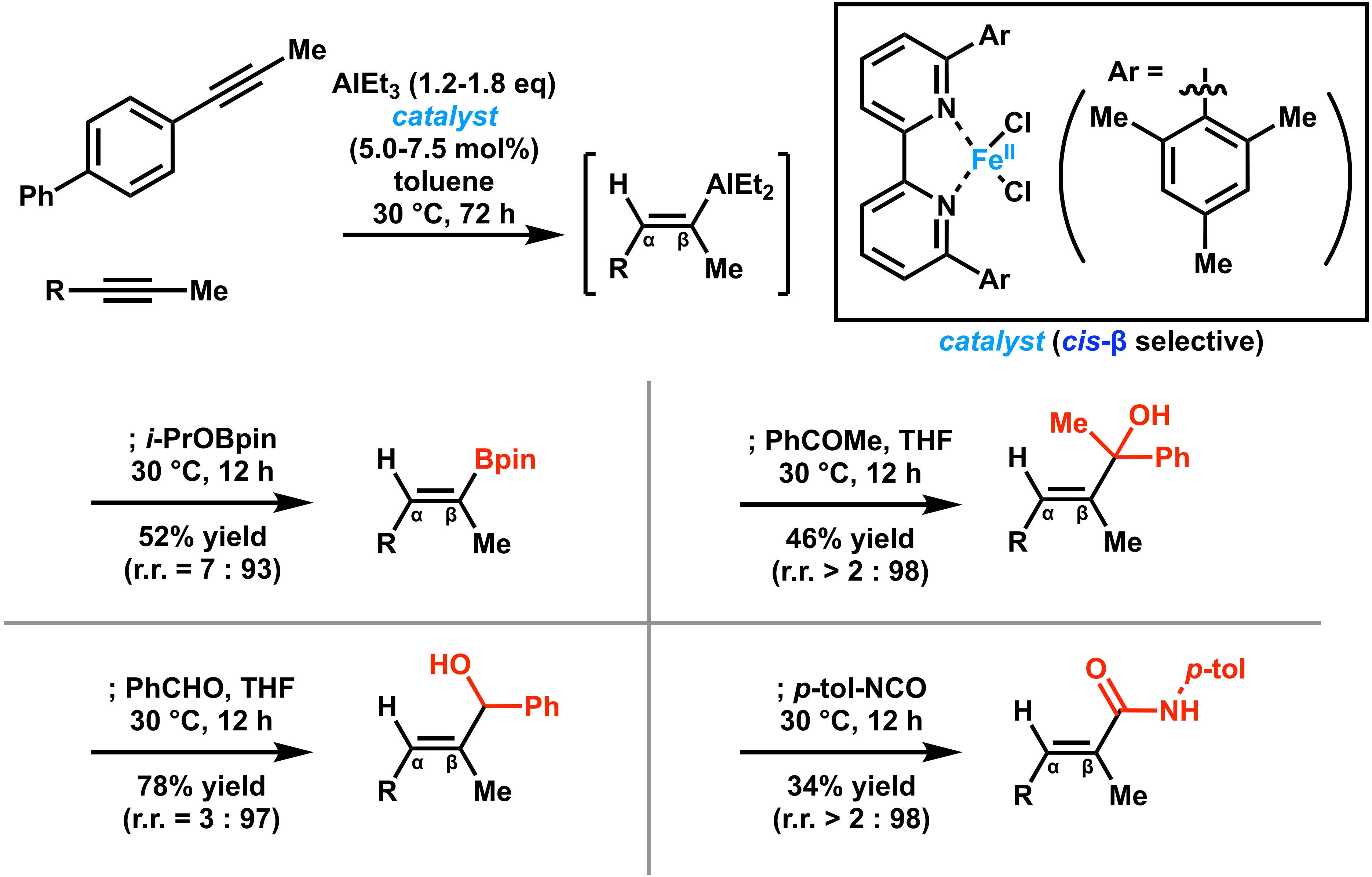
82% yield
(r.r. = 8 : 92)



85% yield
(r.r. = 4 : 96)

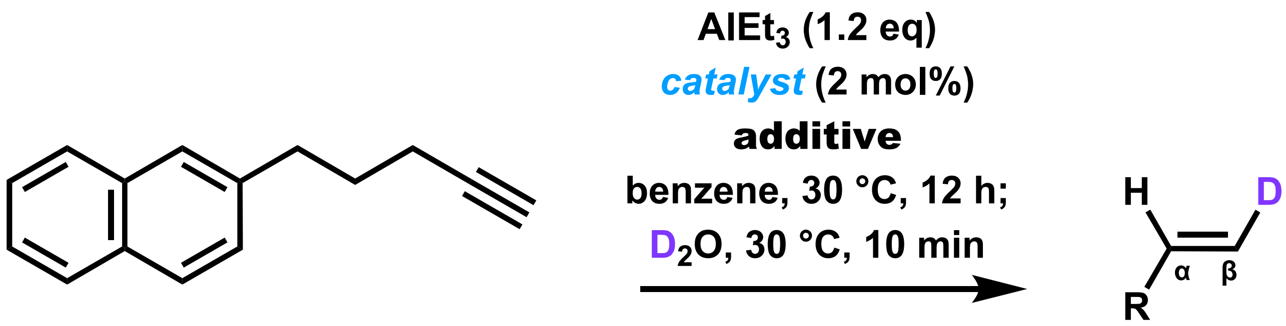
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Transformations of Transfer Hydroalumination Product

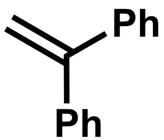


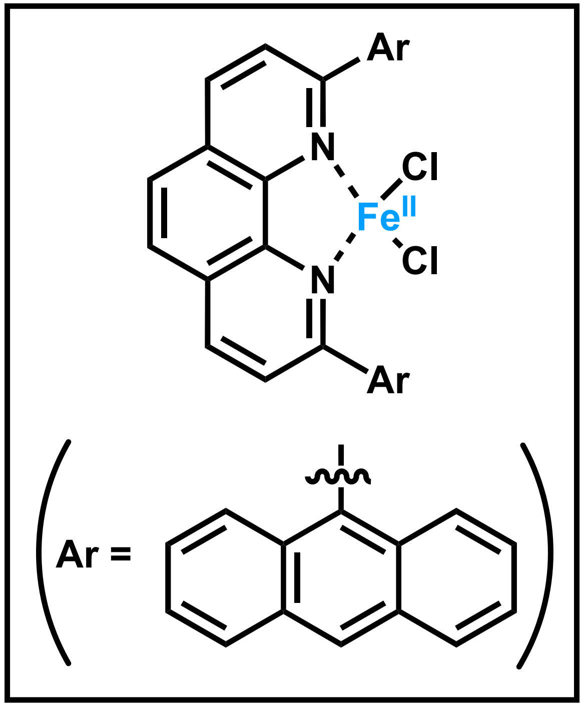
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Mechanism Experiment (1) : Radical Trapping



cis-β

additive	yield	r.r (*cis*-α / *cis*-β)
none	94%	5 : 95
 (radical scavenger)	99%	5 : 95



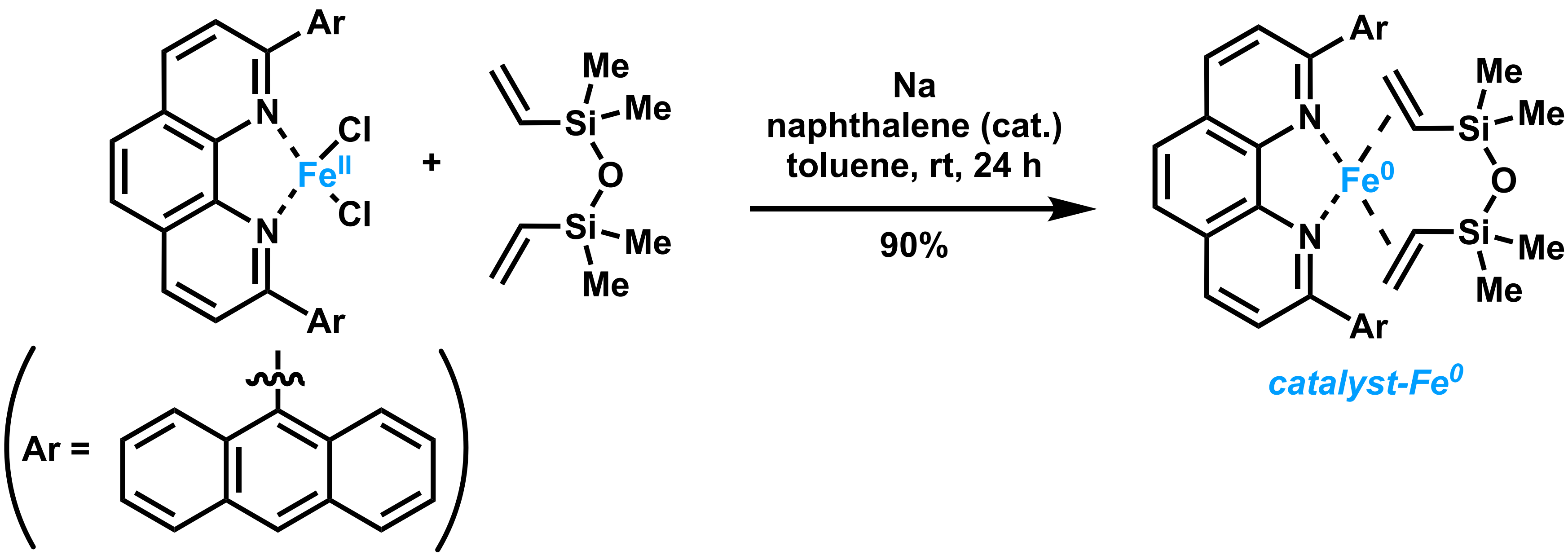
catalyst

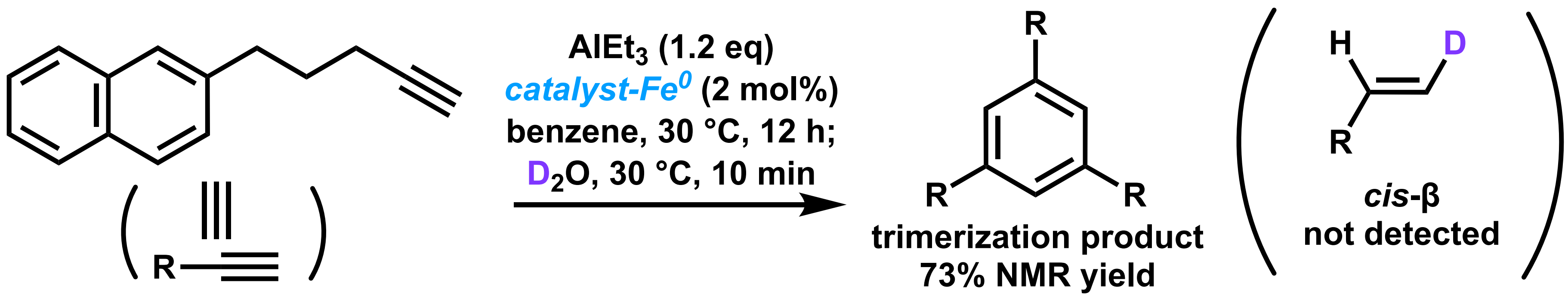
The addition of a radical scavenger did not influence the reaction.

1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc*. **2025**, *147*, 15545.

Mechanism Experiment (2) : Fe(0) Complex

- Synthesis of Fe^0 complex

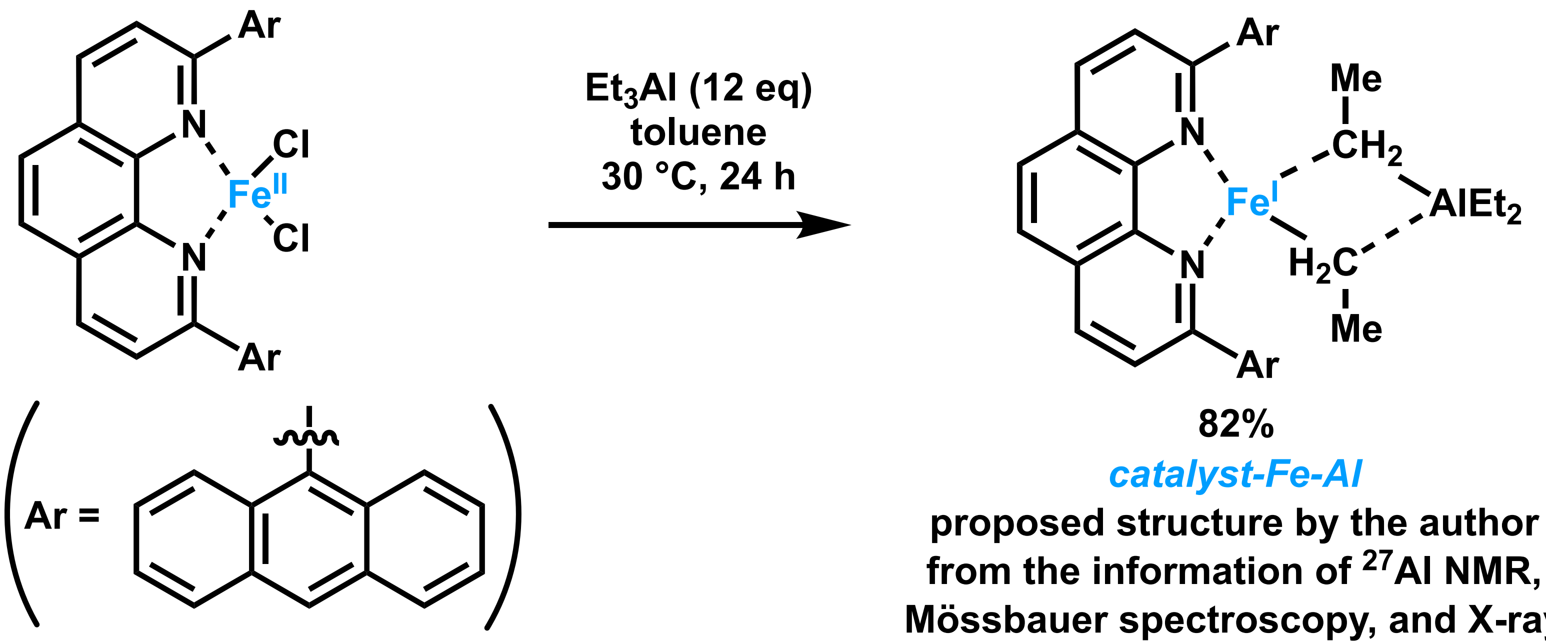




Transfer hydroalumination did not proceed with Fe^0 complex.
Fe^0 complex is unlikely to be the active catalytic species.

1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

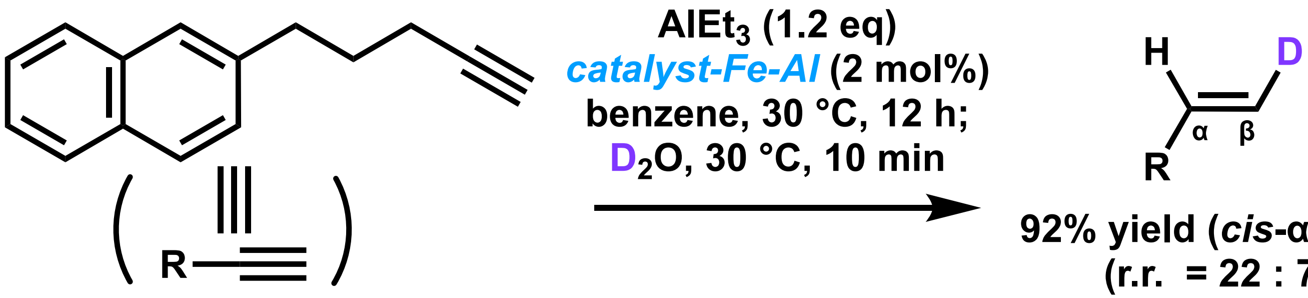
Mechanism Experiment (3) : Fe-Al Complex



82%

catalyst-Fe-Al

proposed structure by the author from the information of ^{27}Al NMR, Mössbauer spectroscopy, and X-ray photoelectron spectroscopy

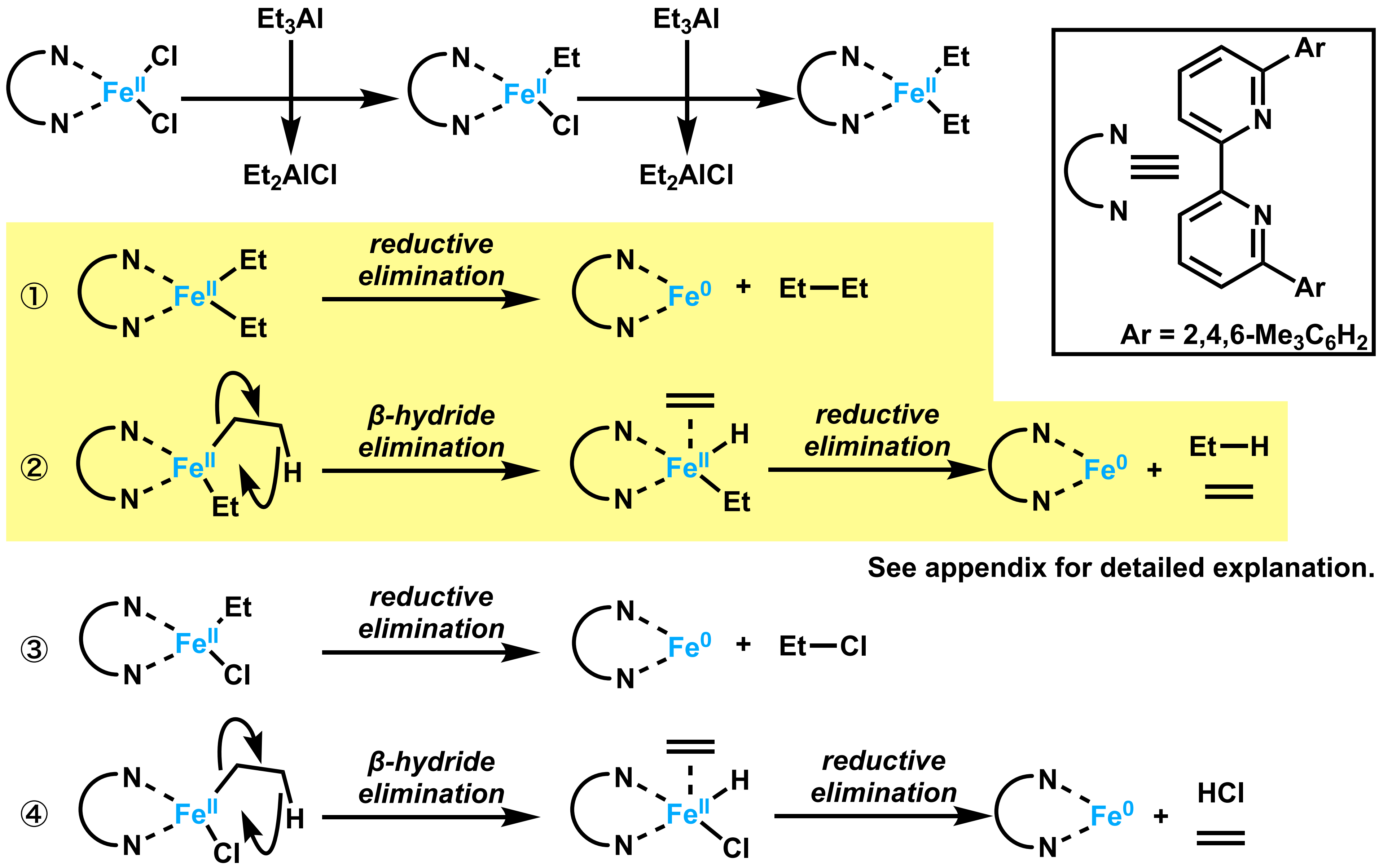


92% yield (*cis*-α+*cis*-β)
(r.r. = 22 : 78)

catalyst-Fe-Al **exhibited good catalytic activity.**
Fe^{I} is likely to be the active catalytic species.

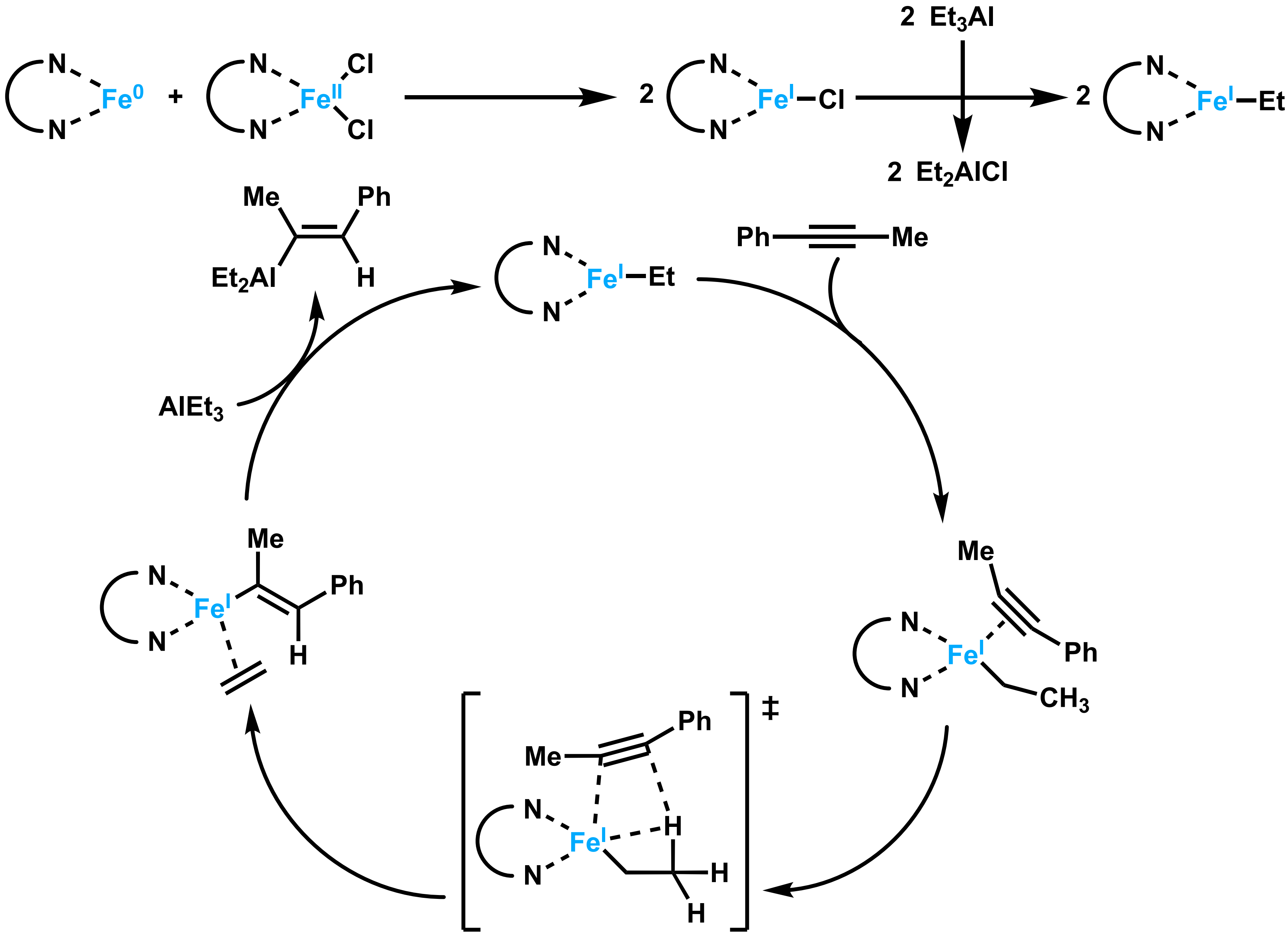
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Possible Mechanism for Generation of Fe^0 Complex



1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

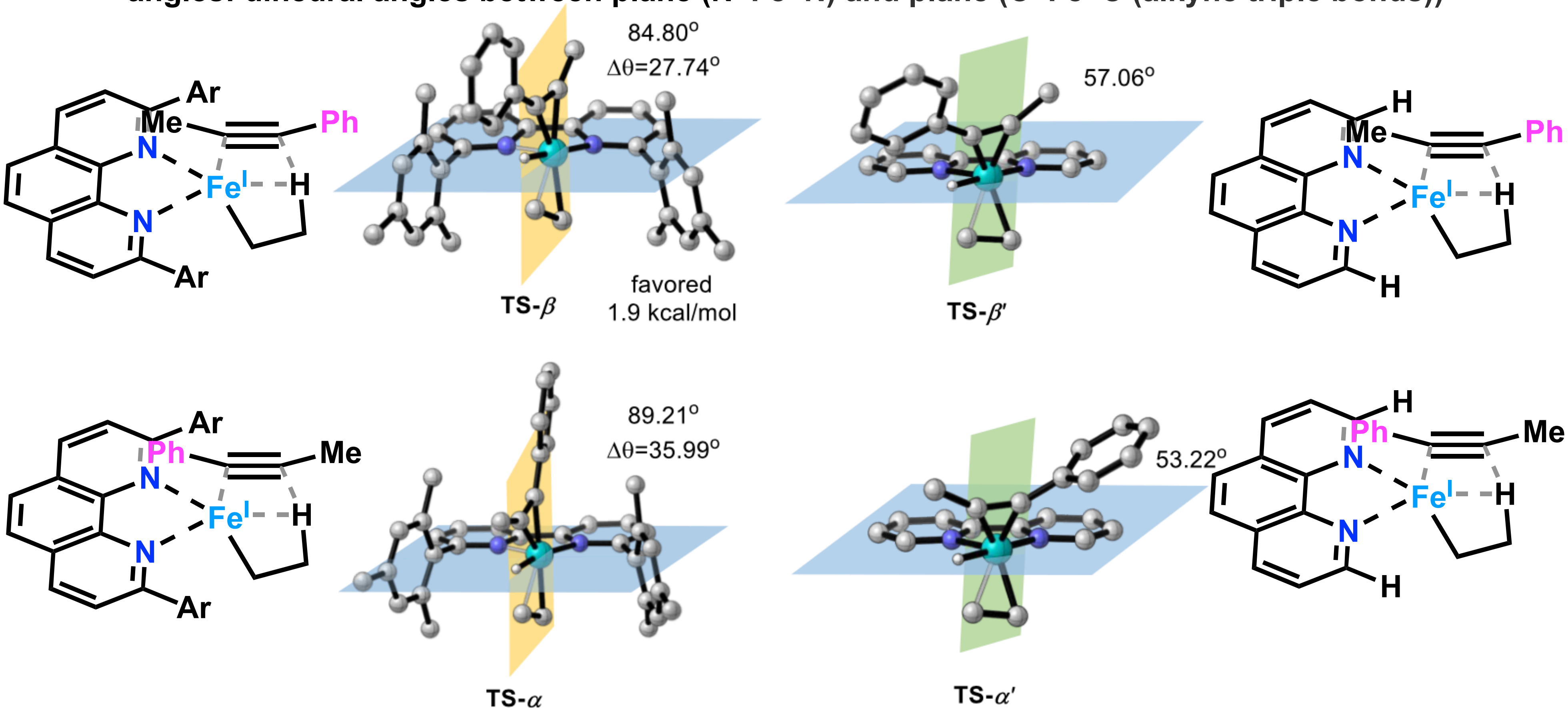
Proposed Catalytic Cycle (Internal Alkyne)



1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Regioselectivity (Internal Alkynes): DFT analysis

angles: dihedral angles between plane (N–Fe–N) and plane (C–Fe–C (alkyne triple bonds))



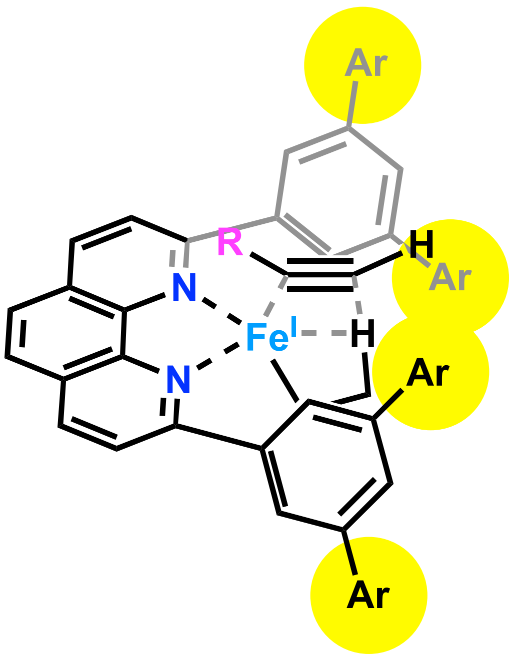
	Aryl-substituted	unsubstituted
Coordination of alkyne to iron :	**hindered by ligand**	**unaffected by steric hindrance**

The smaller deviation angle (Δθ) of TS-β would result in lower energy of TS-β. → β-selectivity

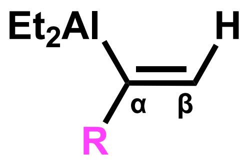
TPSSh-D3(BJ)/def2TZVPP-SMD(toluene)||PBE0-D3(BJ)/6–311G/TZVP(Fe)**

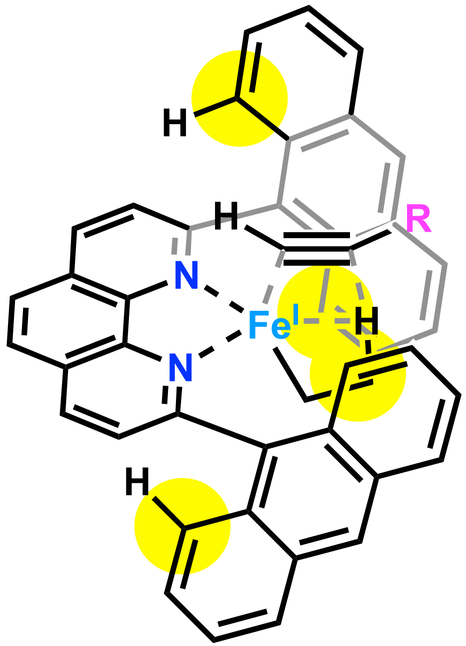
1) Li, W.-T.; Guan, M.-H.; He, P.; Huang, M.-Y.; Zhu, S.-F. *J. Am. Chem. Soc.* **2025**, *147*, 15545.

Proposed Regioselectivity for Terminal Alkynes (My Proposal)

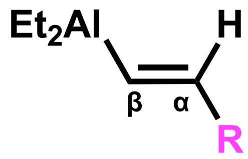


cis-α selective





cis-β selective



: steric hidrance to coordination of alkyne

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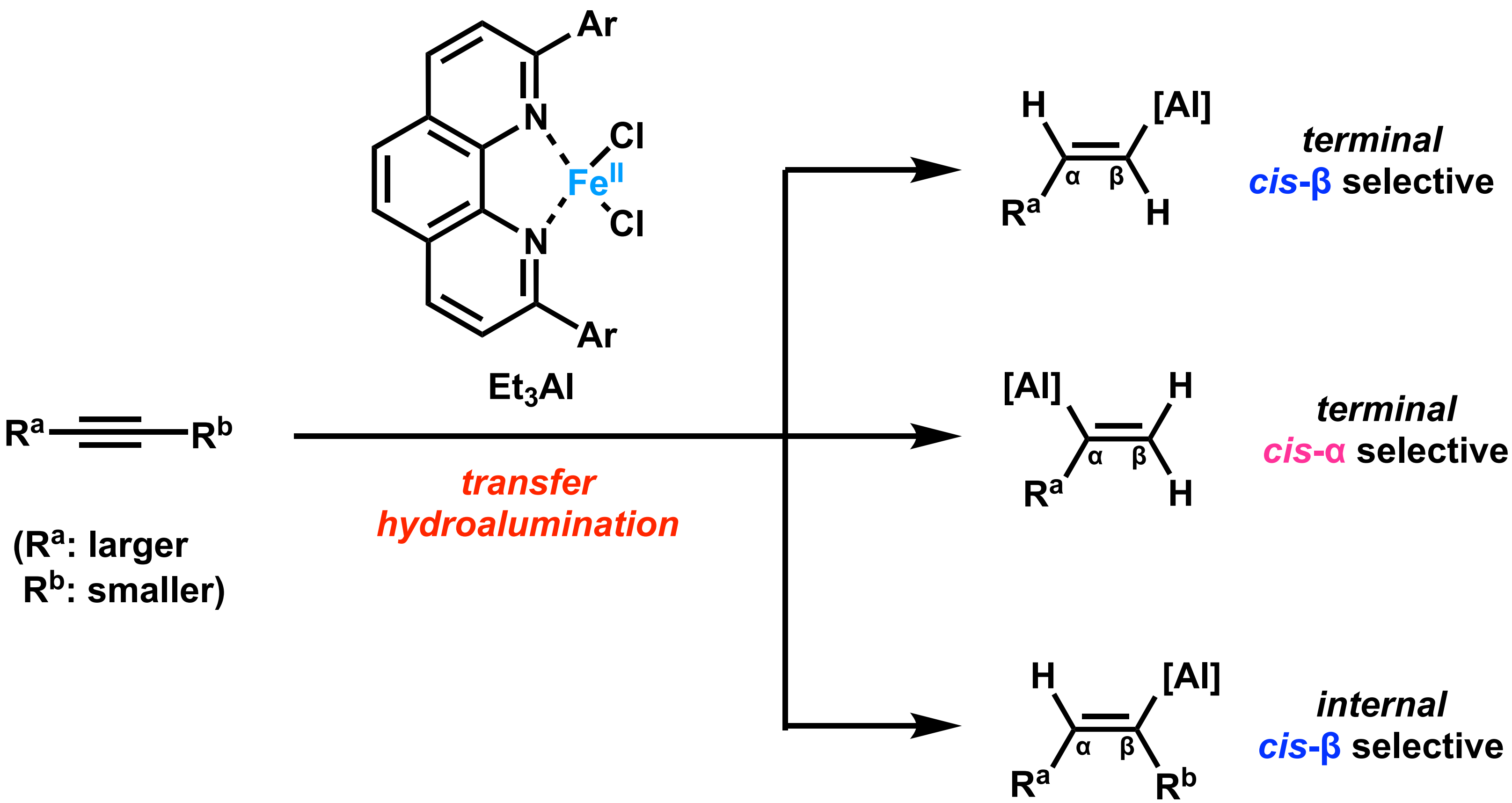
Summary



Ar
N
Cl
Fe^II
Cl
N
Ar
Et3Al
Ra
Rb
(Ra: larger
Rb: smaller)
transfer
hydroalumination
H
[Al]
α
β
Ra
H
terminal
cis-β selective
[Al]
H
α
β
Ra
H
terminal
cis-α selective
H
[Al]
α
β
Ra
Rb
internal
cis-β selective

Appendix

Reasonable pathway in Generation of Fe^0 complex (1)

Pathway ① or ② may be considered more likely.

In iron-catalyzed sp^3-sp^3 cross-coupling reaction, a mixture of coupling products derived from reductive elimination of $Fe^{II}RR'$ complexes (pathway ①) and alkenes or alkanes formed via β-hydride elimination followed by reductive elimination (pathway ②) was obtained [1).
The addition of ligands such as phosphines [2) or amines [3) to the iron center, which increases electron density and/or steric bulk, was found to favor the formation of the coupling product (pathway ①).
In addition, isomerization of Fe^{II}(*t*-Bu) complexes to Fe^{II}(*i*-Bu) complexes [4), as well as dimerization of 2-butene catalyzed by Fe^{II} complexes [5), has been reported, suggesting that β-hydride elimination from $Fe^{II}R$ intermediates may be a feasible process.
On the other hand, isolated $Fe^{II}(X)R$ complexes do not undergo coupling (pathway ③) or β-hydride elimination (pathway ④) [6).

Based on these experimental results, it is more likely that Fe^0 will be generated via reductive elimination (pathway ①) or β-hydride elimination followed by reductive elimination (pathway ②) from $Fe^{II}RR'$ complexes.

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4) Vela, J.; Smith, J. M.; Lachicotte, R. J.; Holland, P. L. *Chem. Commun.* **2002**, 2886.
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Reasonable pathway in Generation of Fe^0 complex (2)

Furthermore, a computational study demonstrated that spin crossover can lower the activation barrier for β-hydride elimination from Fe^{II} complexes [1)].

In Fe^{II} complexes, two electronic configurations are possible: a more stable high-spin state and a less stable low-spin state. During β-hydride elimination, a spin-state transition to the low-spin configuration can create an empty d orbital, which allows the Fe center to accept the two electrons from the β-hydride.
This will be interpreted as the reason for the reduced activation energy.

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