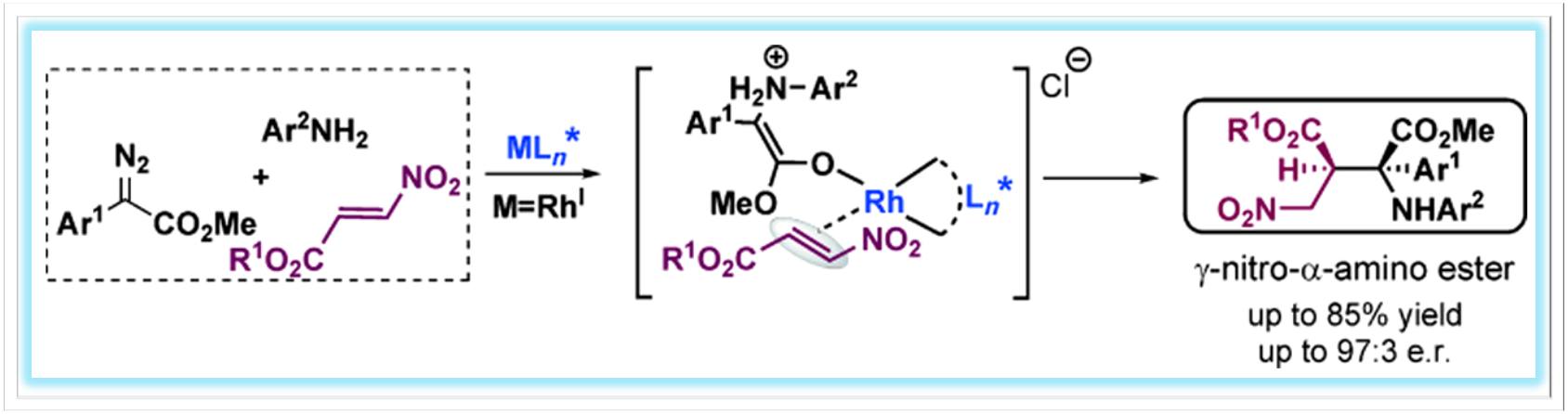
An Ylide Transformation of Rhodium(I) Carbene: Enantioselective Three-Component Reaction through Trapping of Rhodium(I)-Associated Ammonium Ylides by β-Nitroacrylates



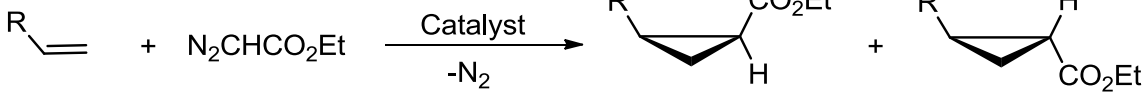
Xiaochu Ma, Jun Jiang, Siying Lv, Wenfeng Yao, Yang Yang, Shunying Liu, Fei Xia, and Wenhao Hu**

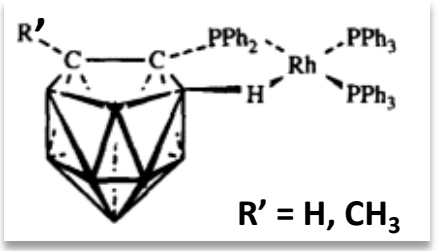
Angew. Chem. Int. Ed. **2014**, *53*, 13136

1. Rhodium(I) carbenes with diazo compounds

1997

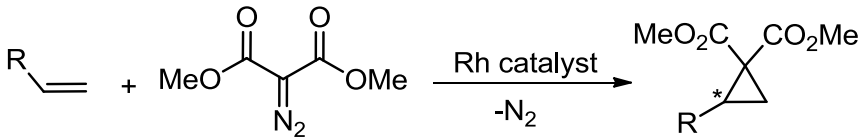
The first example of a Rh(I)-catalyzed cyclopropanation of alkenes with ethyl diazoacetate

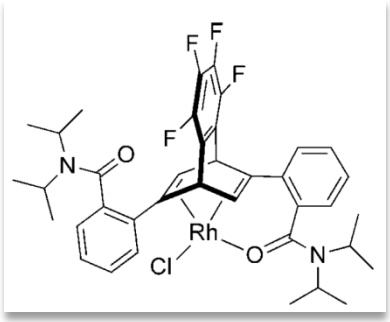




2010

Asymmetric version using dimethyl diazomalonate via Rh(I) carbene intermediates





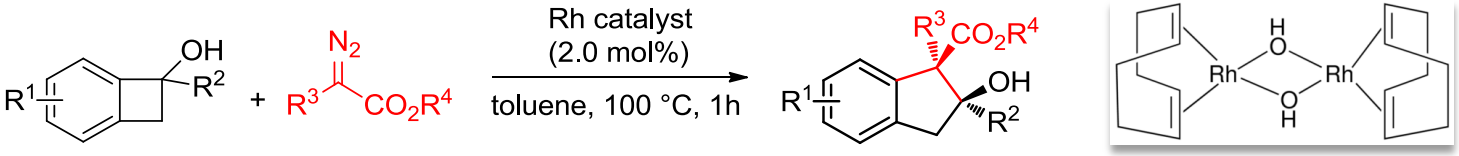
1) A. Demonceau, F. Simal, A. F. Noels, *Tetrahedron Lett.* **1997**, *38*, 7879

2) T. Nishimura, Y. Maeda, T. Hayashi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7324; *Angew. Chem.* **2010**, *122*, 7482

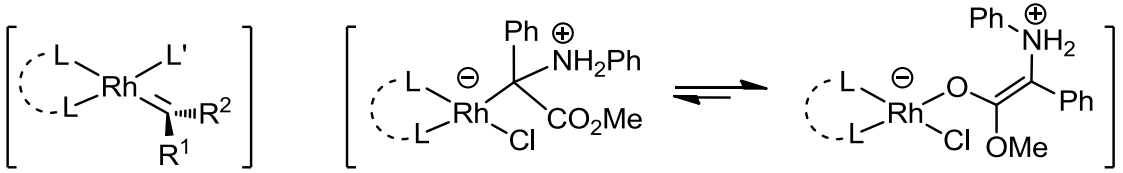
2. Rhodium(I) – associated ammonium ylide

2014

Reaction of Rh(I) carbene insertion into the C-C bond of benzocyclobutenols to construct indanol derivatives



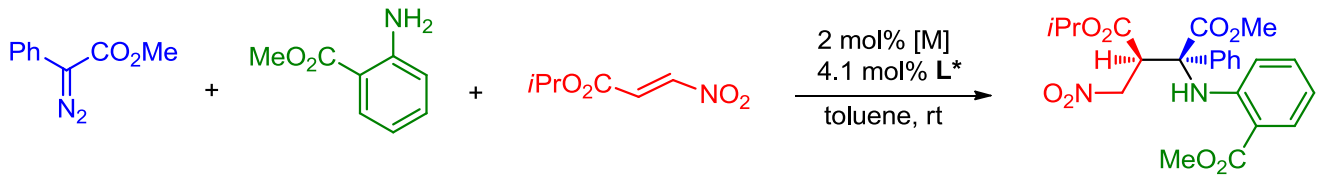
First example of rhodium(I) carbene ylide chemistry



Rh(I) carbene **Rh(I) - associated ammonium ylide**

3) Y. Xia, Z.-X. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J.-B. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 3013

3. Catalyst screening for the three-component reaction

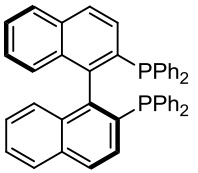


1a 2a 3a 4a

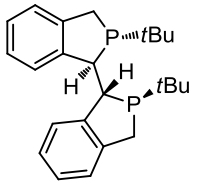
Entry	[M]	L*	Yield [%]	d.r.	e.r.
1	$[Rh(CO)_2Cl]_2$	-	trace	N.D.	N.D.
2	$[Rh(C_2H_4)_2Cl]_2$	-	N.P.	-	-
3	$[Rh(cod)Cl]_2$	-	58	88:12	N.D.
4	$[Rh(cod)Cl]_2$	L_1	42	80:20	60:40
5	$[Rh(cod)Cl]_2$	L_2	N.P.	-	-
6	$[Rh(cod)Cl]_2$	L_3	53	82:18	51:49
7	$[Rh(CO)_2Cl]_2$	L_3	trace	N.D.	N.D.
8	$[Rh(C_2H_4)_2Cl]_2$	L_3	65	95:5	97:3
9	$[Rh(C_2H_4)_2Cl]_2$	L_4	46	95:5	75:25
10	$[Rh(C_2H_4)_2Cl]_2$	L_5	12	70:30	79:21
11	$[Rh(L_3)Cl]_2$	-	62	95:5	96:4

Insufficient ligand exchange

N.D.: not determined, N.P.: no desired product.



L1



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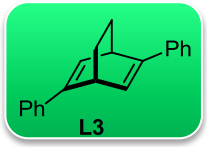
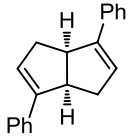
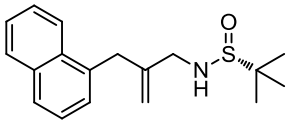


L3

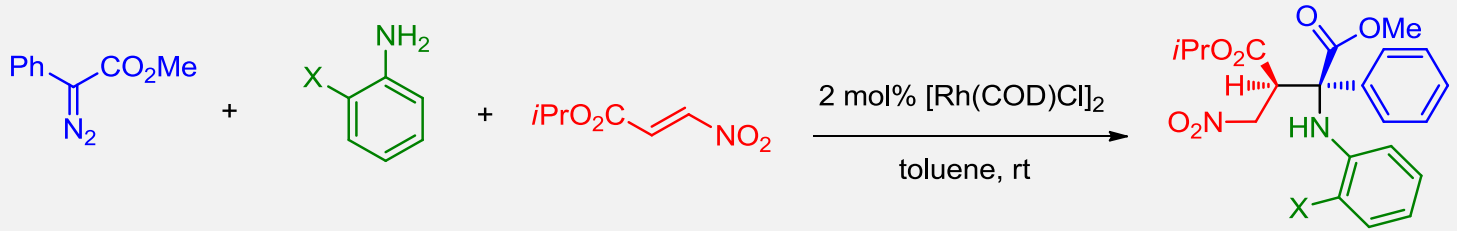


L4



L5

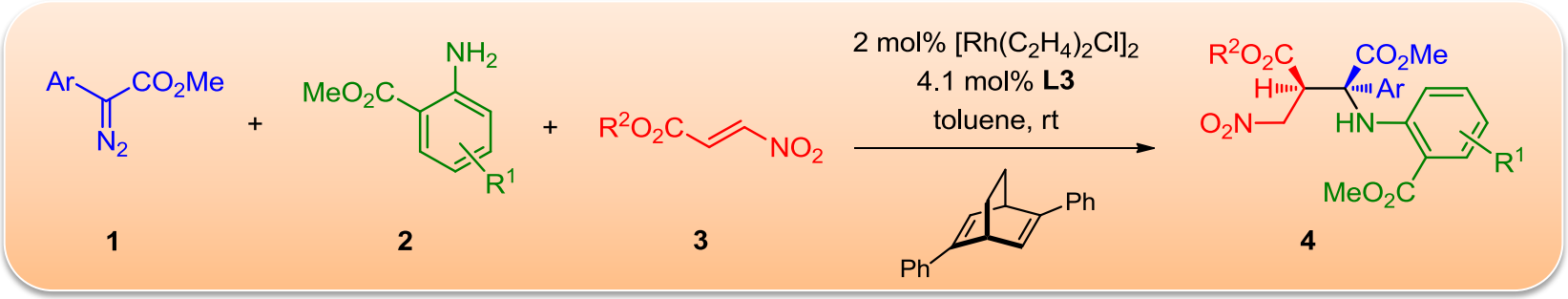
4. Effects of ortho-substituted functional groups on yield and diastereoselectivity

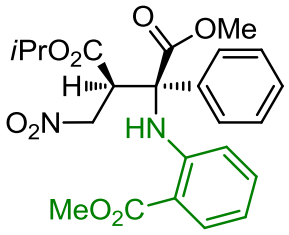


1a 2 3a 4

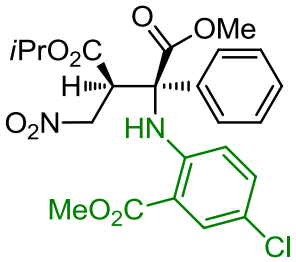
Entry	X	d.r.	Yield [%]
1	I	55:45	**4aa** (52)
2	OCH_3	52:48	**4ab** (66)
3	O*i*Pr	58:42	**4ac** (61)
4	CHO	80:20	**4ad** (10)
5	$COCH_3$	62:38	**4ae** (17)
6	**CO_2CH_3**	**88:12**	**4a (58)**

5. Scope for the three-component reaction

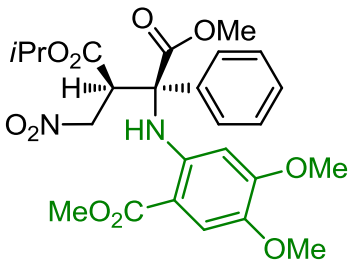




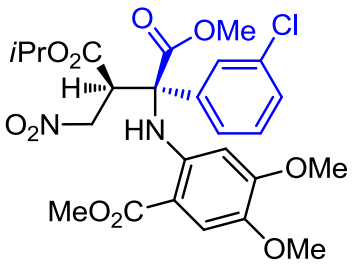
4a, 64% (d.r = 95:5)
e.r = 97:3



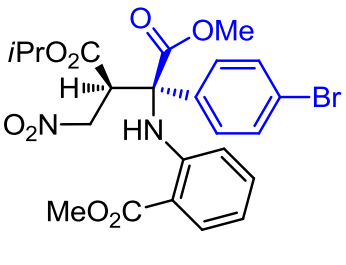
4b, 74% (d.r = 91:9)
e.r = 81:19



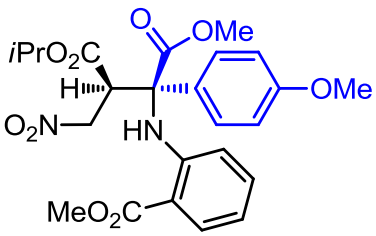
4c, 85% (d.r = 91:9)
e.r = 90:10



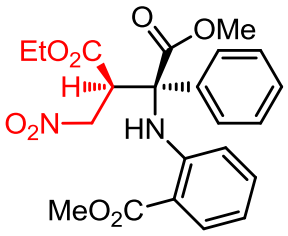
4d, 47% (d.r = 88:12)
e.r = 93:7



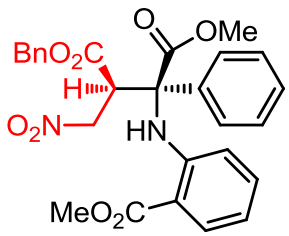
4f, 48% (d.r = 95:5)
e.r = 92:8



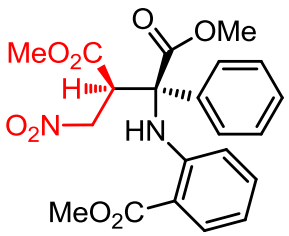
4g, 60% (d.r = 91:9)
e.r = 94:6



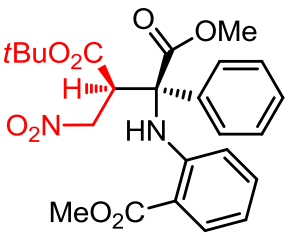
4i, 53% (d.r = 89:11)
e.r = 75:25



4j, 67% (d.r = 86:14)
e.r = 73:27



4k, 72% (d.r = 92:8)
e.r = 92:8

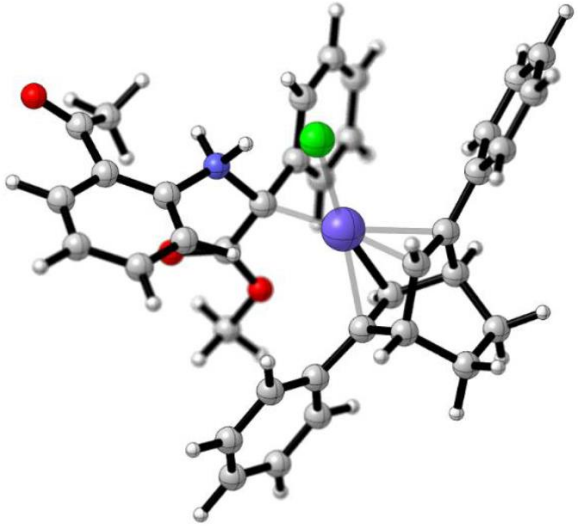


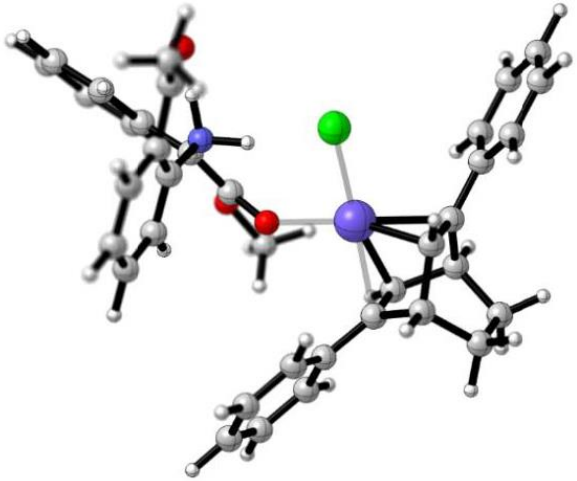
4l, 45% (d.r = 86:14)
e.r = 88:12

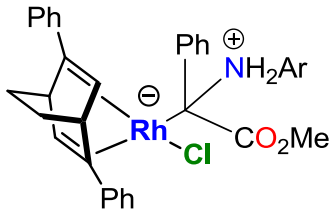
6. Gibbs free energy of the enolate versus the ylide form

ΔE = +14.9 kcal/mol

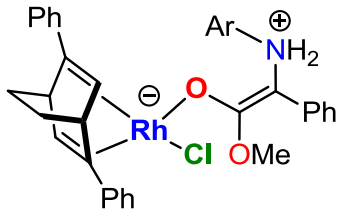
0.0 kcal/mol







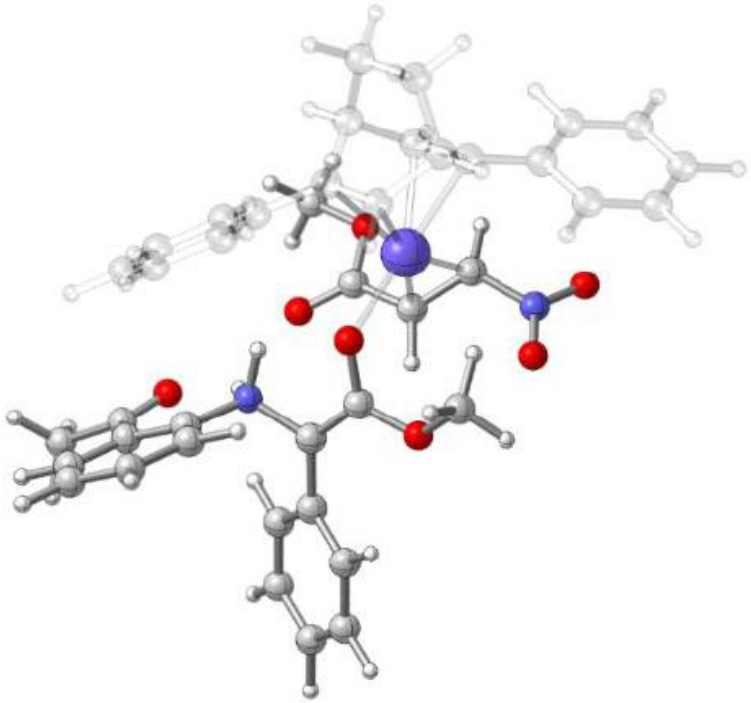
Ar = 2-$COCH_3$Ph



Ylide form **III**

Enolate form **IV**

7. The theoretically calculated transition state V



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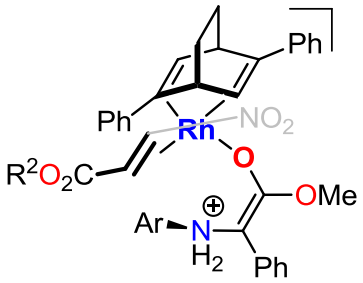
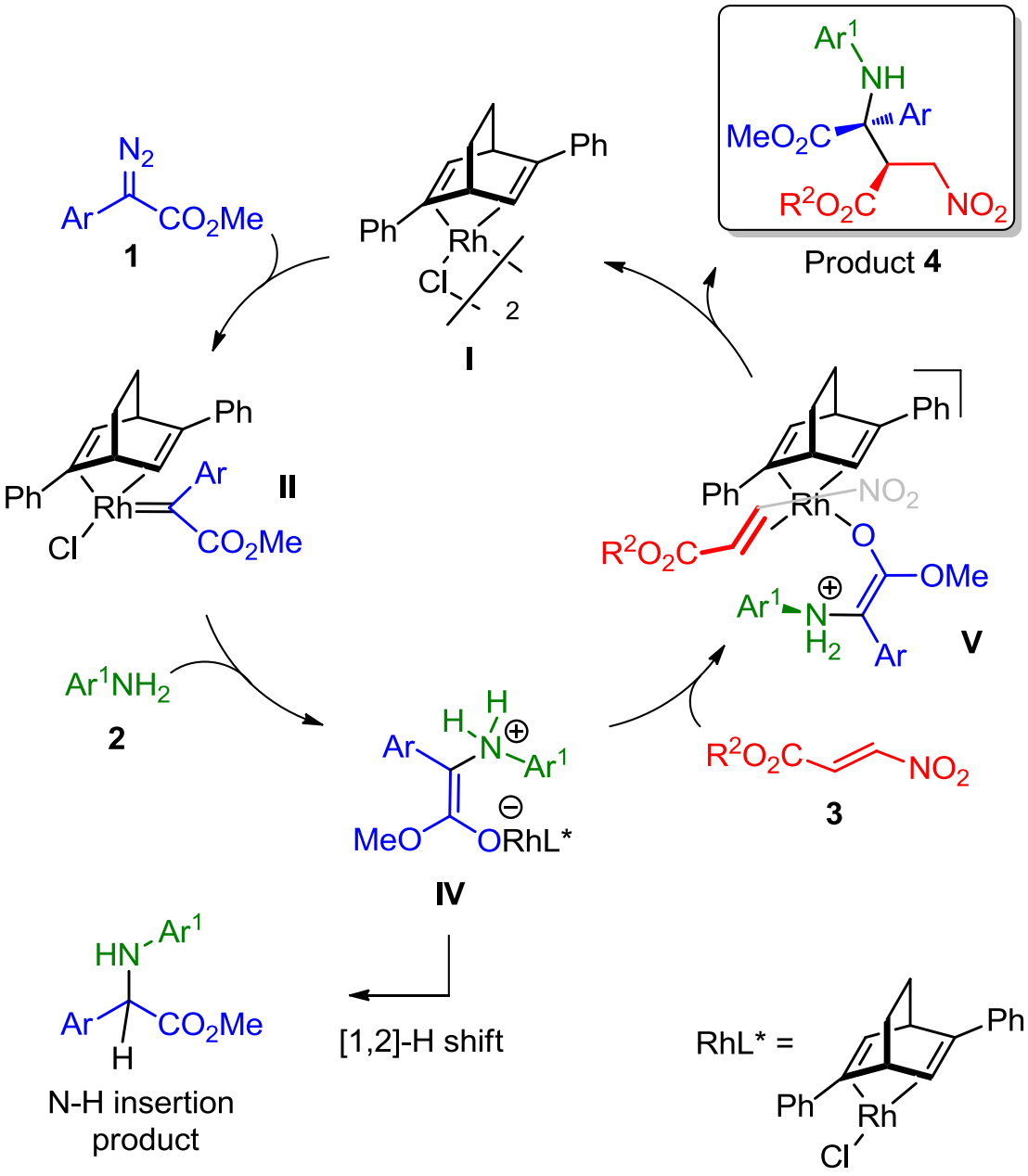


Ar = 2-$COCH_3Ph$

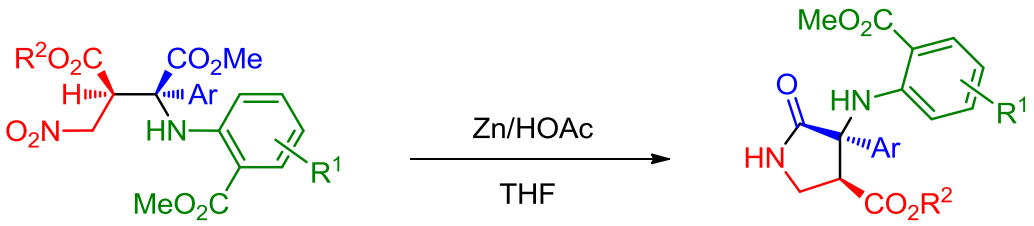
Transition state **V**

An intimate ion pair with chloride is obtained, probably due to the solvent-assisted neutral-to-cationic switch

8. Plausible reaction mechanism

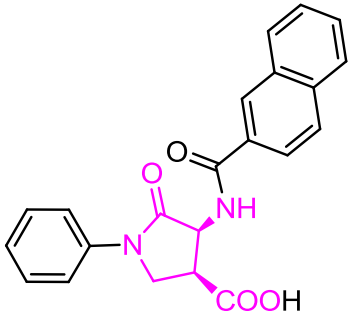


9. Synthesis of 3-aminopyrrolidinone derivatives

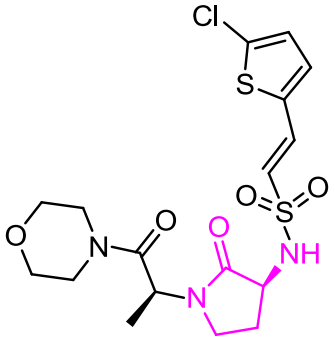


4

5a: Ar = Ph, R^1 = H
90% yield, 98:2 e.r.



CCK-A receptor antagonist



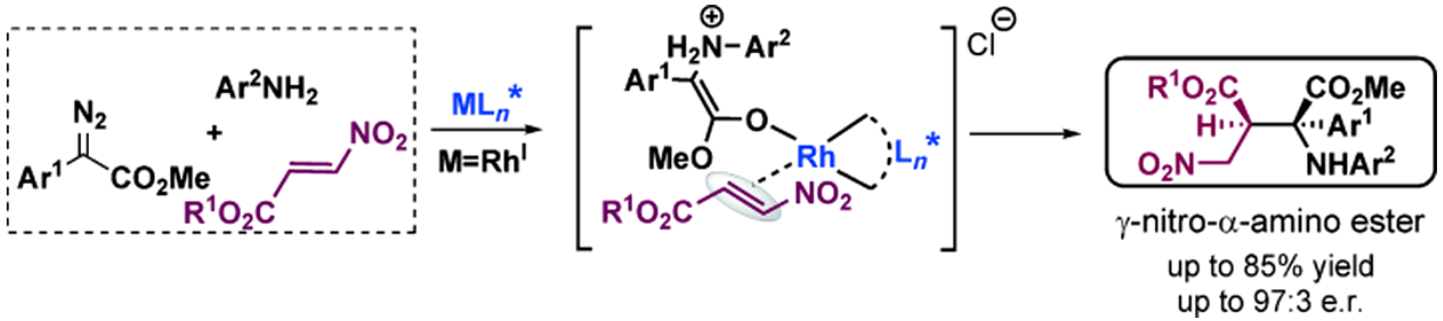
Factor Xa inhibitor

4) D. L. Flynn, C. I. Villamil, D. P. Becker, G. W. Gullikson, C. Moummi, D-C. Yang, *Bioorg. Med. Chem. Lett.* **1992**, *2*(10), 1251

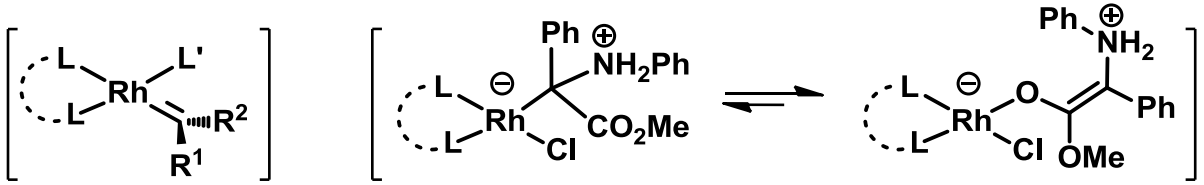
5) C. Chan, A. D. Borthwick, D. Brown, C. L. Burns-Kurtis, M. Campbell, *et al. J. Med. Chem.* **2007**, *50*, 1546

10. Conclusions

❖ The chiral Rh(I)–diene-catalyzed asymmetric three component reaction of aryldiazoacetates, aromatic amines and β-nitroacrylates was achieved to obtain γ-nitro-α-aminosuccinates.



❖ This new transformation represents the first example of Rh(I)-carbene-induced ylide transformation.



Rh(I) carbene **Rh(I) - associated ammonium ylide**