Catalytic Intramolecular Ketone Alkylation with Olefins by Dual Activation

Hee Nam Lim and Guangbin Dong*

Angew. Chem. Int. Ed. **2015**, *54*, 15294-15298

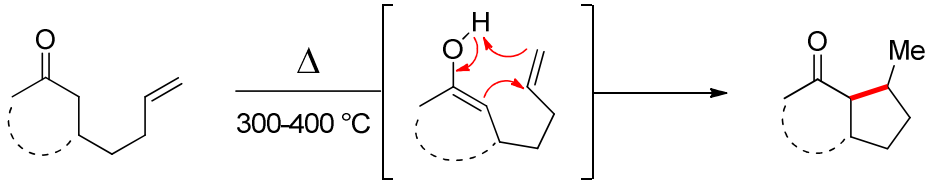
Ophélie Quinonero

08/12/2015

Literature precedents

Conia-ene type reactions

- **Thermal Conia-Ene reaction**

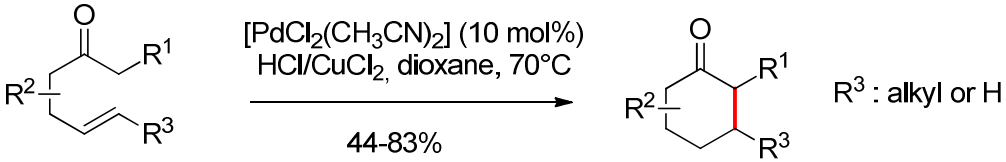


J.M. Conia, P. Le Perchec, *Synthesis* **1975**, 1

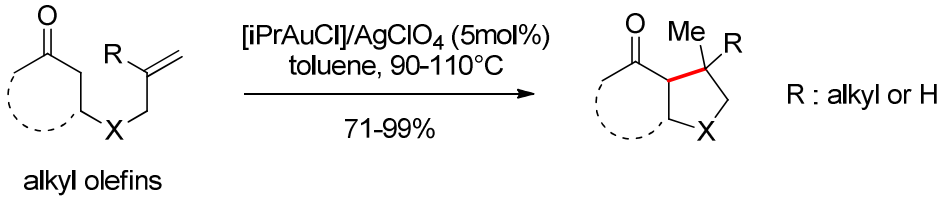
Literature precedents

Catalytic Conia-ene type reactions

- **π-Acid-catalyzed Ketone-Ene Cyclization**



S.Wang, T.Pei, X. Han, R.A. Widenhoefer, *Org. Lett*. **2003**, *5*, 2699

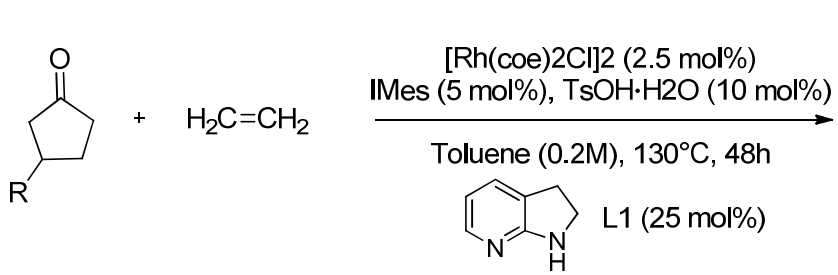


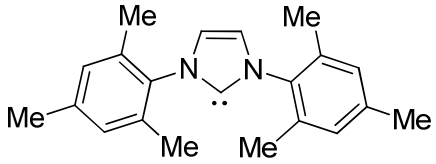
Y.-P. Xiao, X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* **2011**, *50*, 4937

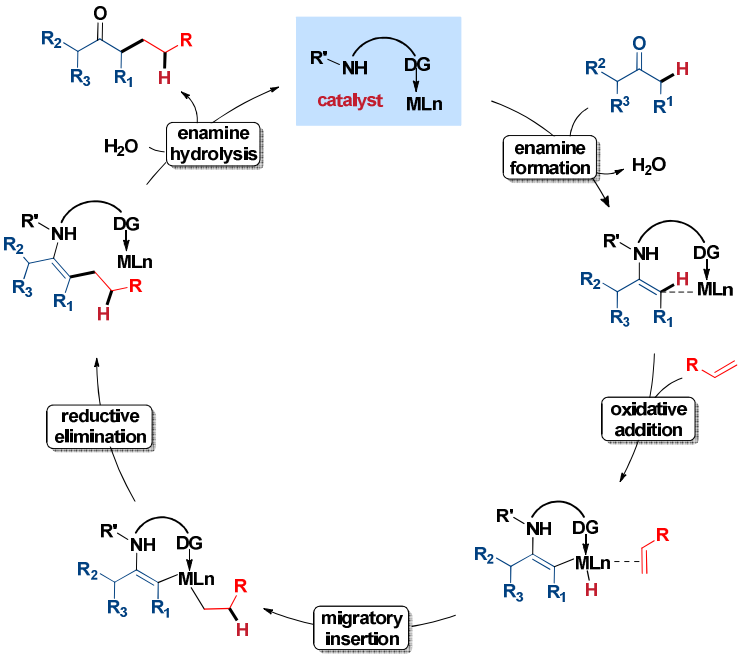
Literature precedents

Intermolecular ketone α-alkylation reaction with simple olefins

- **Bifunctionnal catalysis**



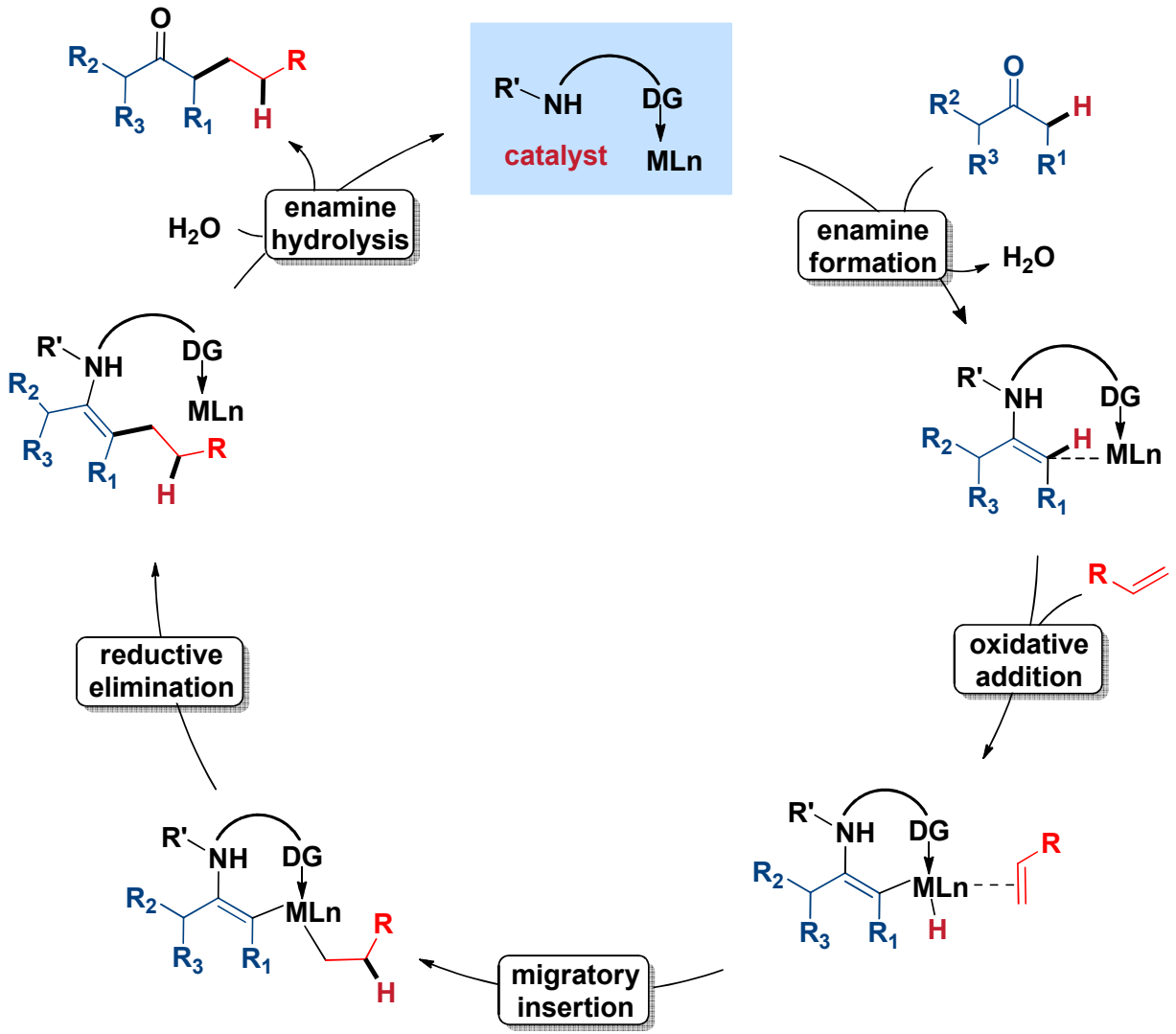




F. Mo, G. Dong, *Science*, **2014**, *345*, 68

Literature precedents

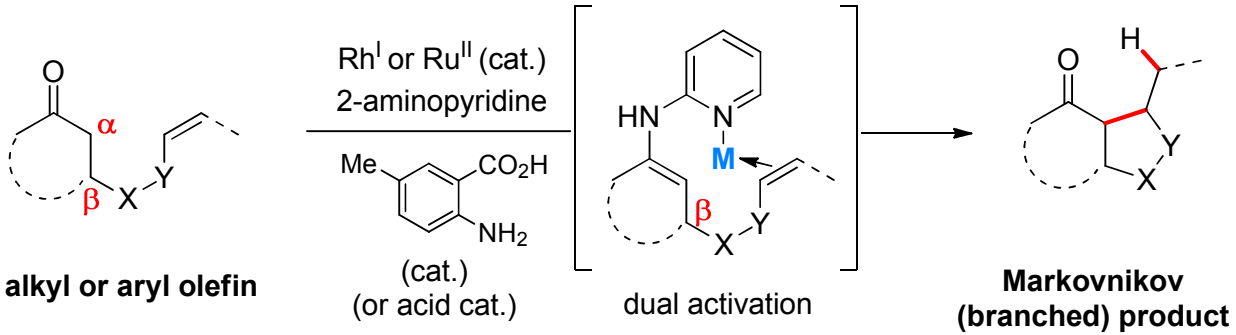
Intermolecular ketone α-alkylation reaction with simple olefins

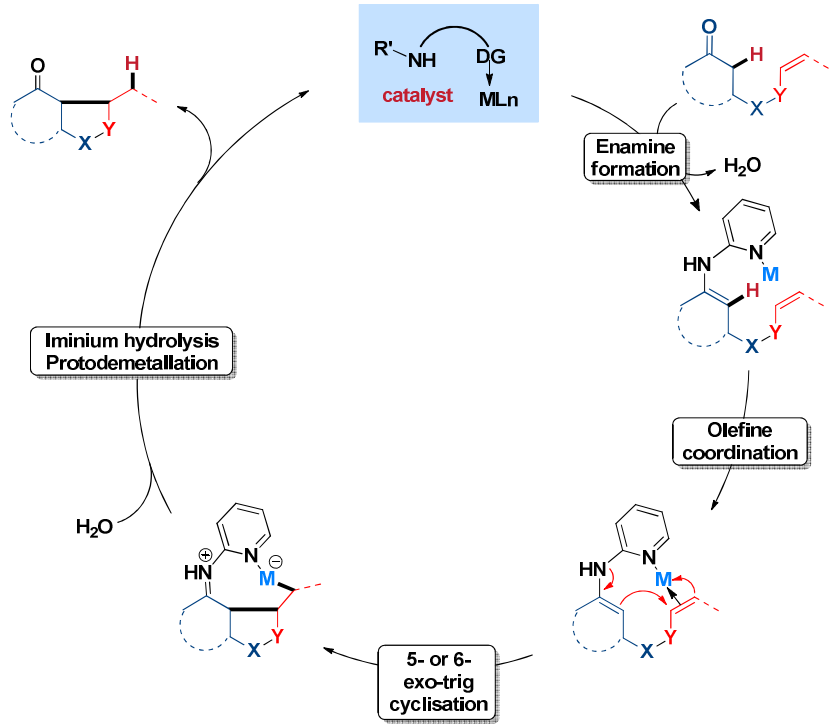


F. Mo, G. Dong, *Science*, **2014**, *345*, 68

This work

Conia-ene type reaction by dual activation





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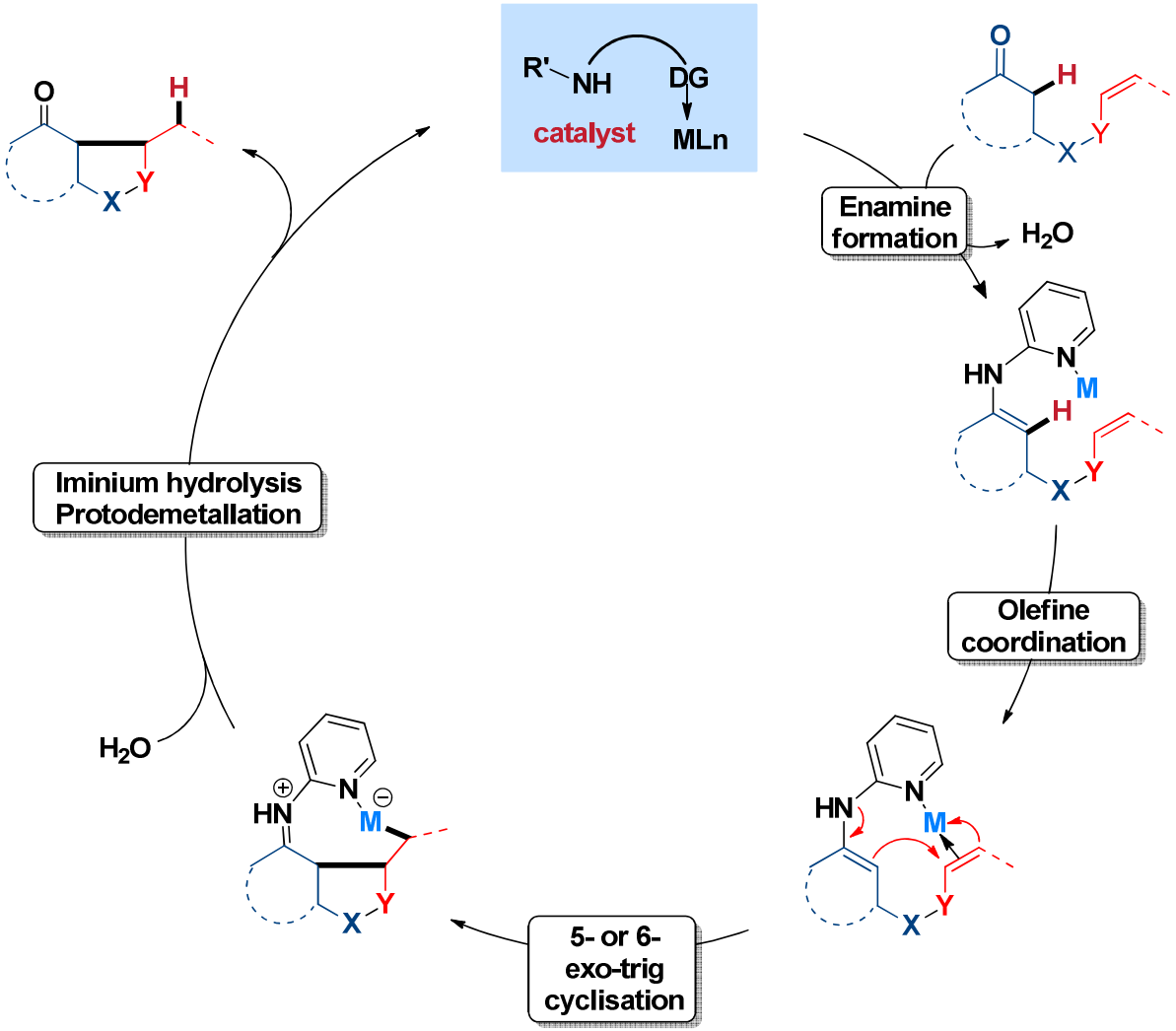
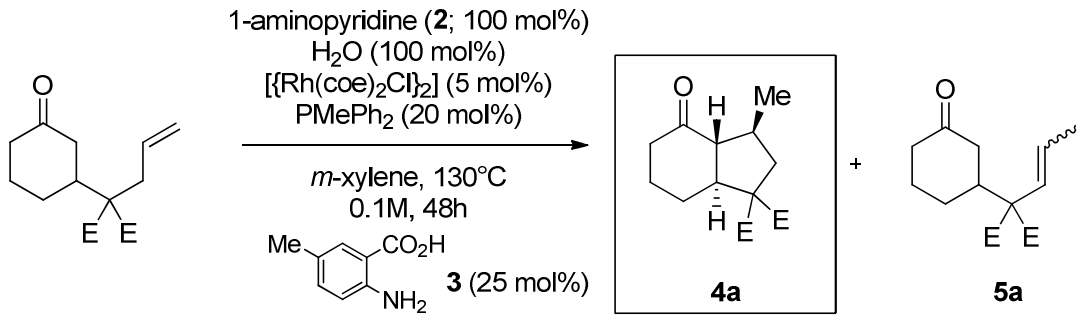


Selected Optimization Studies[a]



Entry	Variations from "conditions A"	**4a** [%][b]	d.r. (4)	**5a** [%][b]
1	-	74 (58)[c]	7:1	2
2	without [{Rh(coe)$_2$Cl}$_2$]	-	-	-
3	without **2**	-	-	12
4	without **3**	8	3:1	-
5	aniline instead of **2**	10	1:1.4	-
6	aniline and pyridine instead of **2**	6	2:1	-
7	[RhCl(PPh$_3$)$_3$] (10 mol%), TsOH·H$_2$O (10 mol%), 2 (25 mol%), *m*-xylene, 150°C, 0.1 M **(conditions B)**	66 (59)	-[d]	-

[a] All reactions were run on 0.1 mmol scale with 1.0 mL of the indicated solvent. [b] Determined by 1H NMR spectroscopy using 1,2-tetrachloroethane as the internal standard. [c] Yield of the isolated major diastereomer. [d] Single diastereomer. coe = cyclooctene.

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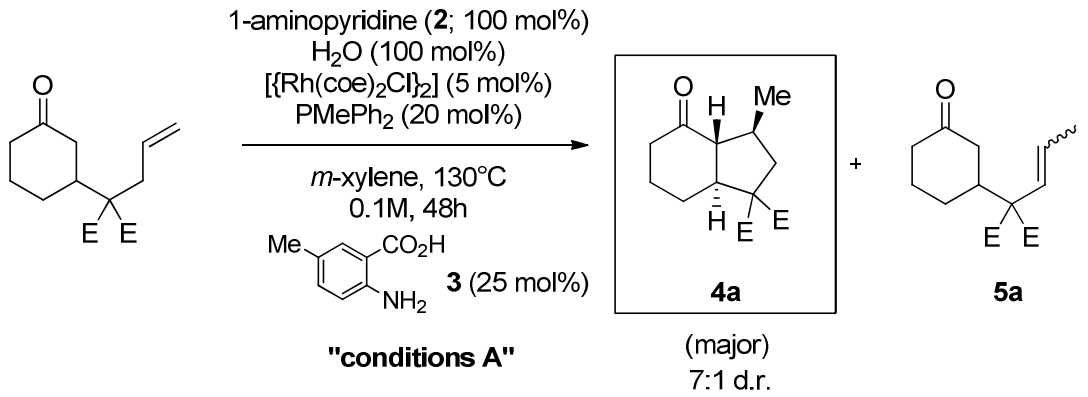

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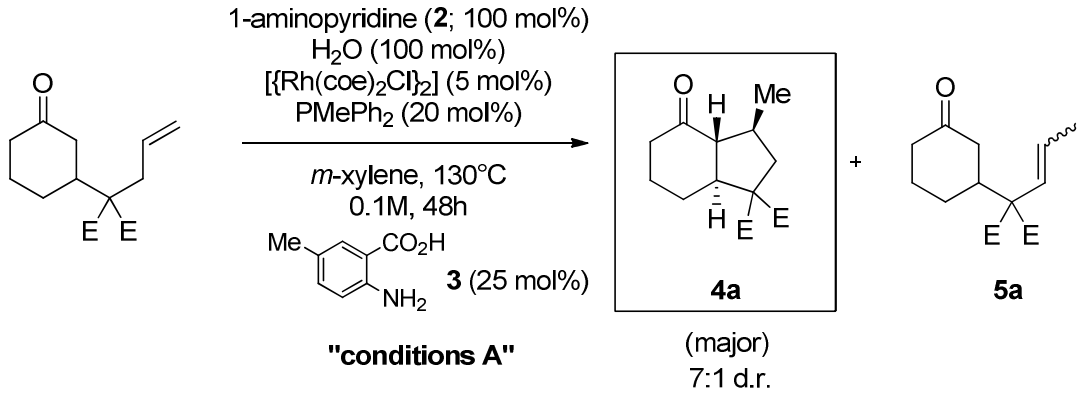

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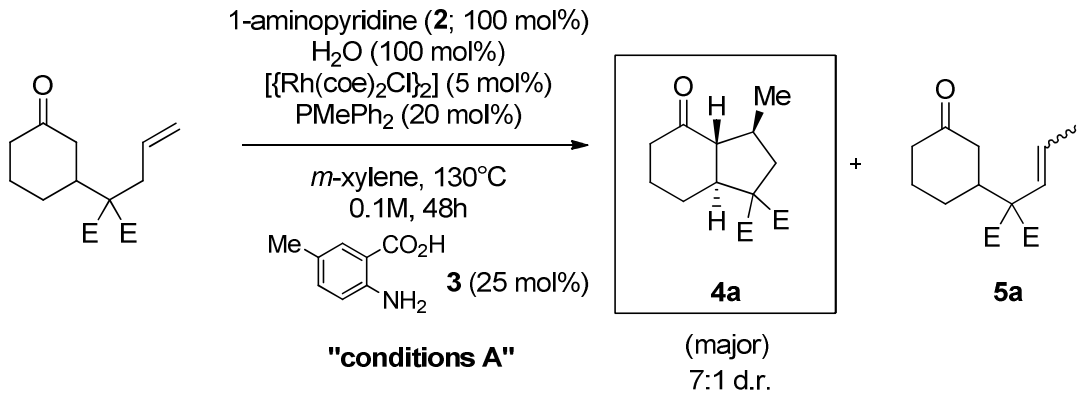

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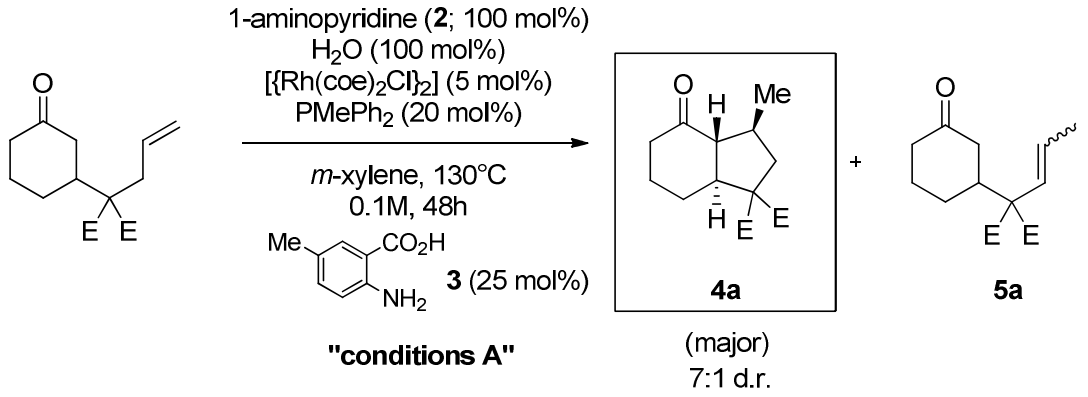

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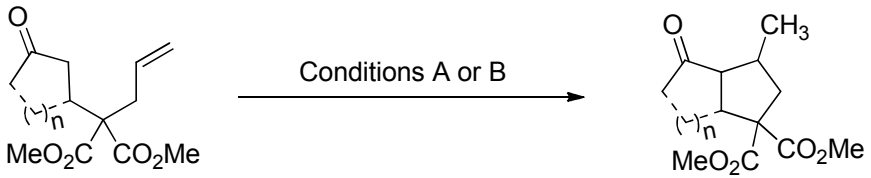
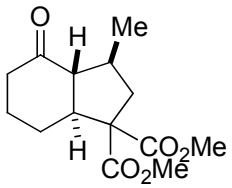
Scope of the reaction

Ketone scope

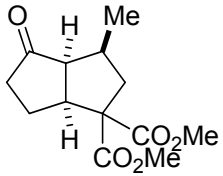


(conditions A)
[{Rh(coe)$_2$Cl}$_2$] (5 mol%)
$PMePh_2$ (20 mol%)
1-aminopyridine (**2**; 100 mol%)
5-methyl-2-aminobenzoic acid (**3**, 25 mol%), H_2O (100 mol%)
m-xylene, 130°C, 0.1M, 48h

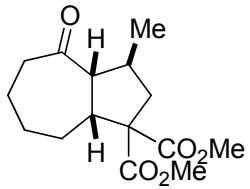
(conditions B)
[RhCl(PPh$_3$)$_3$] (10 mol%),
TsOH·H_2O (10 mol%),
2-aminopyridine (**2**, 25 mol%),
m-xylene, 150°C, 0.1 M



n = 2

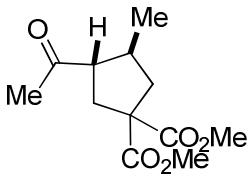


n = 1

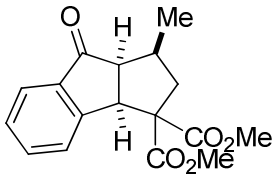


n = 3

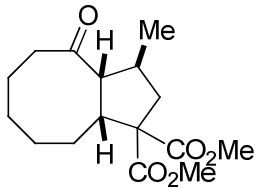
	n = 2	n = 1	n = 3
Conditions A	58%[b] (7:1 d.r.)	71%[c] (>19:1 d.r.)	43%[e] (3.5:1:0.5 d.r.)
Conditions B	59% (>19:1 d.r.)	62%[d] (>19:1 d.r.)	82% (4:1:0.5 d.r.)



acyclic



aryl ketone



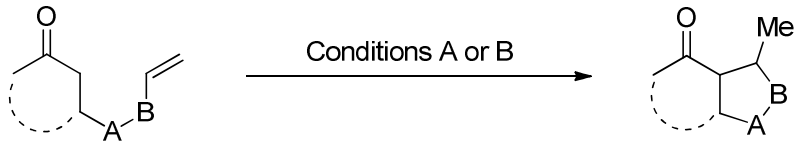
n = 4

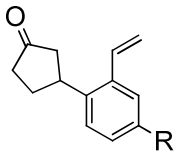
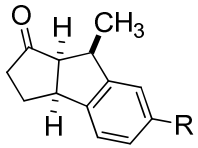
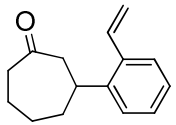
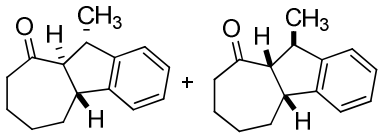
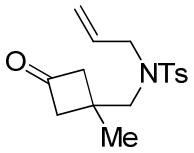
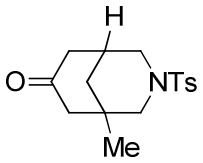
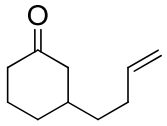
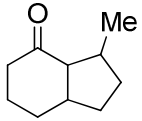
	acyclic	aryl ketone	n = 4
Conditions A	low conversion	low conversion	-
Conditions B	64%[b,f] (7:1 d.r.)	53%[g] (2.6:1 d.r.)	40%[h] (3.6: 2.5 : 1 d.r.)

[a] Yields of isolated products are given. [b] Yield of the major isomer [c] 2-Amino-3-methylpyridine (100 mol%) was used instead of **2**. [d] 2-Amino-3-methyl-pyridine (25 mol%) was used instead of **2.** [e] 150°C
[f] 2-Amino-3-methylpyridine (100 mol%) and $AgPF_6$ (10 mol%) were used. [g] **2** (100 mol%) was used. [h][{Rh(coe)$_2$Cl}$_2$] (5 mol%), tris (3,5-di(trifluoromethyl)phenyl)phosphine (30 mol%), and $AgPF_6$ (10 mol%) were used.

Scope of the reaction

Further substrate scope



Substrate	Product		Cond. A	Cond. B
		R = H R = OMe R = OH	84%[b] 86%[b] 69%[b]	76%[c] 79%[c] 63%[c]
			48%[e] (1.7:1 d.r.)	56% (2:1 d.r.)
			49%	56%
			[f]	-

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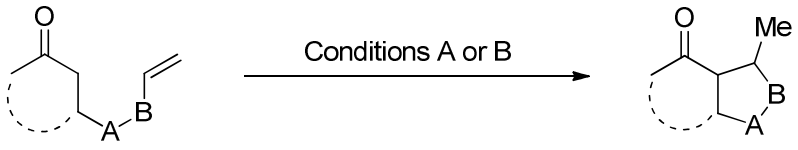
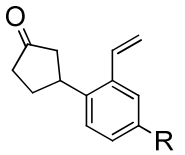
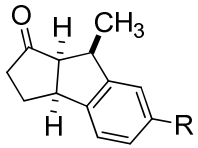
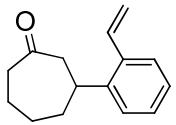
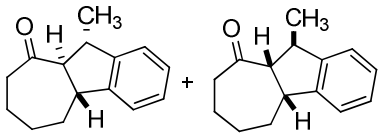
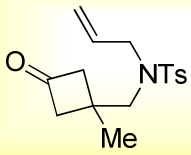
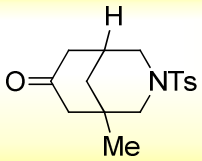
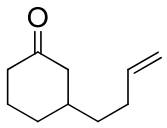
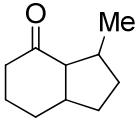
Scope of the reaction

Further substrate scope



Substrate	Product		Cond. A	Cond. B
		R = H R = OMe R = OH	84%[b] 86%[b] 69%[b]	76%[c] 79%[c] 63%[c]
			48%[e] (1.7:1 d.r.)	56% (2:1 d.r.)
			49%	56%
			[f]	-

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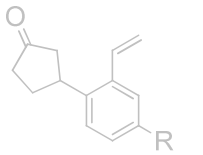
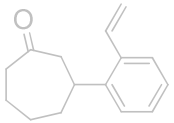
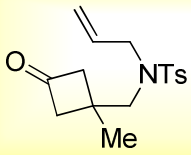
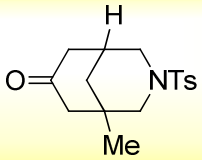
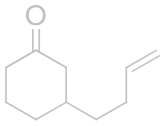
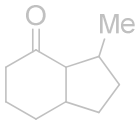
Scope of the reaction

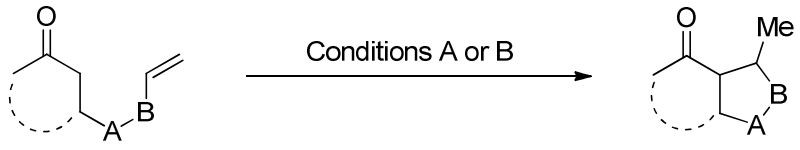
Further substrate scope

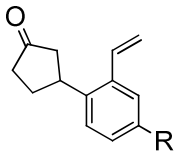
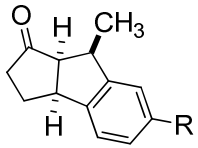
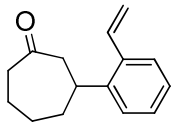
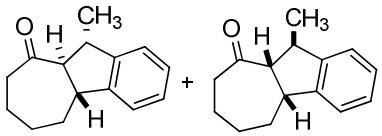
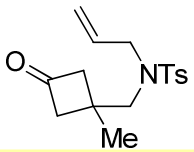
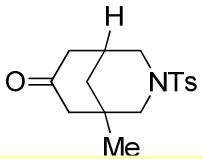
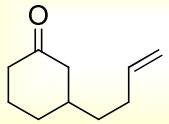
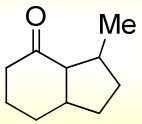
Substrate	Cond. B
	76%[c] 79%[c] 63%[c]
	56% (2:1 d.r.)
 	49% / 56%
 	[f] / -

[a] Unless otherwise mentioned, a single diastereomer was observed [b] 2-Amino-3-methyl-pyridine (100 mol%) instead of **2** [c] 2-Amino-3-methylpyridine (25 mol%) instead of **2**. [d]2-Amino-3-methyl-pyridine (50 mol%), [RhCl(PPh3)3] (15 mol%), 24h. [e] 150°C [f] The desired product was not observed.

Scope of the reaction

Further substrate scope



Substrate	Product		Cond. A	Cond. B
		R = H R = OMe R = OH	84%[b] 86%[b] 69%[b]	76%[c] 79%[c] 63%[c]
			48%[e] (1.7:1 d.r.)	56% (2:1 d.r.)
			49%	56%
			-[f]	-

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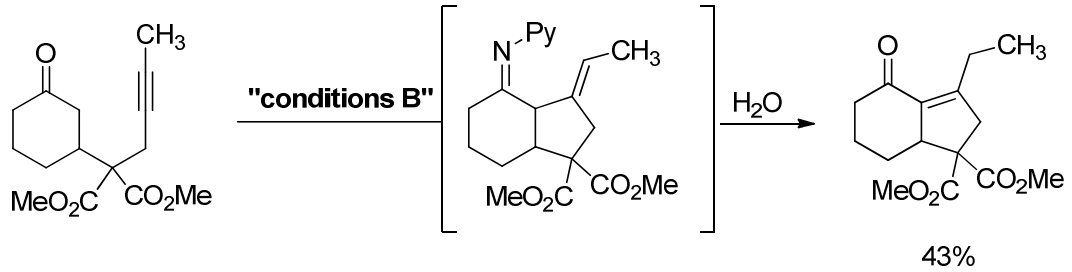

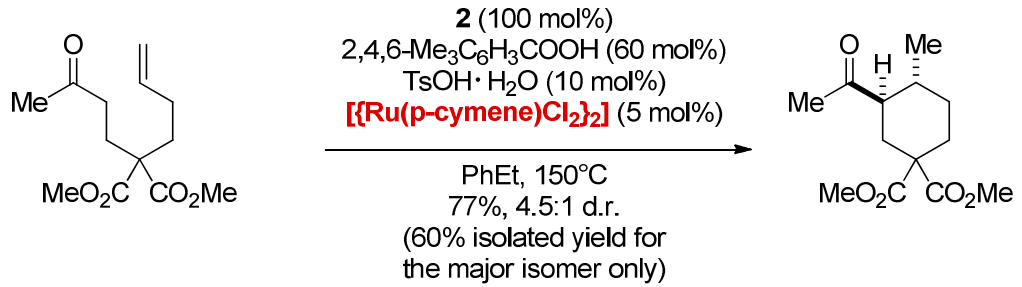

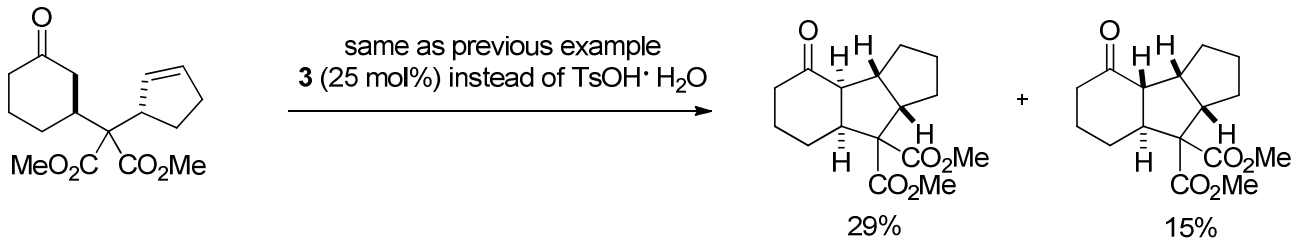

Conclusion

- Catalytic intramolecular ketone-olefin coupling

- 2 atom economical complementary methods

- Unique dual activation mode

- [Rh]-based system : formation of 5-membered ring
- [Ru]-based system : formation of 6-membered ring

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Thank you for your attention