Highly Enantioselective, Intermolecular Hydroamination of Allenyl Esters Catalyzed by Bifunctional Phosphinothioureas

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Jacobsen, E. N. *et al.*
J. Am. Chem. Soc. **2014**, *136,* 17968.

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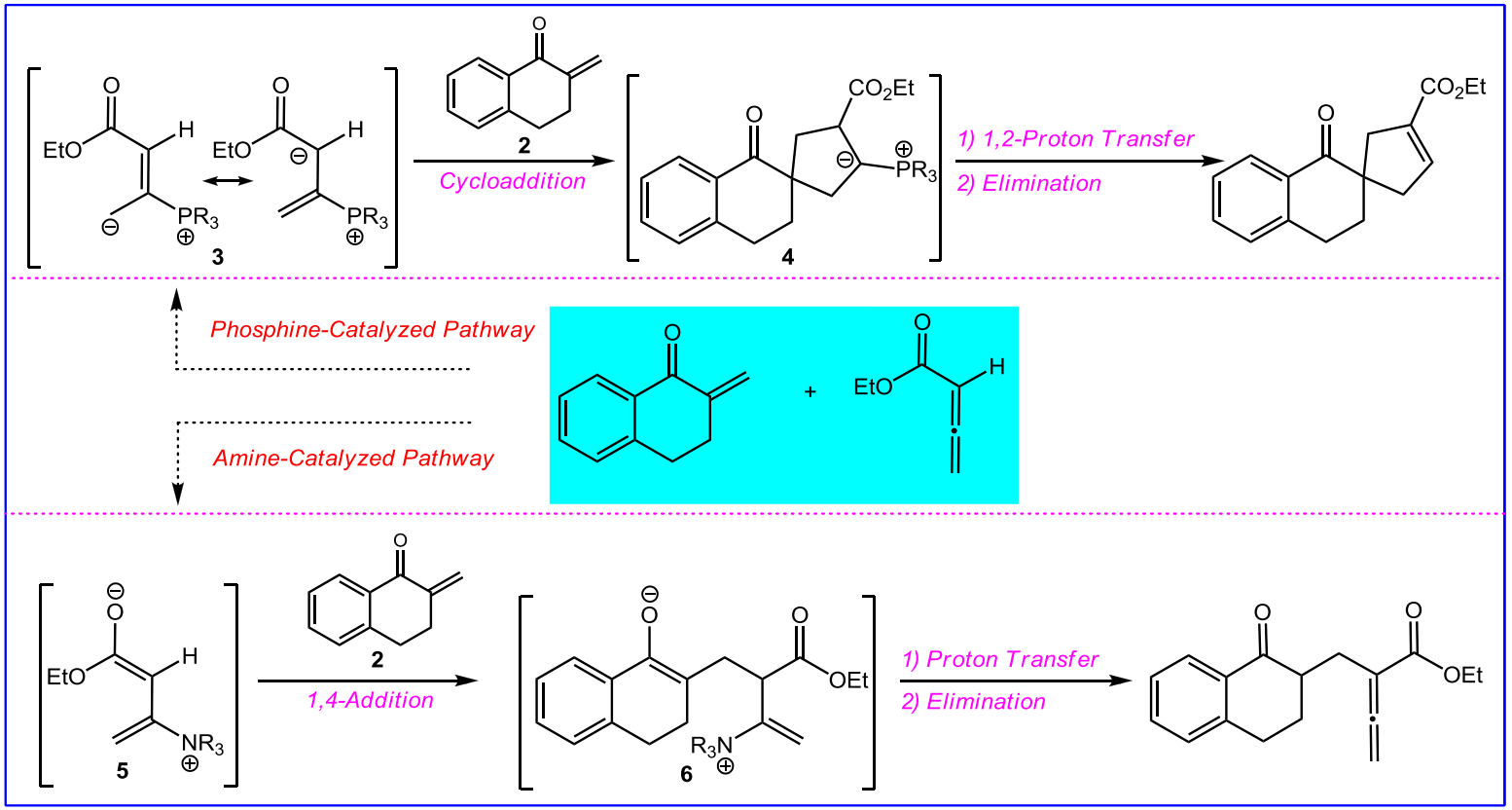
Lewis Base Organocatalysts

Unique Properities of Phosphine:

- weaker basicity and stronger nuclephilicity
- generation of ylide-type intermediate

Introduction

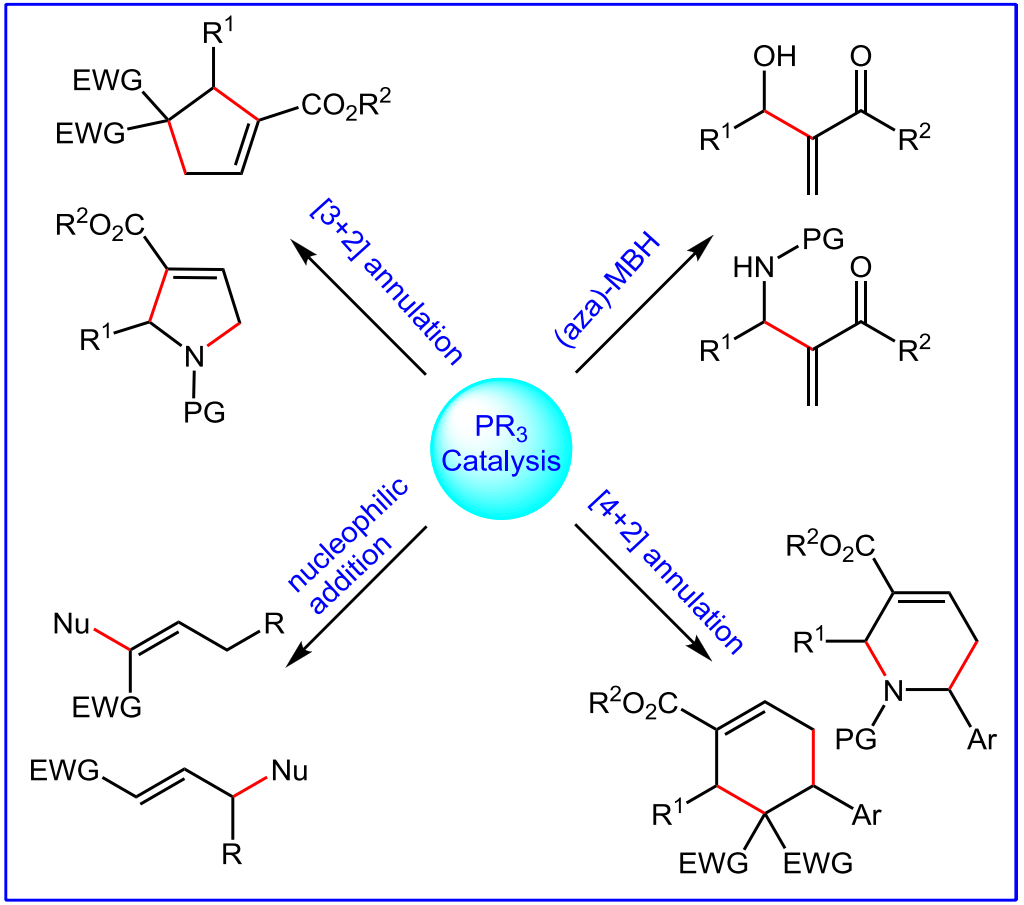
Divergent Pathway of Phosphine- and Amine-Catalyzed Process



Miller, S. J. *et al. J. Am. Chem. Soc.* **2003**, *125*, 12394.

Introduction

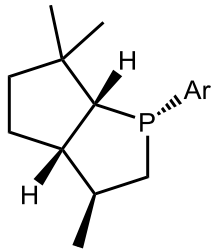
Selected Examples of Phosphine-Promoted Reactions

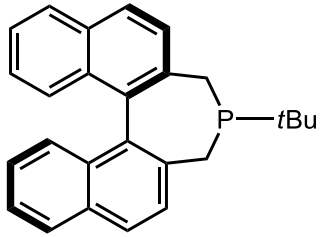


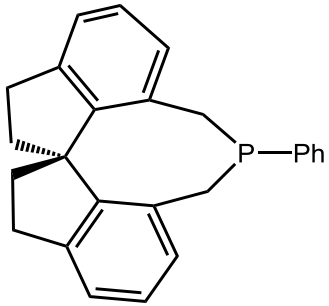
Lu, Y. *et al. Synlett* **2011**, 2766.

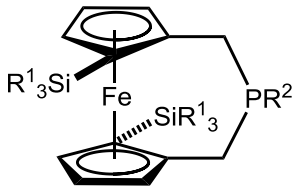
Introduction

Cyclic Phosphines



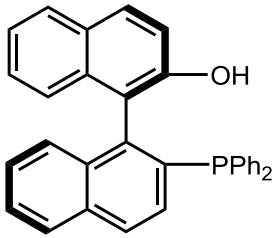


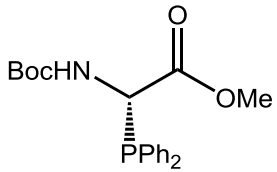


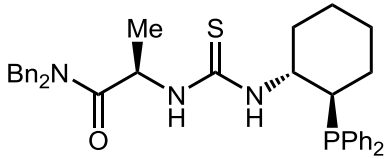


Chiral induction ⇨ Steric effects

Acyclic Phosphines



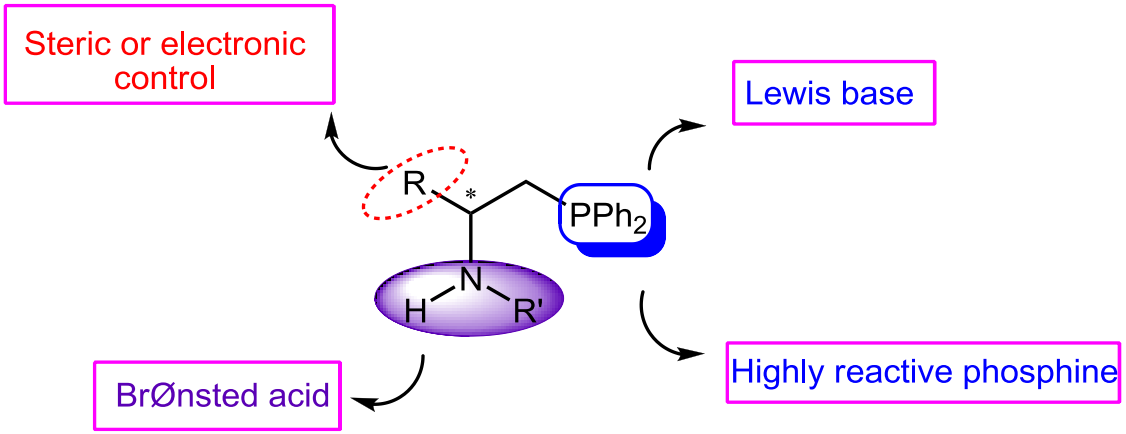


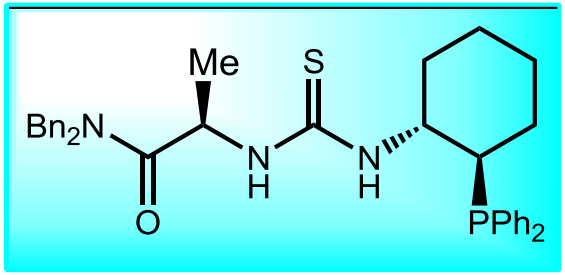


Chiral induction ⇨ Secondary interactions

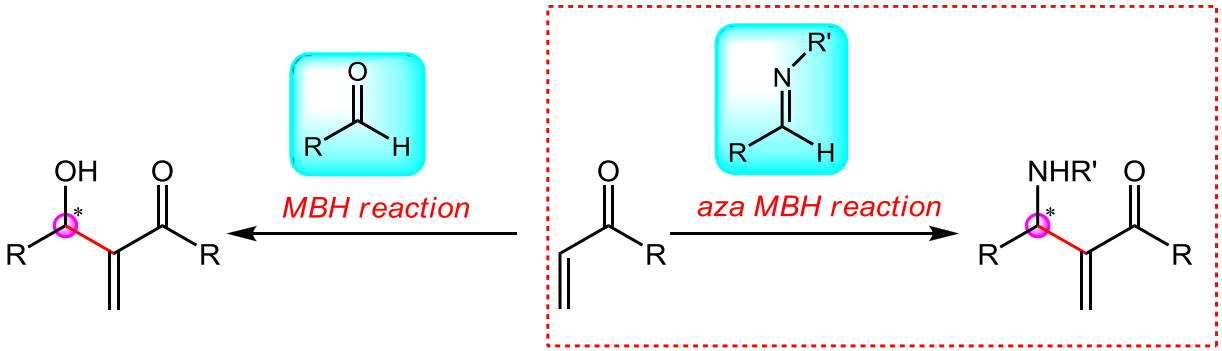
Introduction

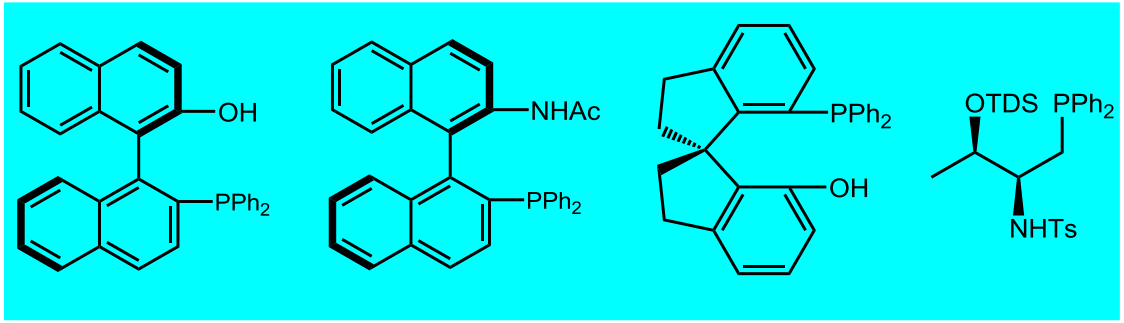
Design of Amino Acid Chiral Phosphine



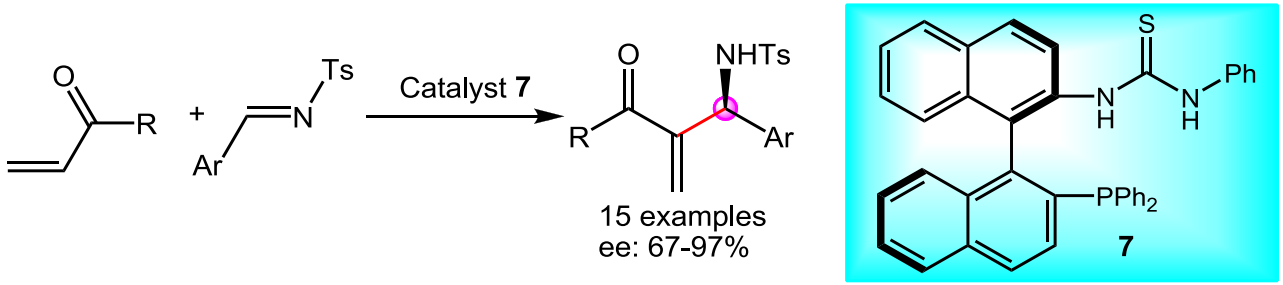


(Aza)-Morita-Baylis-Hillman Reaction

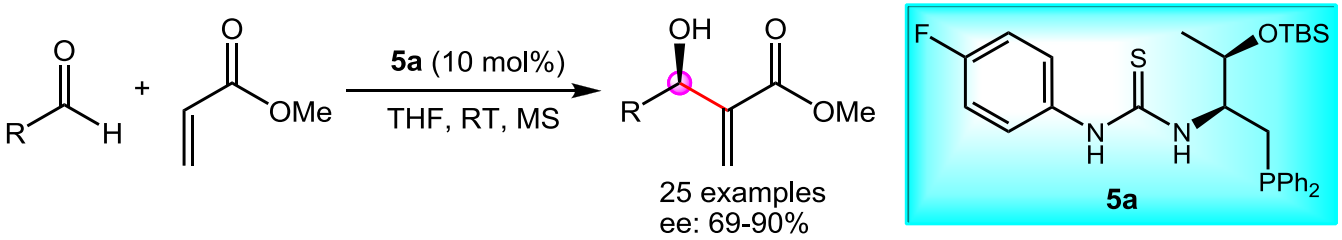




(Aza)-Morita-Baylis-Hillman Reaction

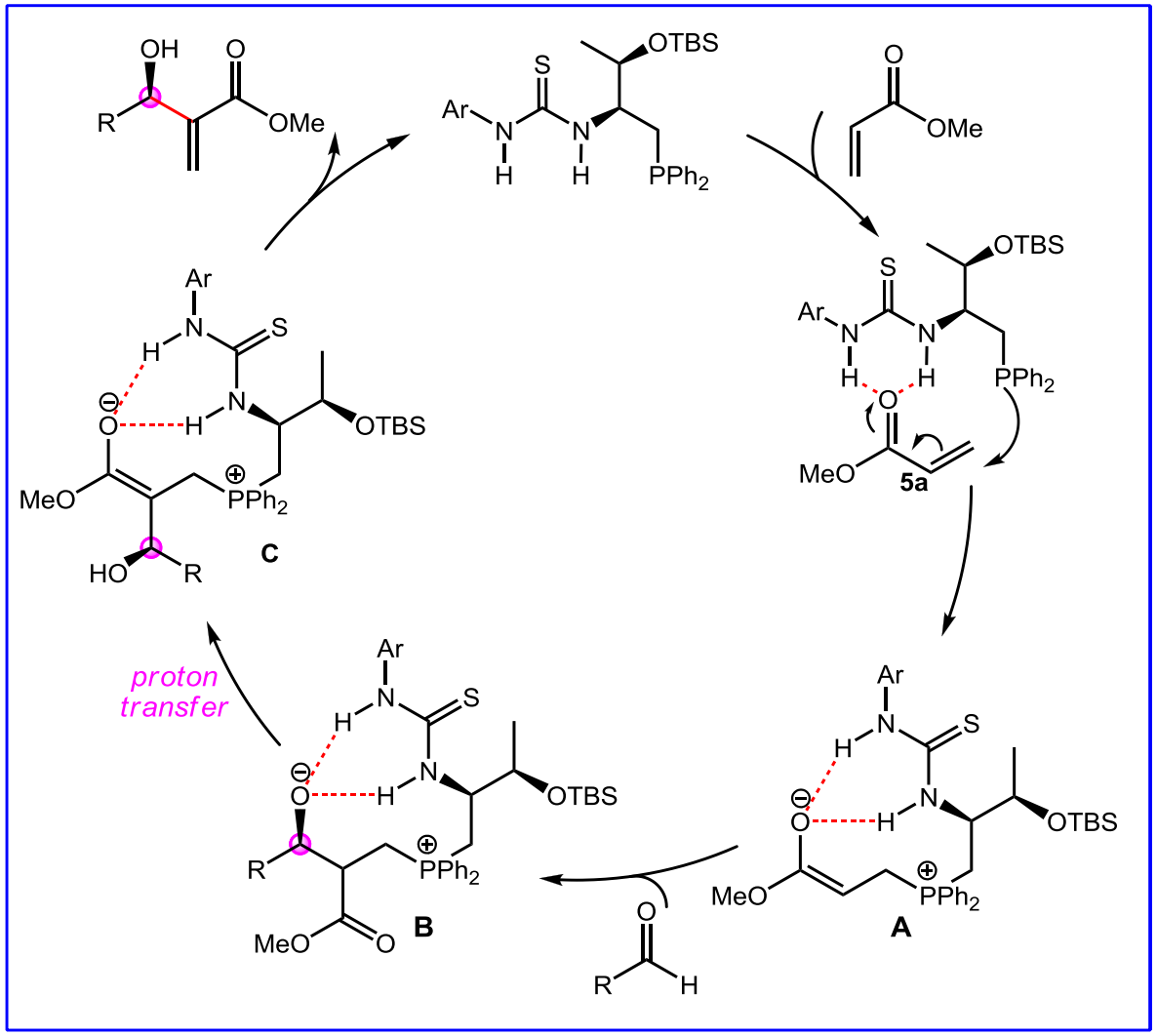


Shi, M. *et al. Adv. Synth. Catal.* **2007**, *349*, 2129.



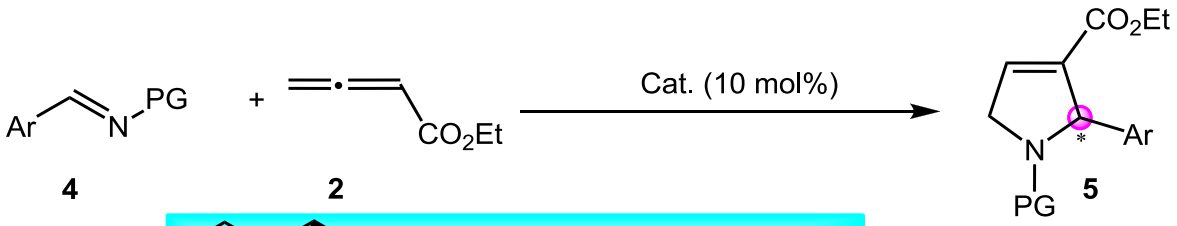
Lu, Y. *et al. Org. Biomol. Chem.* **2011**, *9*, *6734*.

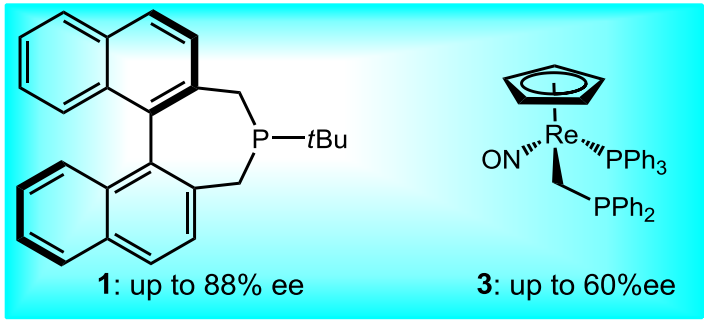
(Aza)-Morita-Baylis-Hillman Reaction

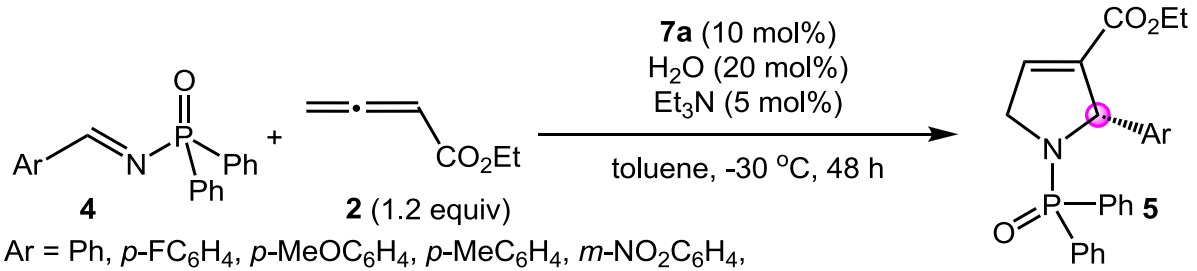


Lu, Y. *et al. Org. Biomol. Chem.* **2011**, *9, 6734.*

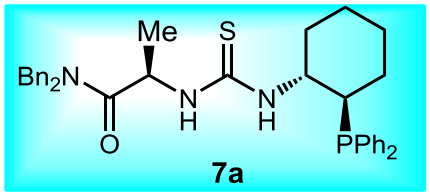
Imine-Allene [3+2] Cycloaddition





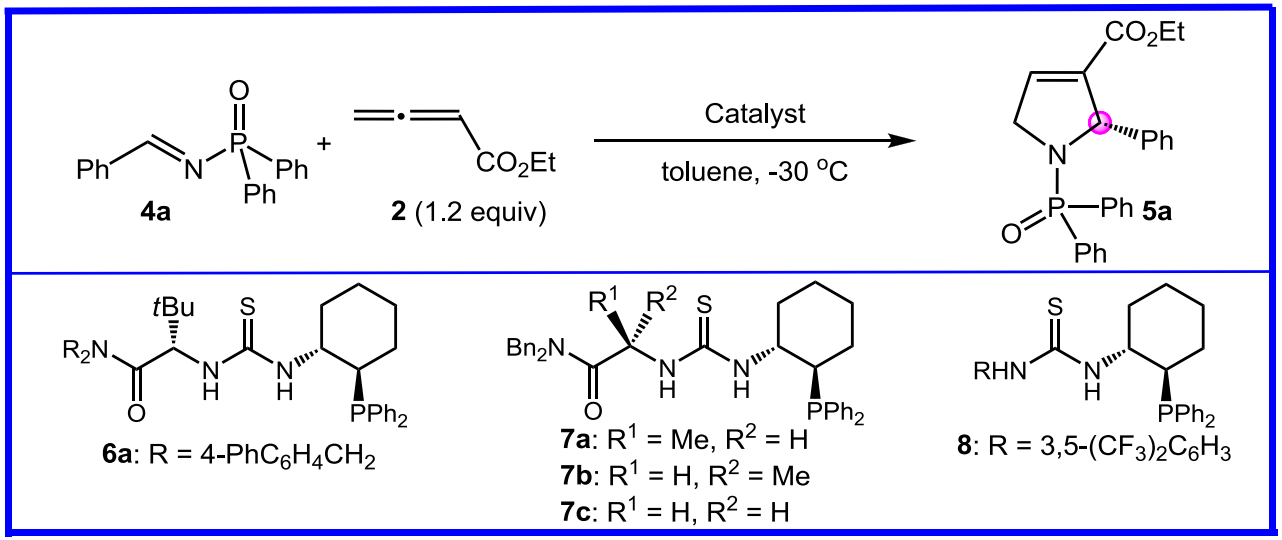


Ar = Ph, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *m*-$NO_2C_6H_4$,
3,4,5-$(MeO)_3C_6H_2$, 3-pyridyl, 4-pyridyl, 2-furyl, 2-thienyl



Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2008**, *130,* 5660.

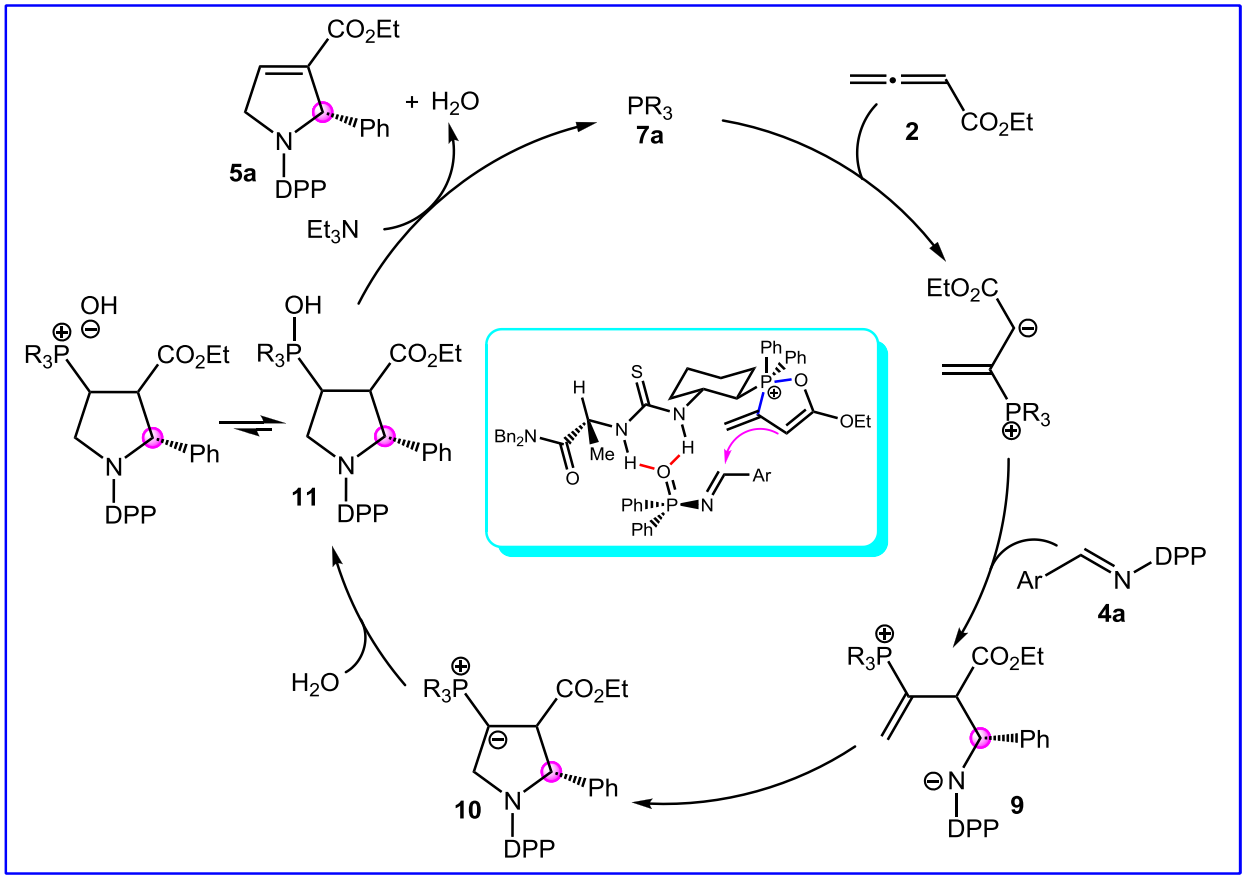
Imine-Allene [3+2] Cycloaddition



entry	Cat.	Et_3N (mol%)	H_2O (mol%)	conversion (%)	ee (%)
1	**6a**	--	--	45	93 (*R*)
2	**6a**	5	--	70	n.d.
3	**6a**[a]	5	--	70[b]	n.d.
4	**6a**	--	20	86[c]	n.d.
5	**6a**	5	20	88[d]	93 (*R*)
6	**7a**	5	20	100	98 (*S*)
7	**7b**	5	20	17	87 (*S*)
8	**7c**	5	20	23	88 (*S*)
9	**8**	5	20	5	42 (*S*)

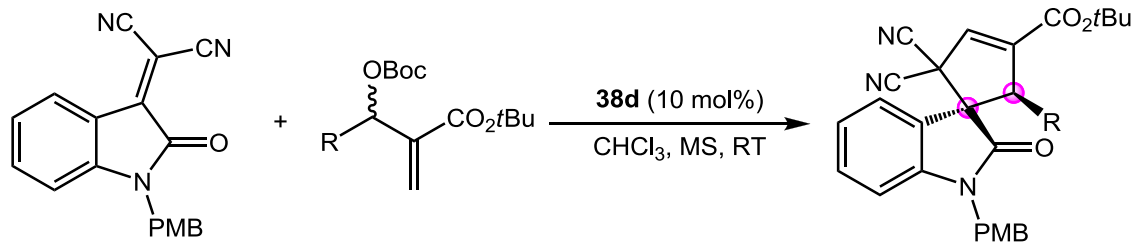
[a] Reaction run with the addition of MS. [b] Complex mixture, < 20% yield. [c] 70% yield. [d] 76% yield.

Imine-Allene [3+2] Cycloaddition

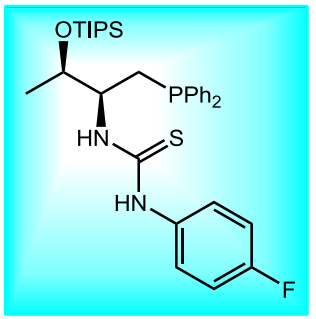


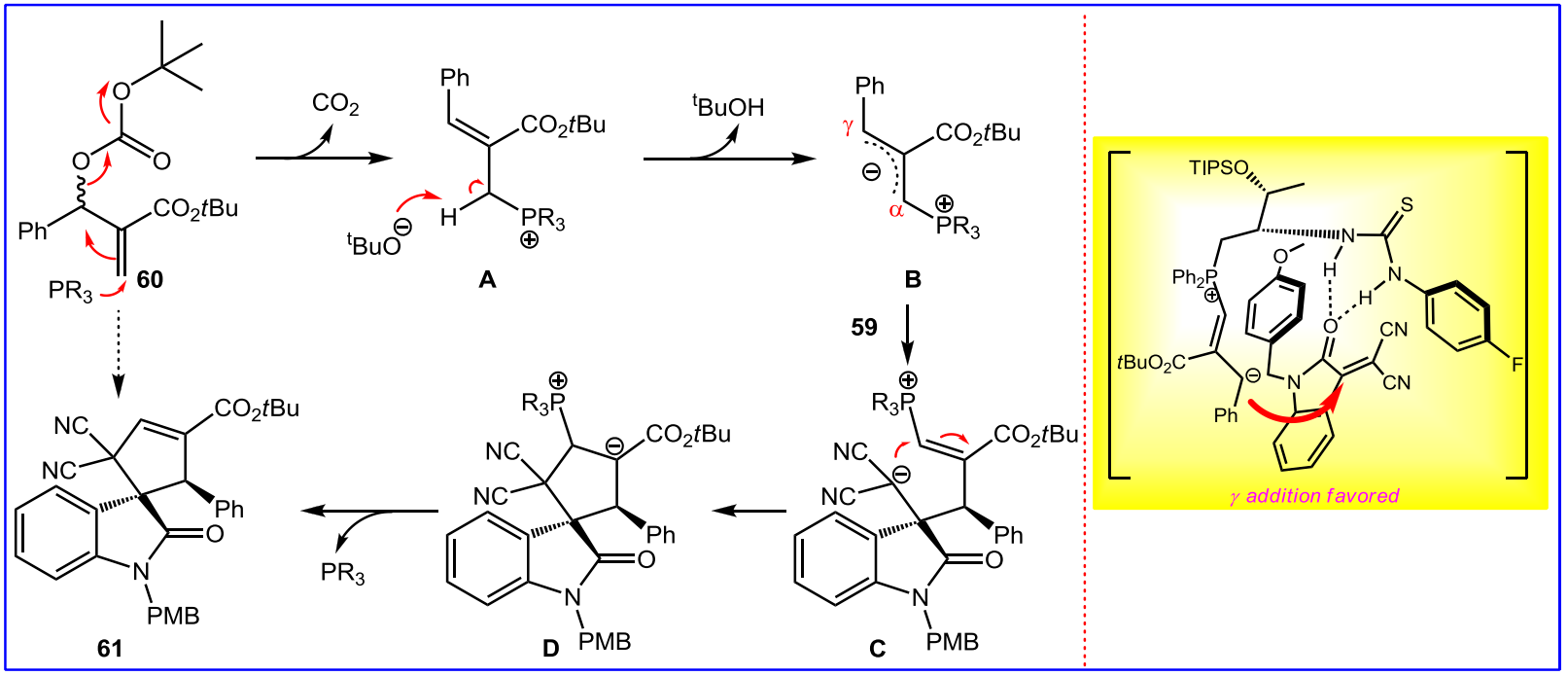
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2008**, *130*, 5660.

[3+2] Annulation of MBH Adduct



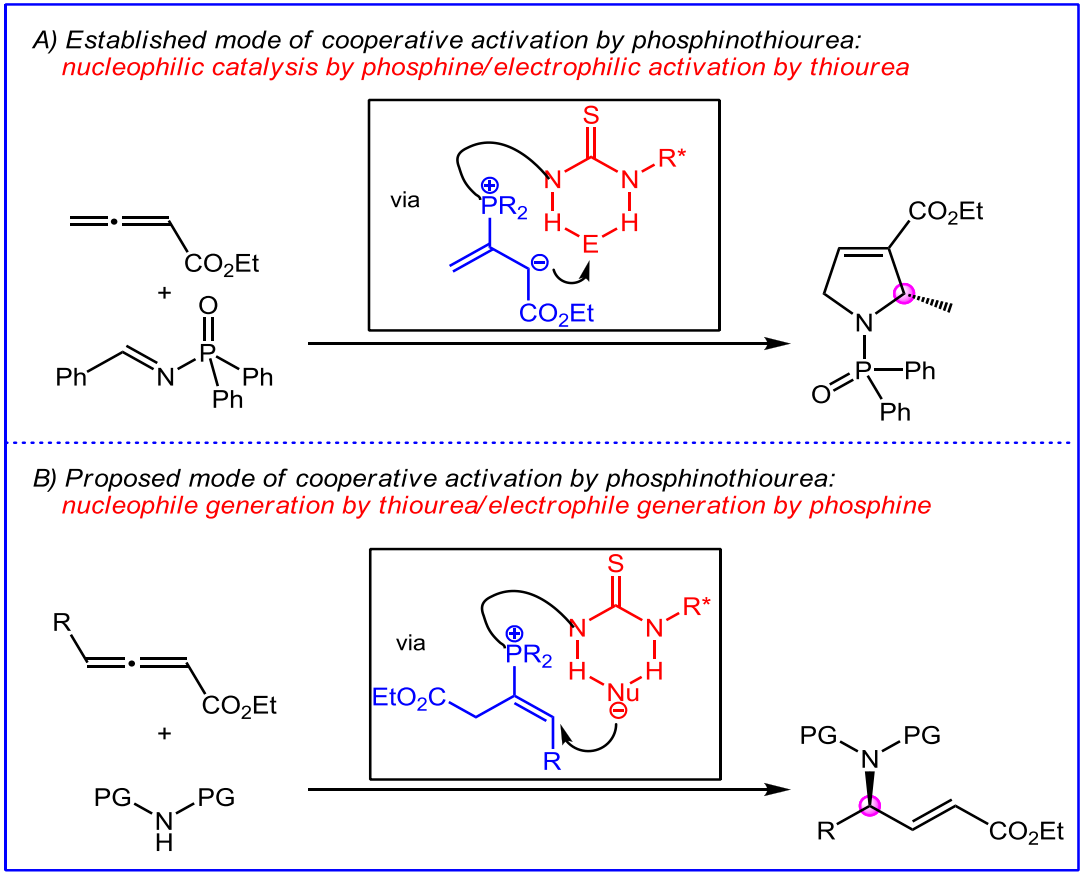
23 examples
yield: 82-96%
ee: 65-99%
γ/α: 1:1-25:1





Lu, Y. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 7837.

Intermolecular Hydroamination



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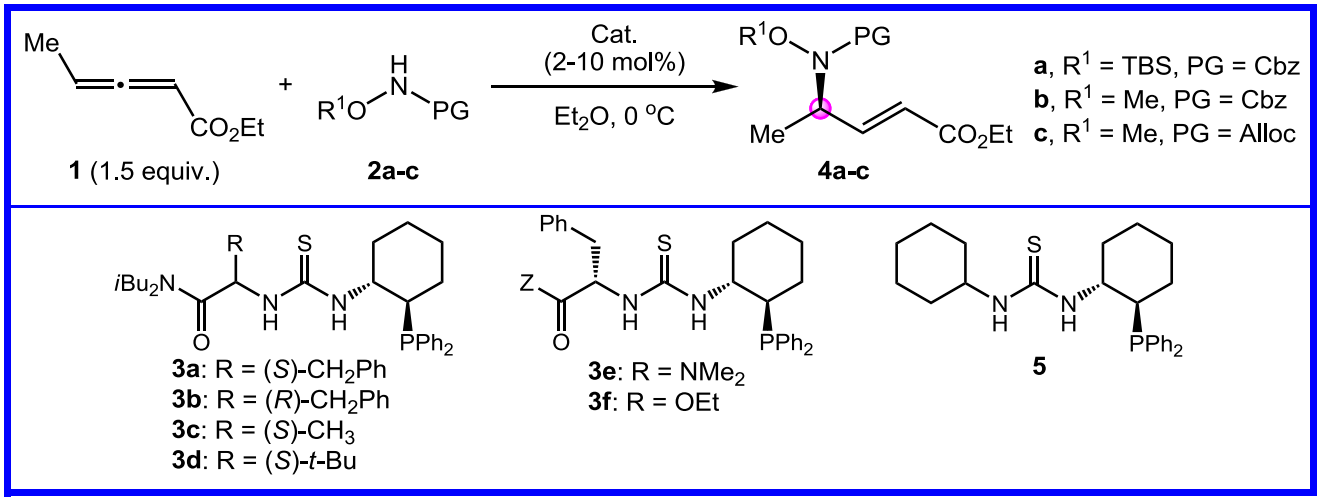
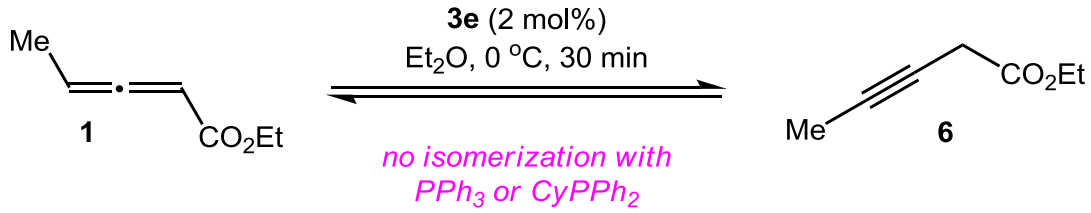
Intermolecular Hydroamination

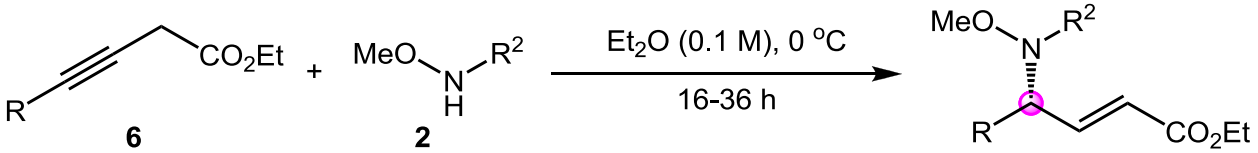


entry[a]	Nu	Cat.	yield (%)	ee (%)
1	**2a**	**3a**	65	92
2	**2a**	**3b**	93	88
3	**2a**	**3c**	66	88
4	**2a**	**3d**	72	88
5	**2b**	**3a**	99[b]	82
6	**2c**	**3a**	99[b]	92
7[e]	**2c**	**3e**	90	92
8	**2c**	**3f**	92[c]	88
9	**2c**	**5**	77	50
10	**2c**	$CyPPh_2$	36[d]	--
11[f]	**2c**	**3e**	96	93

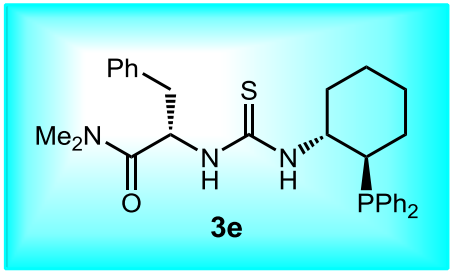
[a] In all cases the γ-adduct was the only detectable product (γ/α >100:1), 10 mol% Cat. [b] Conversion. [c] γ/α = 50:1. [d] γ/α = 20:1. [e] 1 mol% Cat. [f] 2 mol% Cat.

Intermolecular Hydroamination





11 examples
yield: 79-99%
ee: 90- 99%



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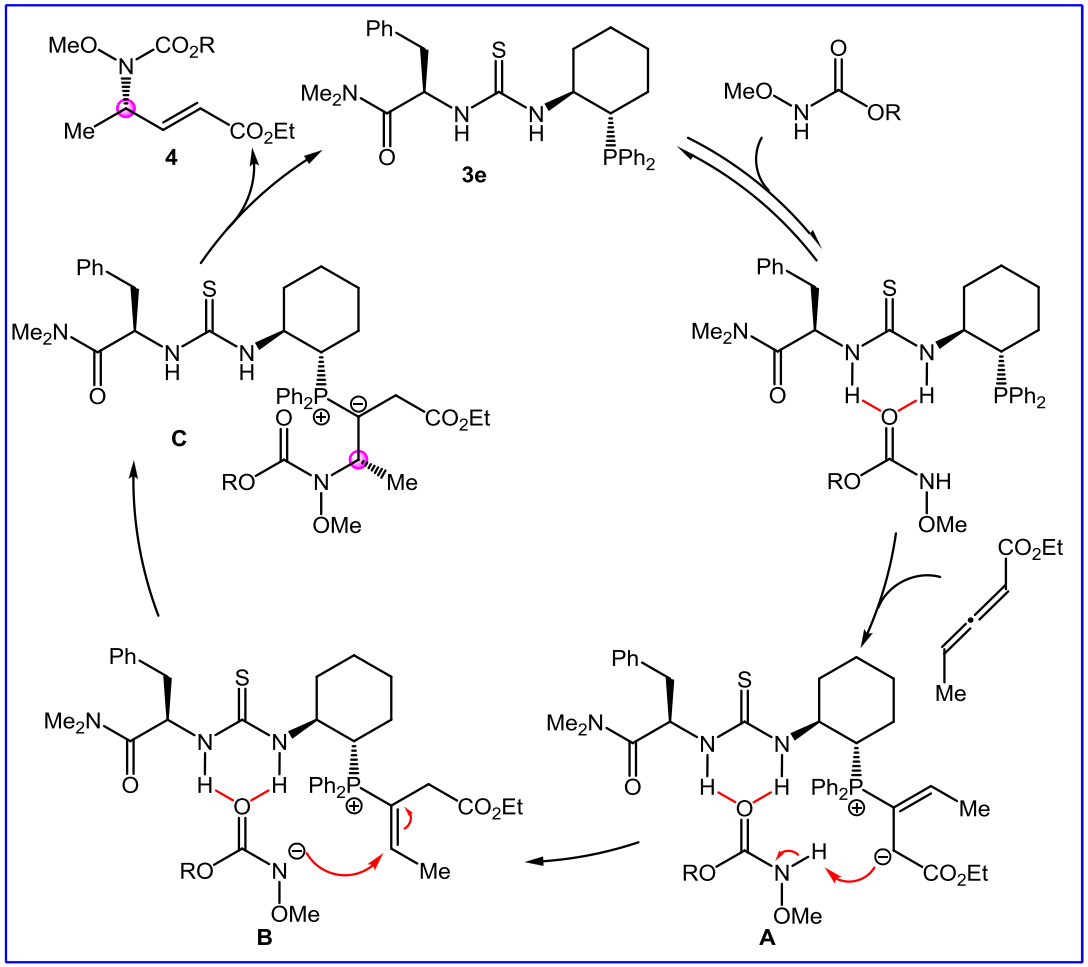
Intermolecular Hydroamination



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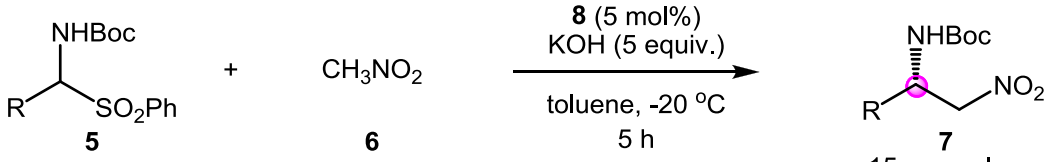
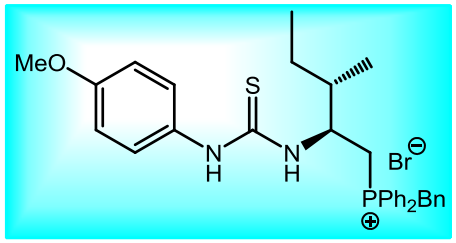
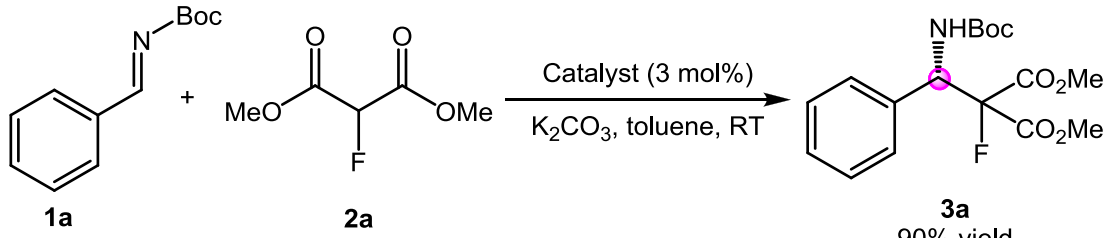
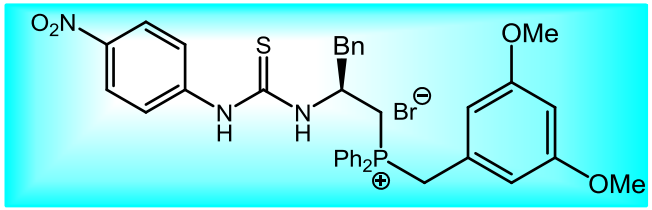
Mannich-Type Reactions



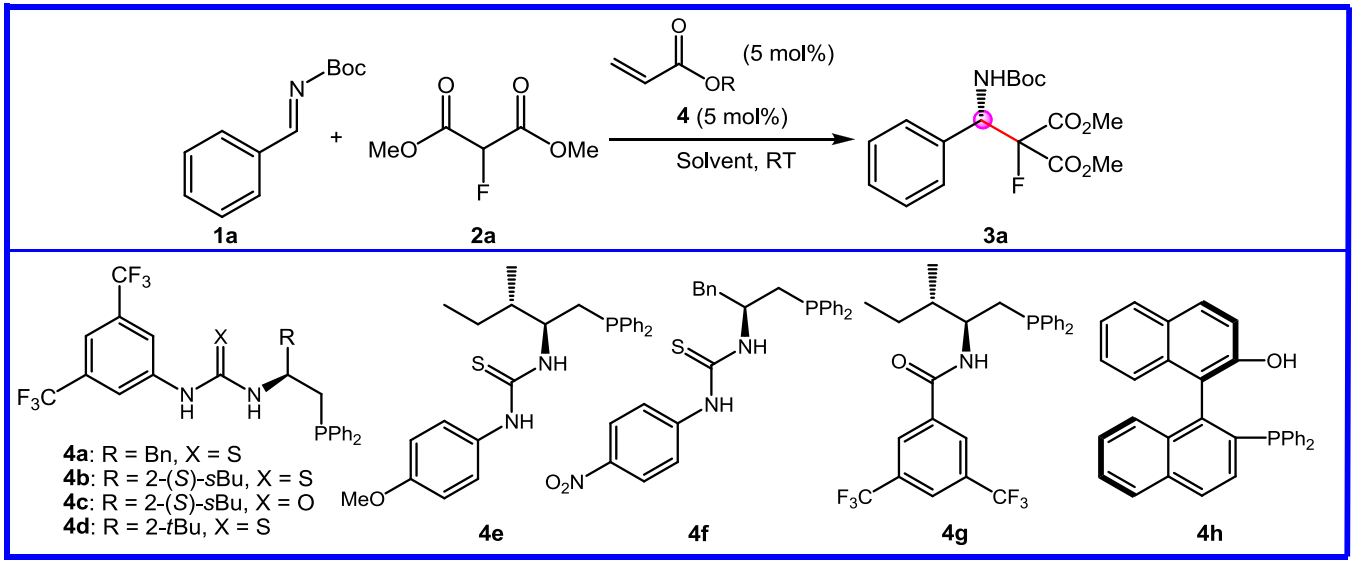






Zhao, G. *et al. Chem. Commun.* **2013**, *49*, 5972.

Mannich-Type Reactions



entry[a]	Cat.	solvent	yield (%)[b]	ee (%)
1	**4a**	toluene	90	85
2	**4b**	toluene	93	82
3	**4c**	toluene	94	56
4	**4d**	toluene	92	78
5	**4e**	toluene	91	78
6	**4f**	toluene	92	90
7	**4g**	toluene	50	10
8	**4h**	toluene	trace	n.d.
9	**4f**	DCM	93	92

[a] 5 mol% catalyst. [b] Isolated yield

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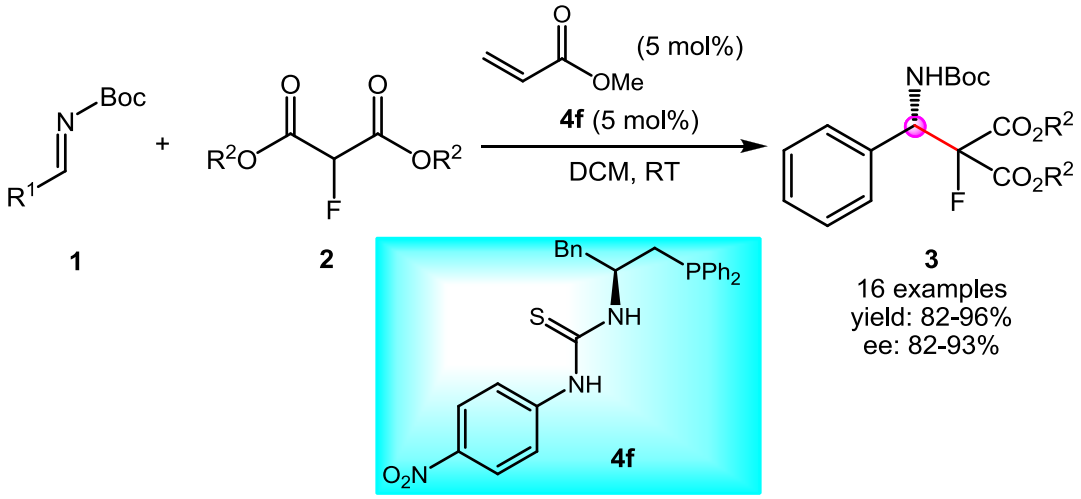
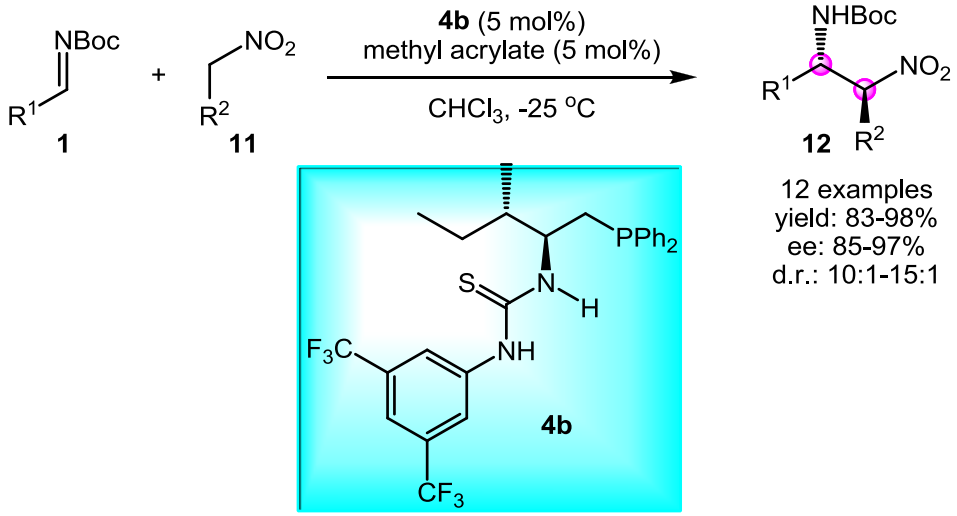
Mannich-Type Reactions





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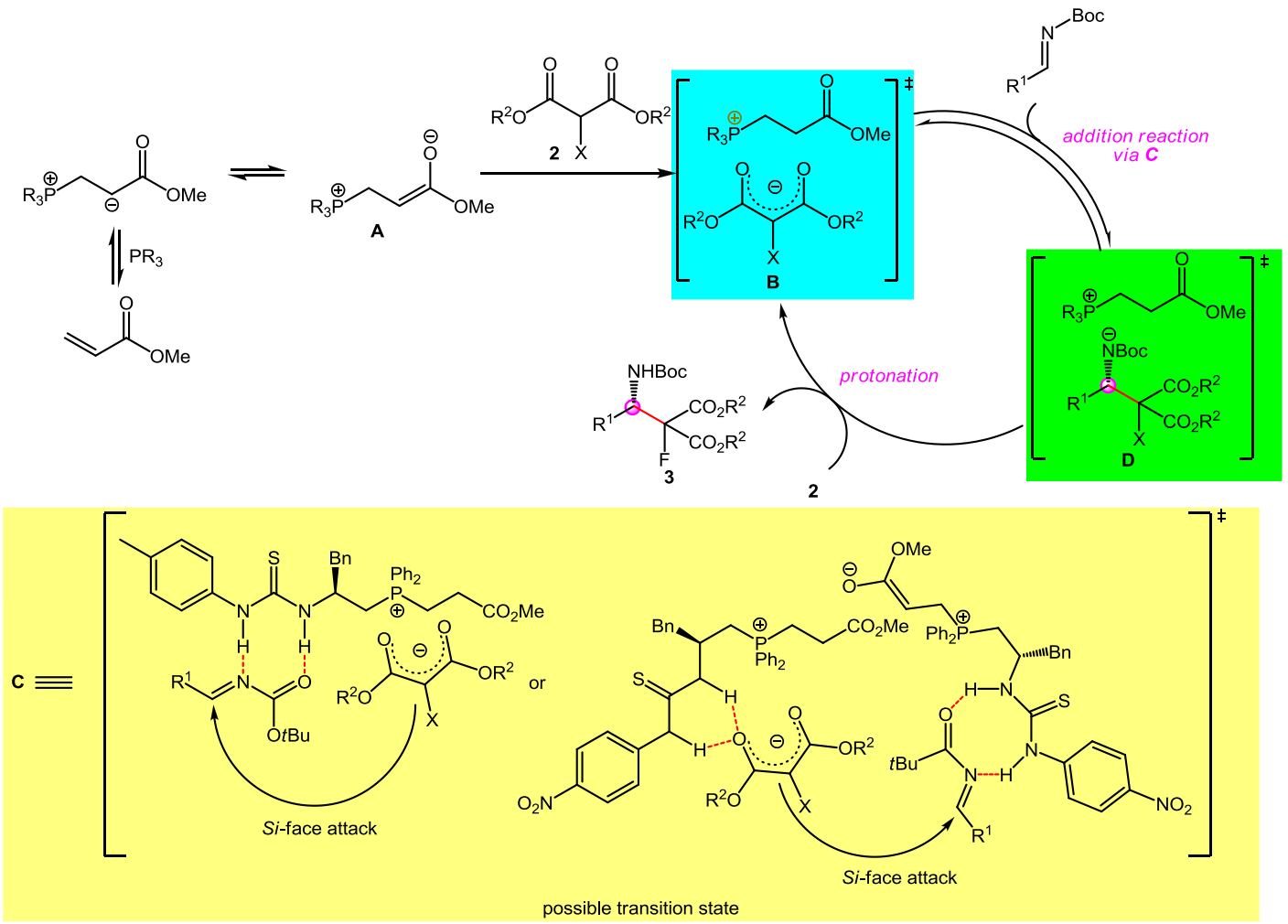
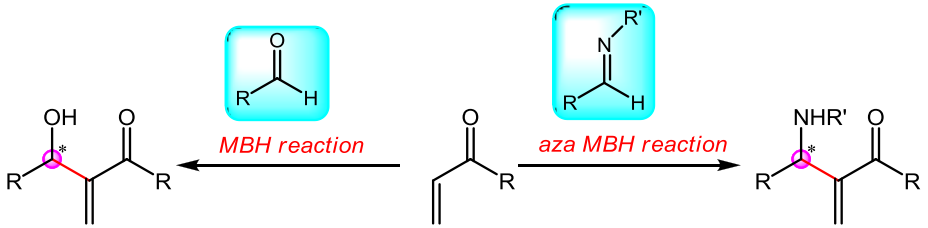
Mannich-Type Reactions

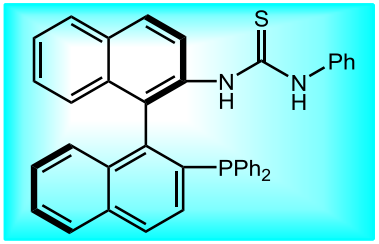


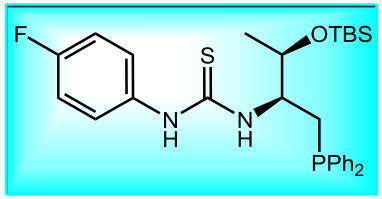
Zhao, G. *et al. Angew. Chem. Int. Ed.* **2014**, *ASAP.*

Summary

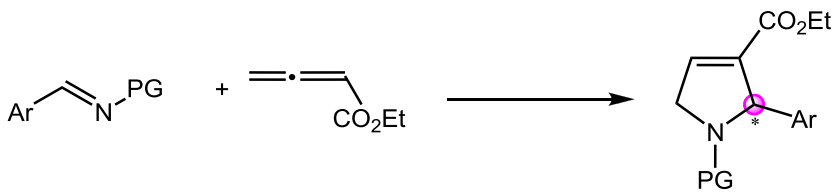
(Aza)-MBH Reaction

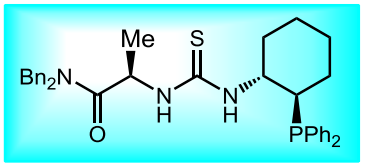


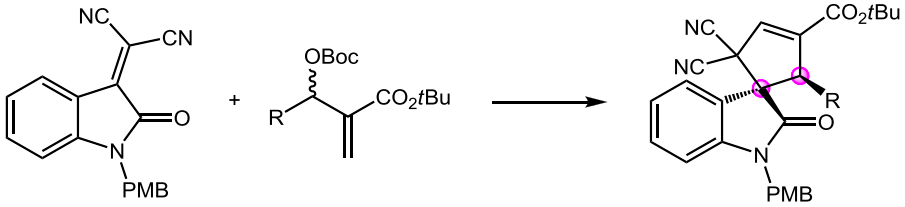


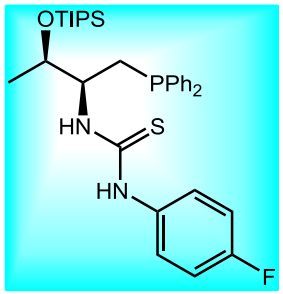


[3+2] Annulation



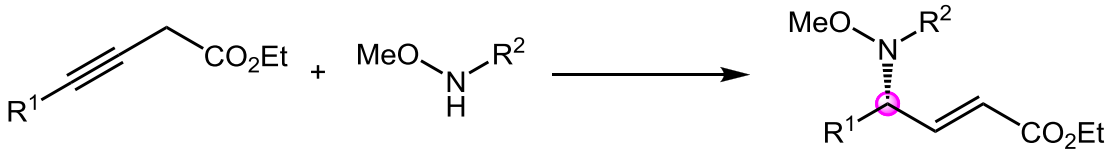


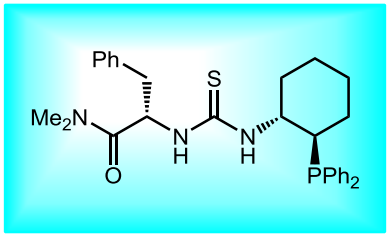




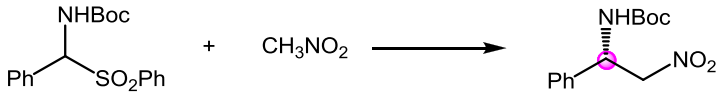
Summary

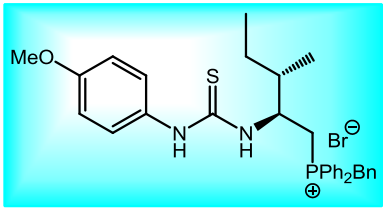
Intermolecular Hydroamination

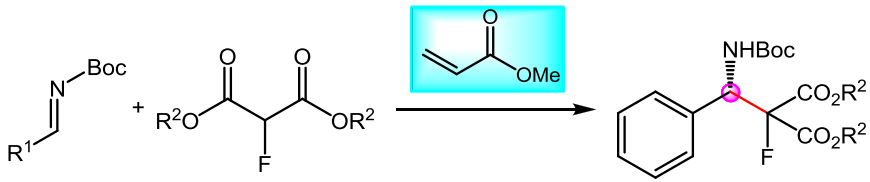


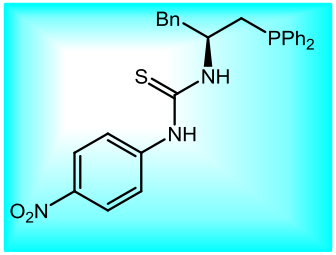


Mannich-Type Reactions









Small, polyfunctional molecules capable of cooperative activation and precise positioning of reacting partners hold tremendous potential in selective catalysis. Recently, we reported the development of a family of phosphinothiourea catalysts that promote imine-allene [3+2] cycloadditions via nucleophilic activation of the allene by the phosphine with simultaneous imine activation by hydrogen bonding to the thiourea (Scheme 1A). We were intrigued by the potential of a complementary reactivity mode with the same family of catalysts, wherein the H-bond donor would promote formation of a reactive nucleophile by anion binding, while the phosphine component could induce generation of an activated vinyl phosphonium electrophile (Scheme 1B).

We report here the successful development of this strategy, with the application of this new type of cooperative activation to the highly regio- and enantioselective γ-hydroamination of allenyl and propargyl esters. This methodology provides practical access to synthetically valuable α,β-unsaturated γ-amino esters in highly enantioenriched form.

The utility of chiral phosphinothioureas has thus been extended into a new, anion-binding manifold with the highly enantioselective γ-hydroamination of allenyl esters. Further studies into the reactivity and selectivity of these versatile polyfunctional catalysts are ongoing.