Bifunctional Thiourea-Catalyzed Diastereo- and Enantioselective Aza-Henry Reaction

Takemoto *et*. *al*. *Chem*. *Eur*. *J*. **2006**, *12*, 466-476.

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Outline

- Organocatalysts

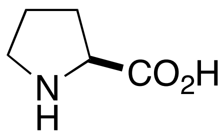
  Thiourea catalysts/Hydrogen Bonding

- Catalytic Asymmetric Aza-Henry Reaction (Shibasaki, Jorgensen, Jacobsen, & Palomo Group)

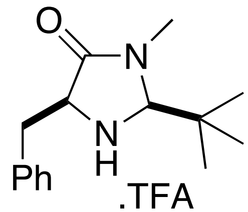
- Title Paper

- Summary

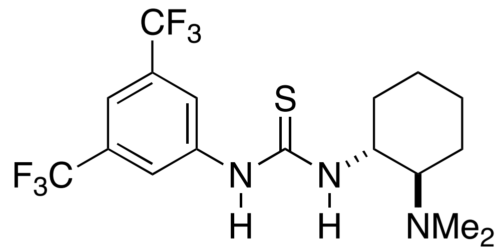
Organocatalysts



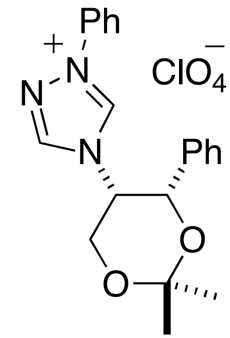
(L)-Proline



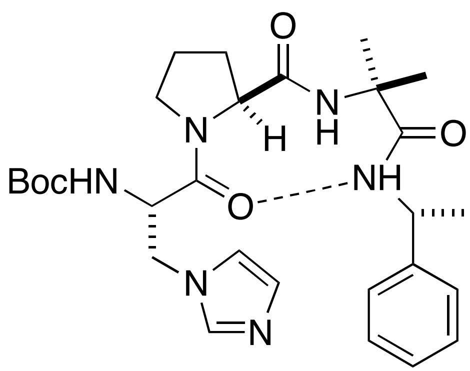
Imidazolium catalyst
MacMillan



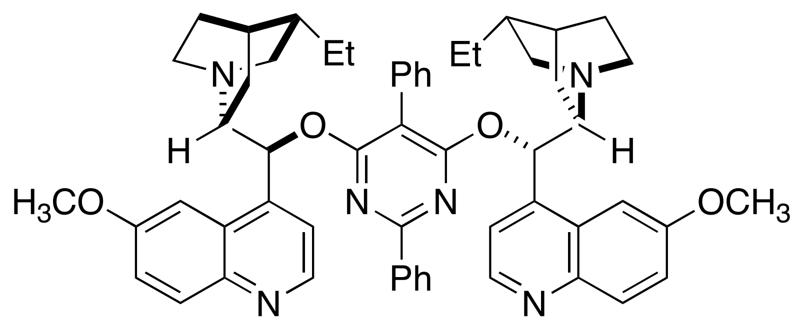
Thiourea catalyst
Takemoto



Triazolium catalyst
Enders

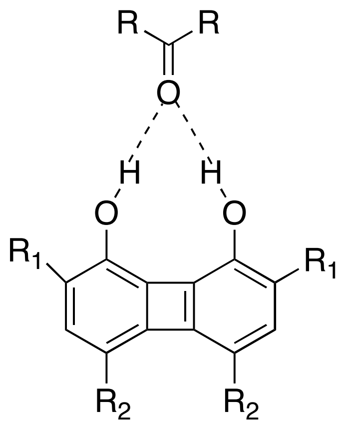


Peptide based catalyst
Miller



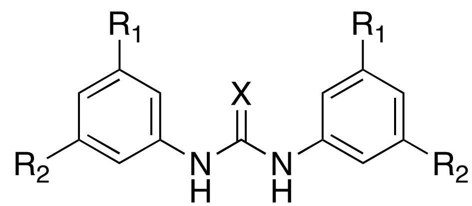
Cinchona alkaloid catalyst
Deng

Organocatalysts: Double Hydrogen Bonding Activation



1 $R_1 = R_2 = H$
Hine biphenylenediol catalyst

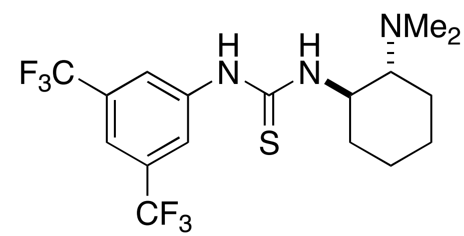
2 $R_1 = n$Pr, $R_2 = NO_2$
Kelly biphenylenediol catalyst



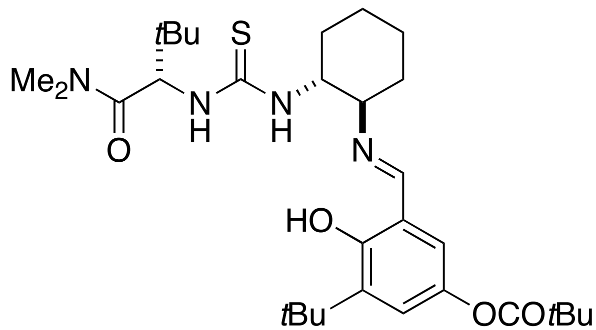
3a $R_1 = NO_2$, $R_2 = H$, X = O
Etter urea catalyst

3b $R_1 = CF_3$, $R_2 = CO_2C_8H_{17}$, X = O
Curran's diarylurea

3c $R_1 = R_2 = CF_3$, X = S
Schreiner thiourea catalyst

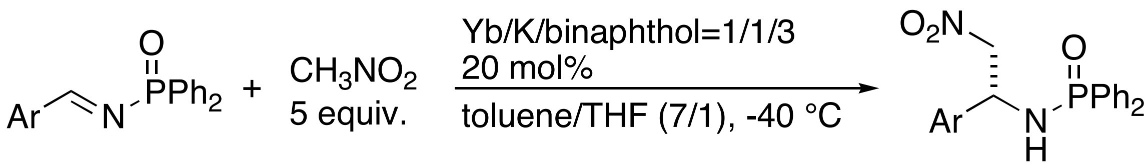


4 Takemoto thiourea catalyst

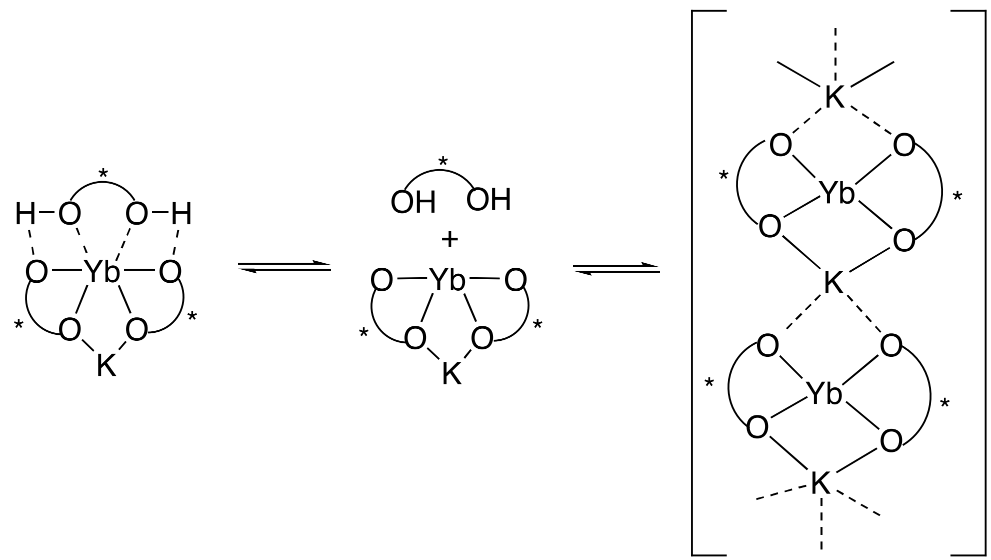


5 Jacobsen thiourea catalyst

Catalytic Asymmetric Aza-Henry Reaction Promoted by Heterobimetallic complex

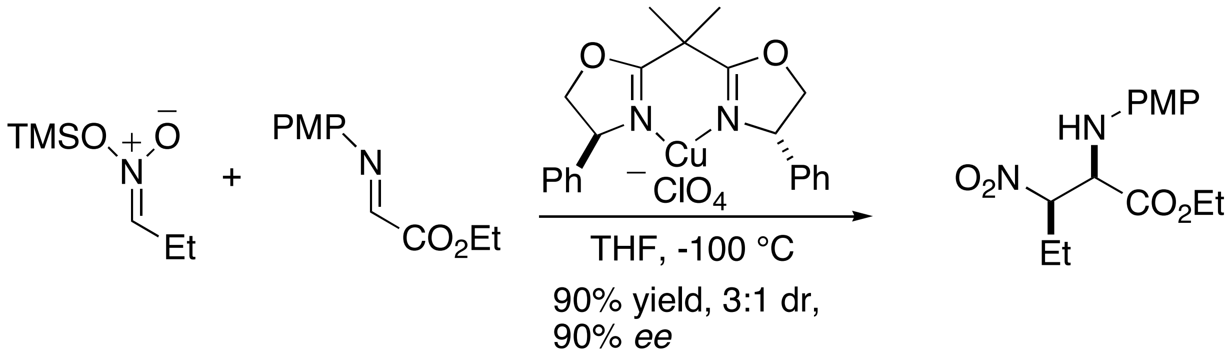


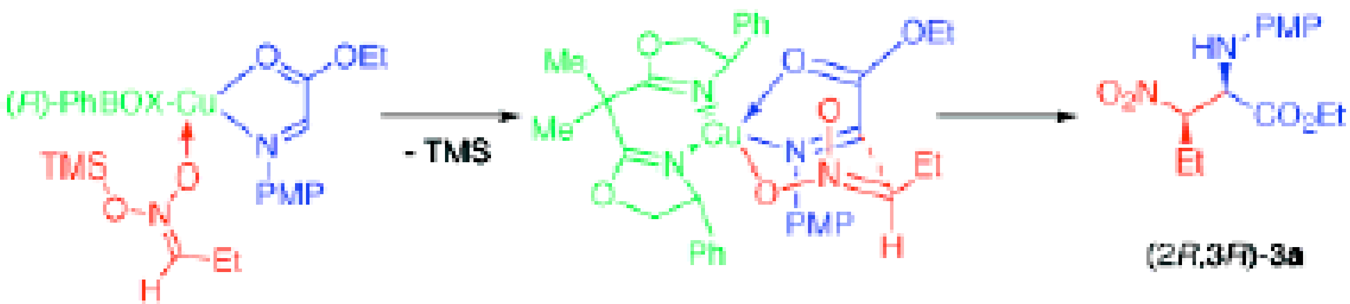
Entry	Ar	Time (h)	Yield (%)	*ee* (%)
1.	Ph	60	79	91
2.	4-Cl-C_6H_4	60	93	87
3.	*p*-tolyl	168	85	89
4.	2-furyl	168	57	83
5.	2-thiophenyl	168	41	69



Shibasaki et al. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504-3506.

Catalytic Asymmetric Aza-Henry Reaction of Nitronates with Imines

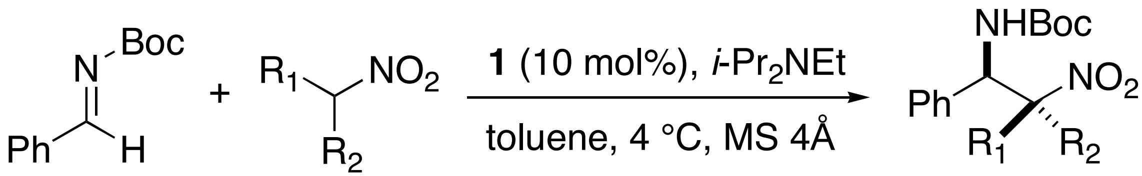


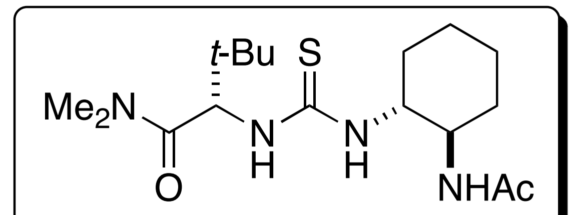


10 11 (2R,3R)-3a

Jorgenson et al. *J.Am.Chem.Soc*. **2001**, *123*, 5843-5844.

Catalytic Asymmetric Aza-Henry Reaction using Thiourea Catalyst





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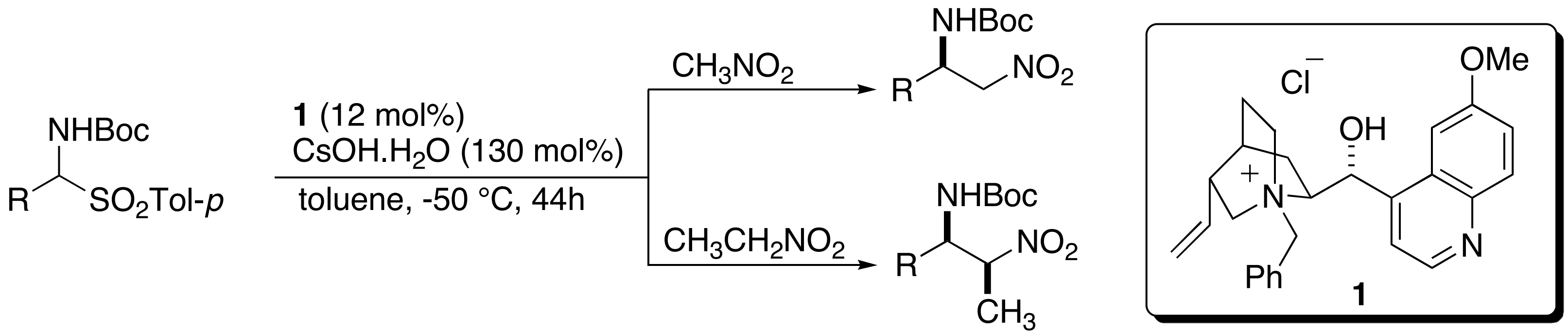
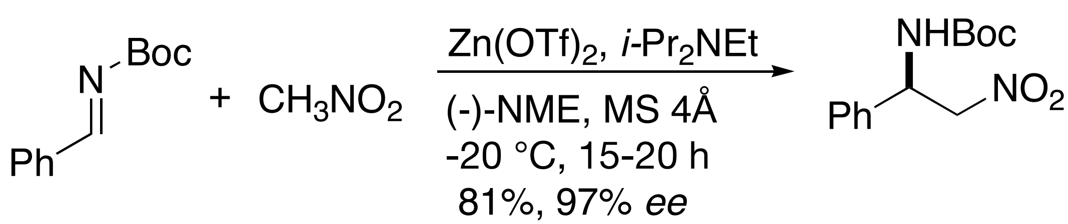
Entry	Nitroalkane	R_1	R_2	Yield (%)	dr (*syn*:*anti*)	*ee* (%)
1.	1-nitropropane	Et	H	99	7:1	95
2.	nitromethane	H	H	87	-	92
3.	2-nitropropane	Me	Me	87	-	92
4.	$TBSOCH_2CH_2NO_2$	$TBSOCH_2$	H	85	4:1	95

Jacobsen et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 466-468.

Catalytic Asymmetric Aza-Henry Reaction

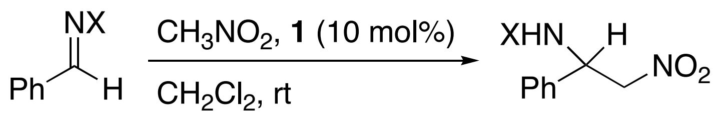


Entry	R	R_1NO_2	Yield (%)	*ee* (%)
1.	$PhCH_2CH_2$	CH_3NO_2	83	96
2.	$(CH_3)_2CH$	CH_3NO_2	81	95
3.	4-MeOC_6H_4	CH_3NO_2	82	91
4.	4-$F_3CC_6H_4$	CH_3NO_2	80	82 (90)
5.	4-MeOC_6H_4	$CH_3CH_2NO_2$	87	90 (95:5)



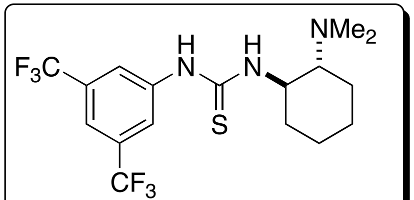
Palomo et al. *J. Am. Chem. Soc.* **2005**, *127*, 17622-17623.
Palomo et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 117-120.

Enantioselective Aza-Henry Reaction:(Title Paper)



Entry	(X)	Time (h)	Yield (%)	*ee* (%)
1.	Ts	4.5	99	4
2.	P(O)Ph_2	24	87	67 (*S*)
3.	Ac	24	95	63
4.	CO_2Me	24	64	83
5.	CO_2Bn	24	68	85
6.	Boc	24	76	90 (*R*)
7.[a]	Boc	24	90	94 (*R*)

[a] Reaction was performed at -20 °C



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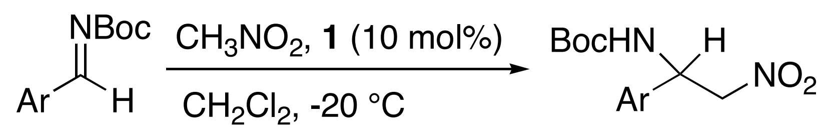
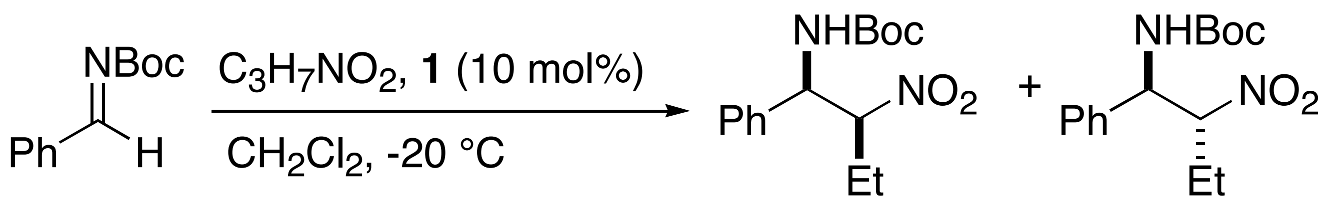
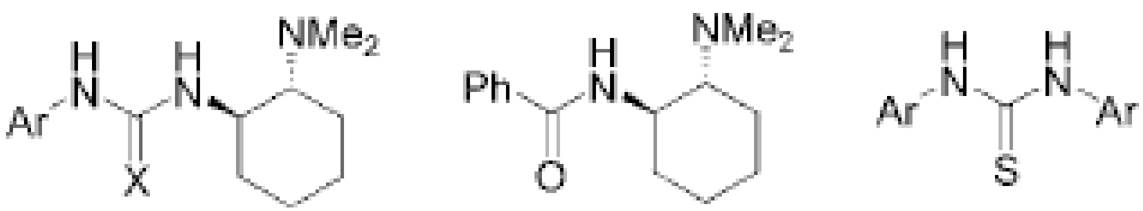


Entry	Ar	Time (h)	Yield (%)	*ee* (%)
1.	*p*-$CF_3C_6H_4$	24	80	98
2.	*p*-MeC_6H_4	24	82	93
3.	*p*-$MeOC_6H_4$	60	71	95
4.	1-naphthyl	24	85	95
5.	2-naphthyl	48	85	85
6.	2-furyl	60	81	91
7.	3-pyridyl	24	89	98

Enantio/Diastereoselective Aza-Henry Reaction of Nitropropane with organocatalysts



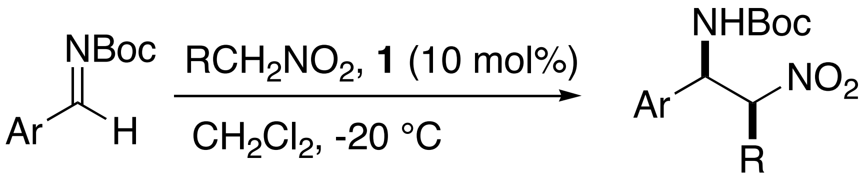
1a: 90%, 88/12 (95% *ee*)
1b: 84%, 89/11 (92% *ee*)
1c: 12%, 52/48 (7% *ee*)
1d: 0%



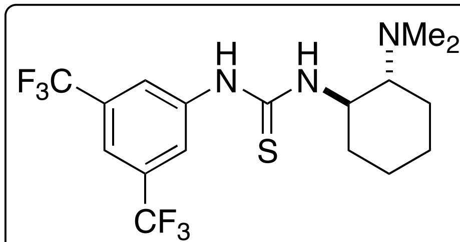
1a: X = S, Ar = 3,5-$(CF_3)_2C_6H_3$ **1c** **1d** (Ar = 3,5-$(CF_3)_2C_6H_3$)
1b: X = O, Ar = 3,5-$(CF_3)_2C_6H_3$

Both, thiourea and tertiary amine functionality is required

Enantio- and Diastereoselective Aza-Henry Reaction



Entry	Ar	R	Yield (%)	dr	*ee* (%)
1.	Ph	CH_3	92	90/10	93
2.	Ph	C_5H_{11}	82	93/7	99
3.	Ph	CH_2Ph	84	83/17	97
4.	Ph	CH_2OH	75	75/25	90
5.	Ph	CH_2OBn	80	86/14	95
6.	Ph	$(CH_2)_2OBn$	86	93/7	94
7.	Ph	$(CH_2)_3OBn$	80	91/9	92
8.	Ph	$(CH_2)_3OH$	80	92/8	89
9.	Ph	$(CH_2)_3OTf$	78	93/7	90
10.	*p*-$CF_3C_6H_4$	CH_2Ph	94	97/3	95
11.	*p*-MeC_6H_4	CH_2Ph	90	93/7	92
12.	3-pyridyl	CH_2Ph	93	83/17	93



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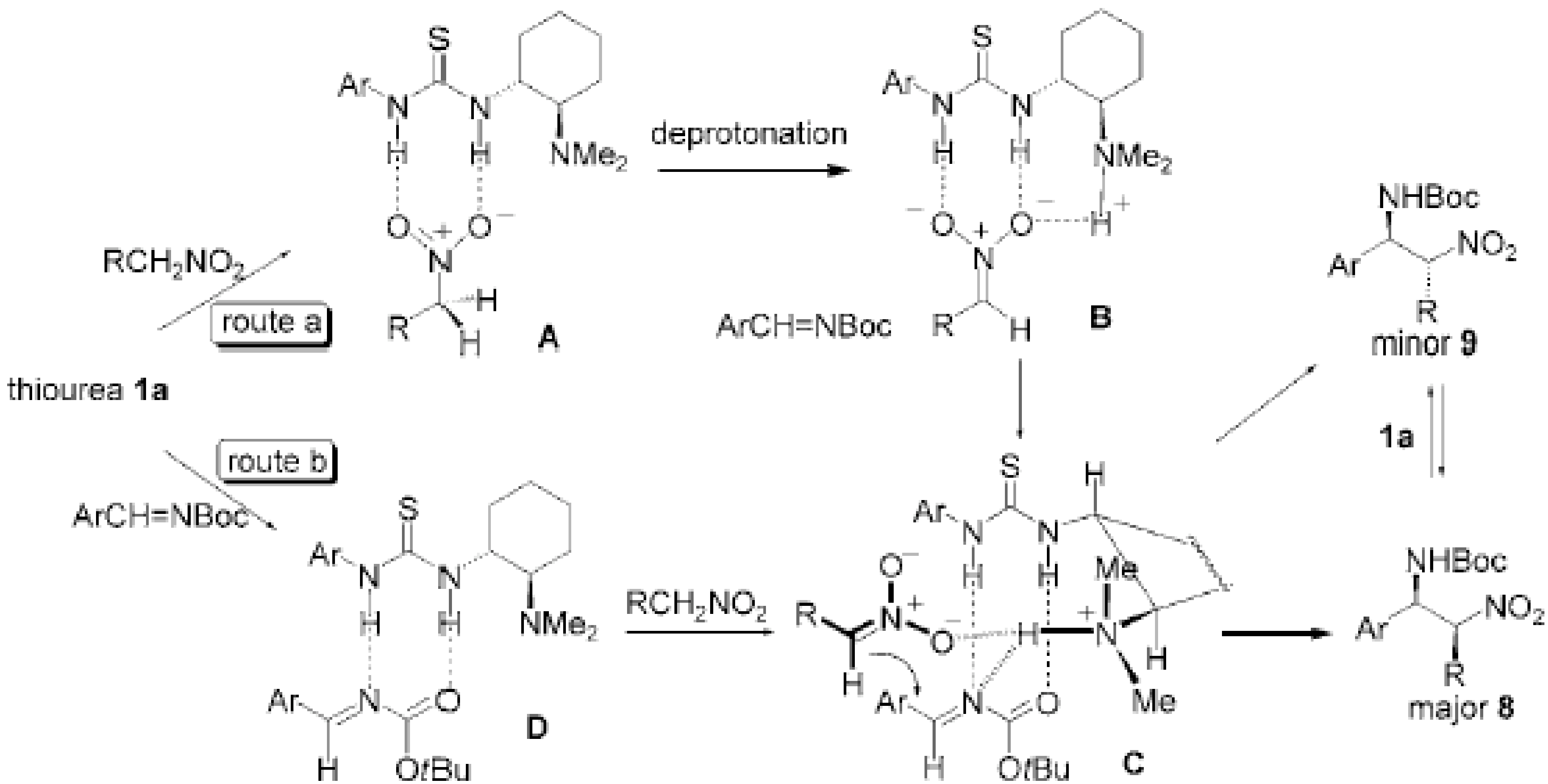
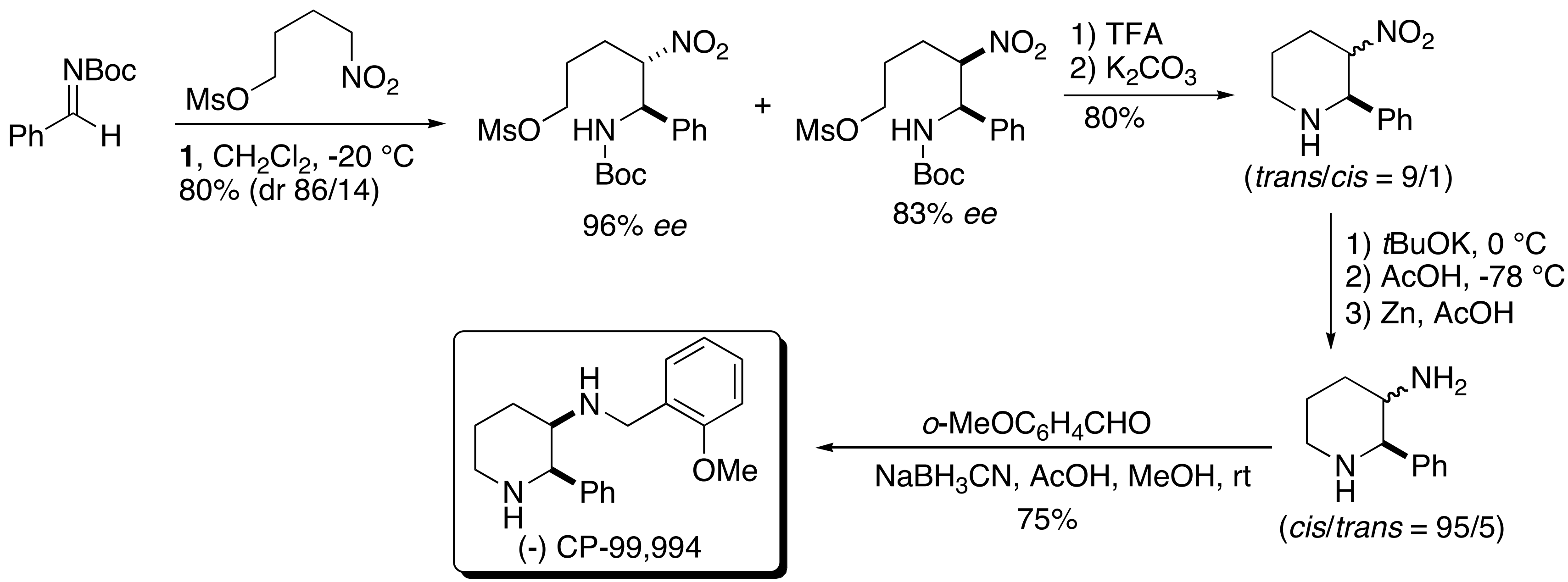
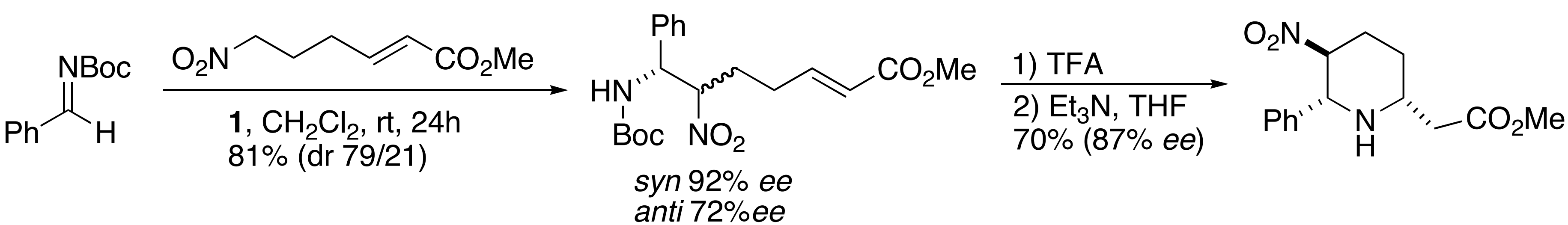
Proposed Model for the Thiourea-Catalyzed Aza-Henry Reaction



Applications of Aza-Henry Reaction



Potent neurokinin-1 receptor antagonist



Summary

- Catalytic Asymmetric Aza-Henry reaction: good diastereo- and enantioselectivity
- *Syn*-β-nitroamines as major products
- Thiourea and tertiary amine functionality in the catalyst are required
- Tolerance of aryl, alcohol, ether, and ester groups
- No additional reagents required