Literature Report

Catalytic Enantioselective Synthesis of Isoindolinones through a Biomimetic Approach

Reporter : Zhong Yan

Checker : Ji Zhou

Date : 2017-12-22

Min, C.; Lin, Y.; **Seidel, D.** *Angew. Chem. Int. Ed.* **2017**, *56*, 15353.

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CV of Daniel Seidel

Daniel Seidel

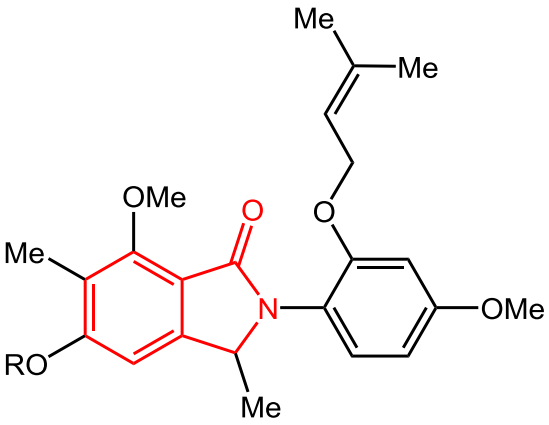
Research:

- C-H Functionalization
- Asymmetric Catalysis

Education:

- **1993–1998** Diplom, Friedrich-Schiller-Universität Jena, Germany
- **1998–2002** Ph.D., University of Texas at Austin (Jonathan L. Sessler)
- **2002–2005** Postdoc., Harvard University (David A. Evans)
- **2014–2017** Professor, Rutgers University
- **2017–Now** Professor, University of Florida

Introduction



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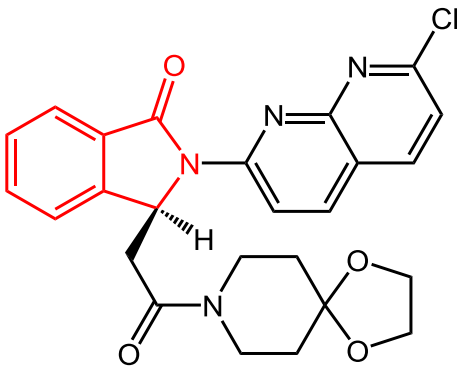

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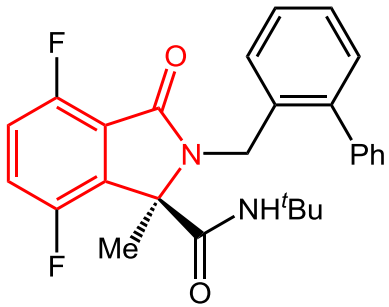

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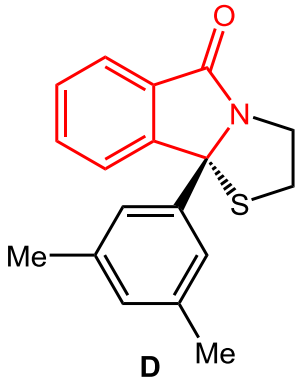
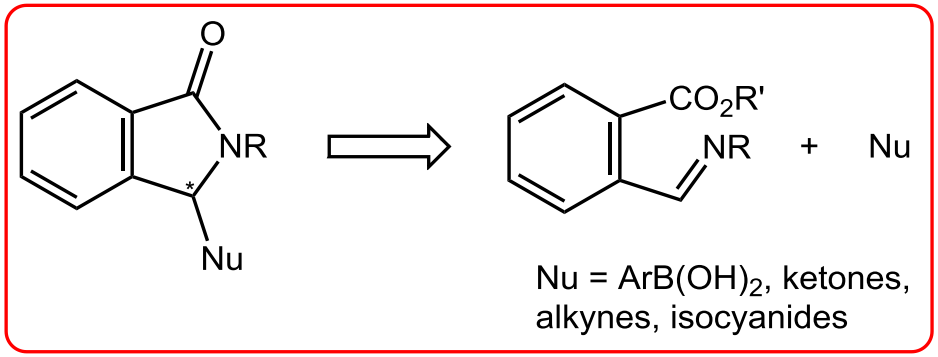
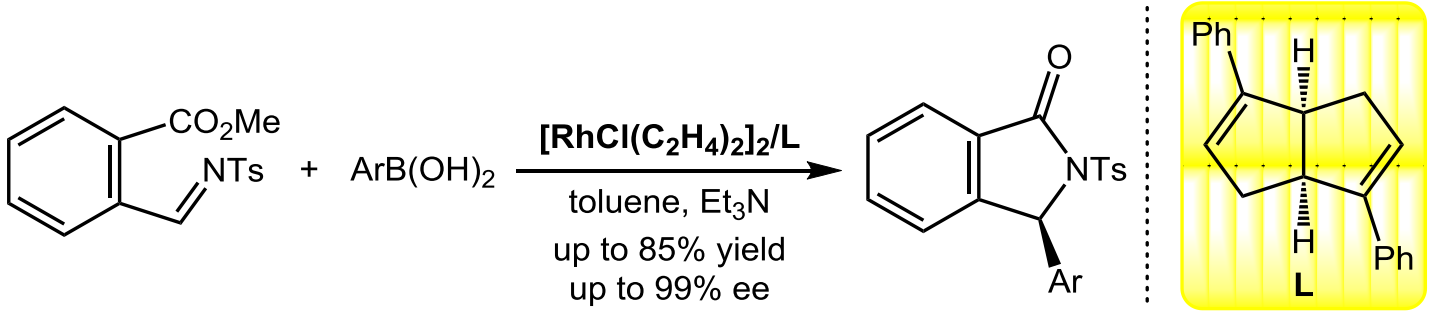


D

Catalytic Synthesis of Chiral Isoindolinones

Strategy 1: Addition of nucleophiles to ortho-formylbenzoate-derived imines, with subsequent ring closure.





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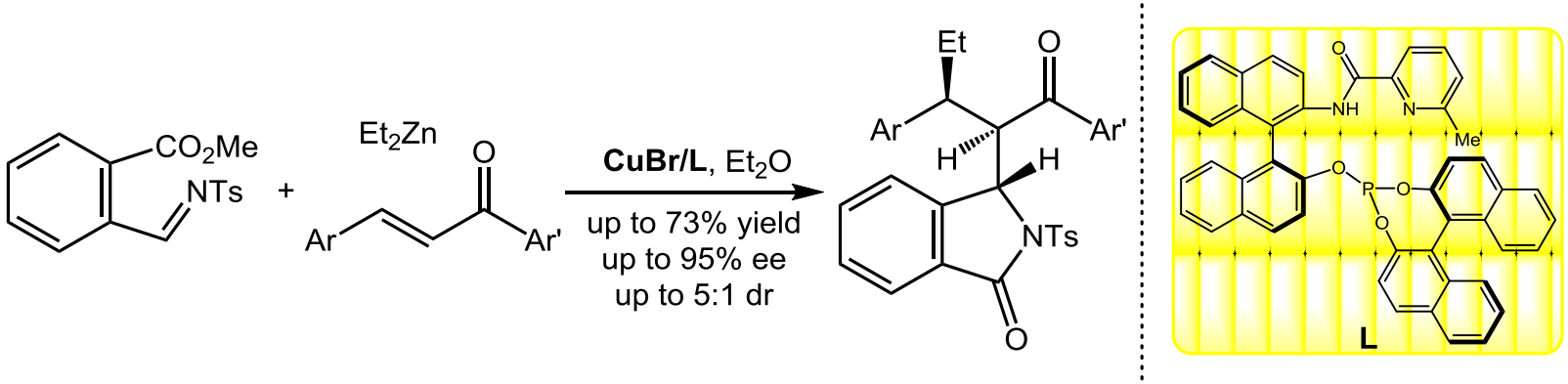
Catalytic Synthesis of Chiral Isoindolinones



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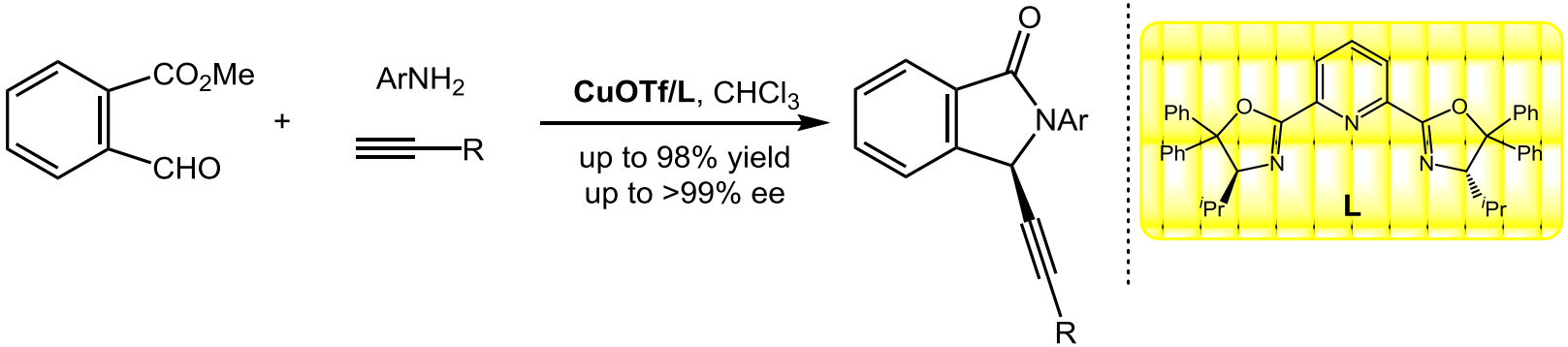
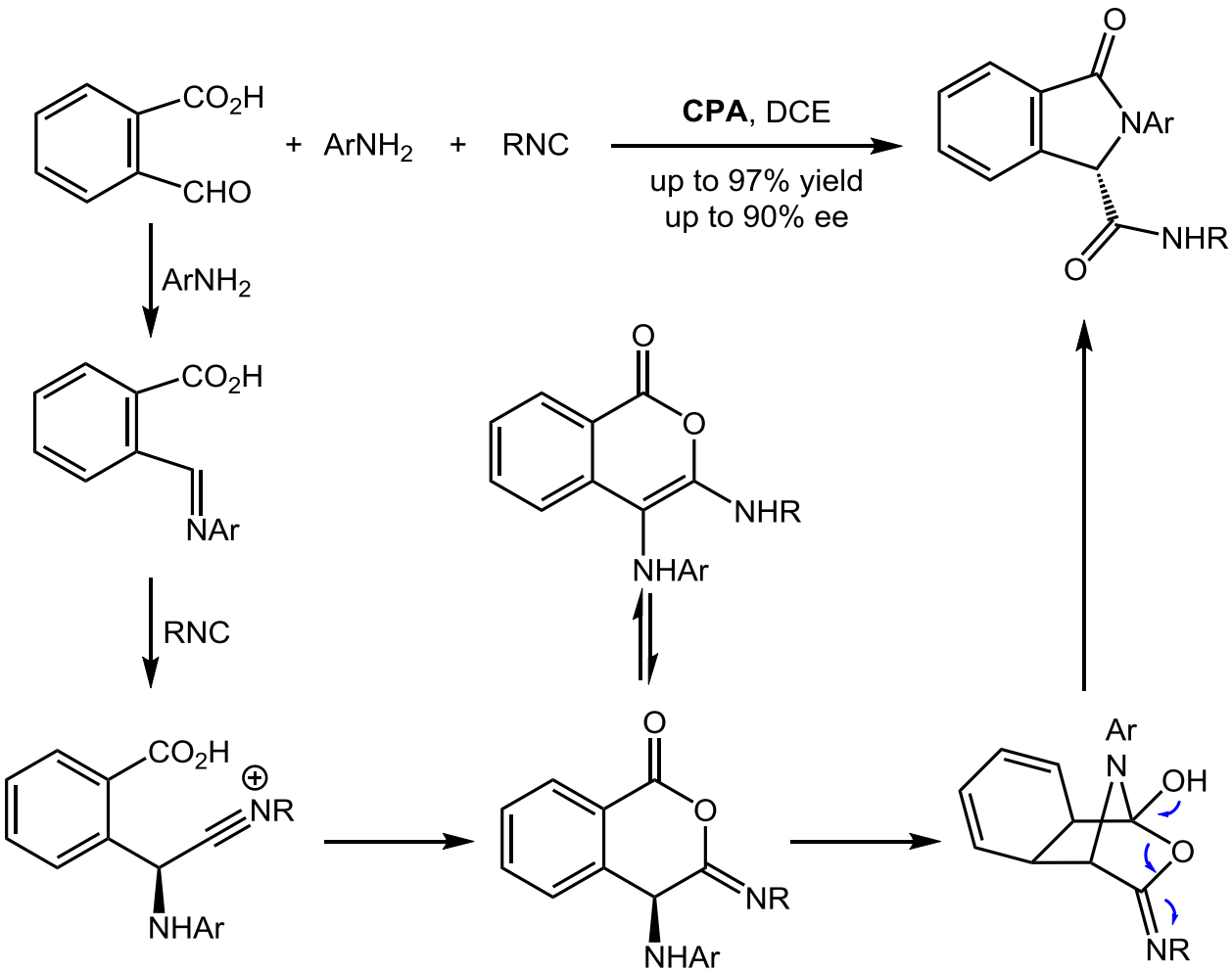


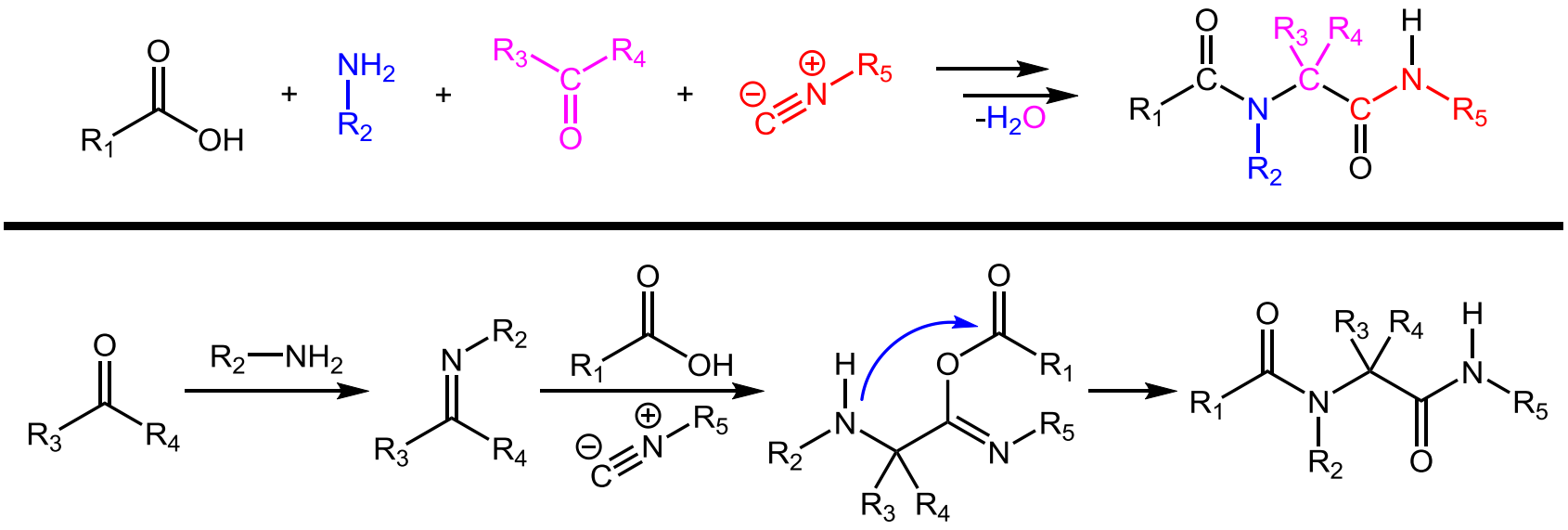
Bisai, V.; Suneja, A.; **Singh, V. K.** *Angew. Chem. Int. Ed.* **2014**, *53*, 10737.

Catalytic Synthesis of Chiral Isoindolinones



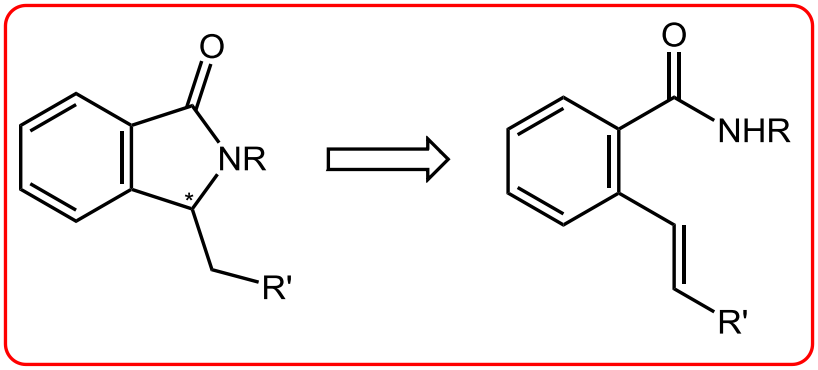
Zhang, Y.; Wang, D.-X.; Wang, M.-X.; **Zhu, J.-P.** *Angew. Chem. Int. Ed.* **2016**, *55*, 5282.

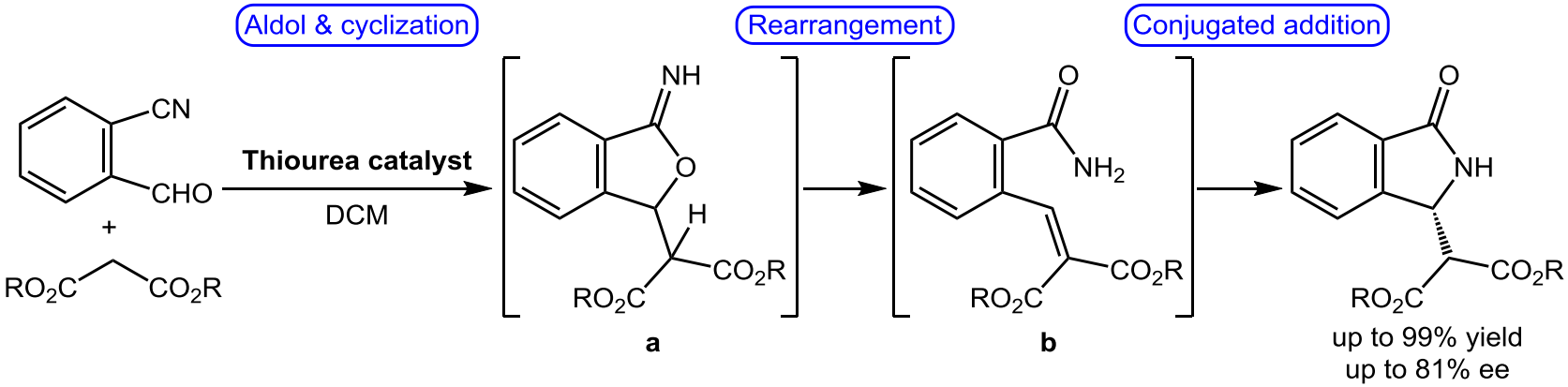
Ugi Reaction



Catalytic Synthesis of Chiral Isoindolinones

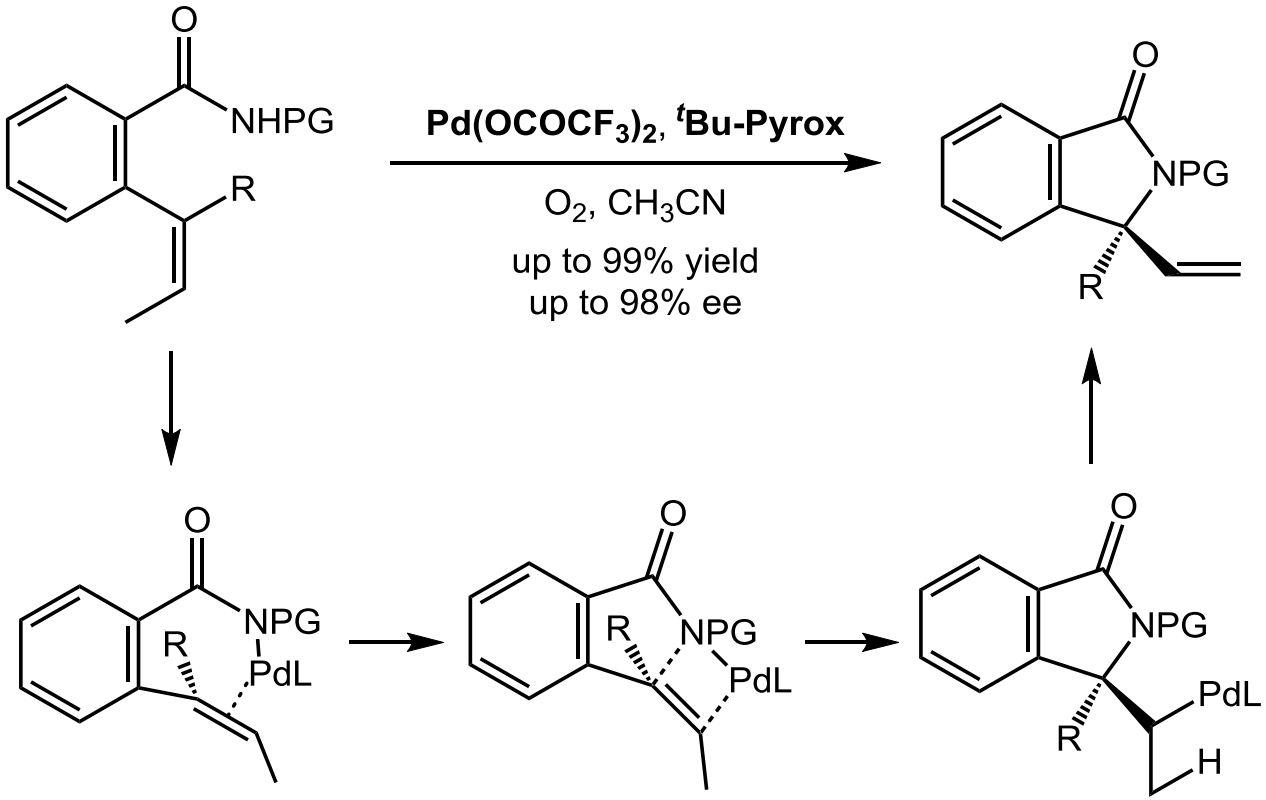
Strategy 2: Intramolecular addition of benzamides to ortho olefins.





More, V.; Rohlmann, R.; Mancheño, O. G.; **Massa, A.** *RSC Adv*. **2012**, *2*, 3592.

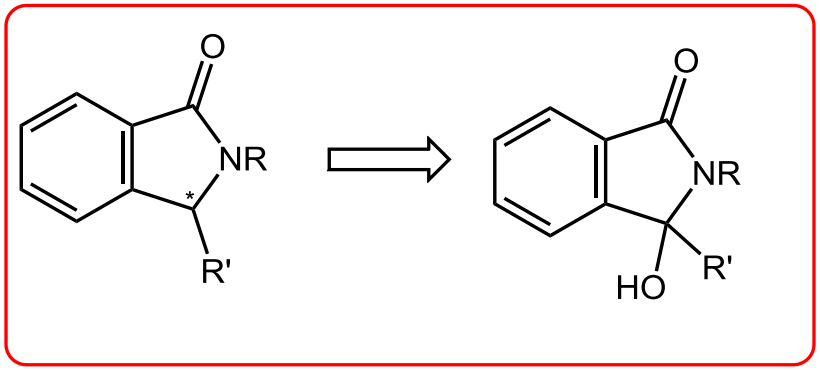
Catalytic Synthesis of Chiral Isoindolinones

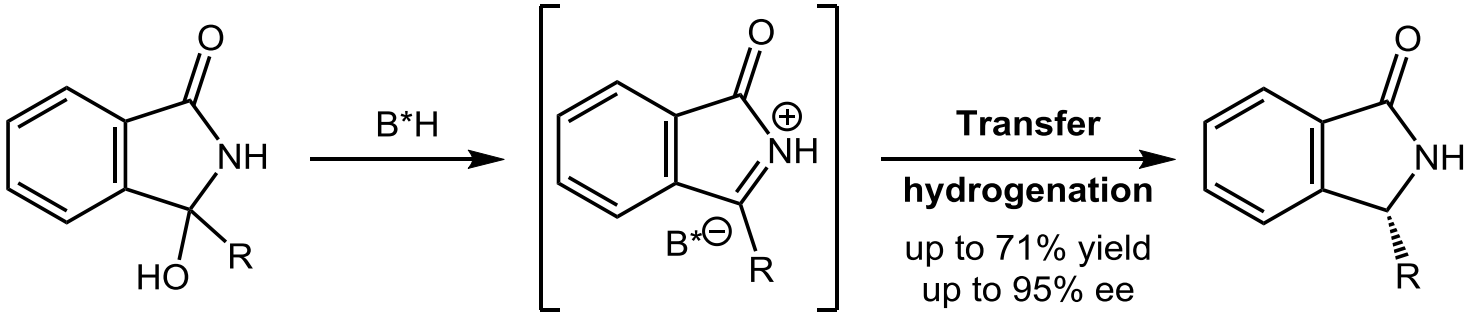


Yang, G.; Shen, C.; **Zhang, W.** *Angew. Chem. Int. Ed.* **2012**, *51*, 9141.

Catalytic Synthesis of Chiral Isoindolinones

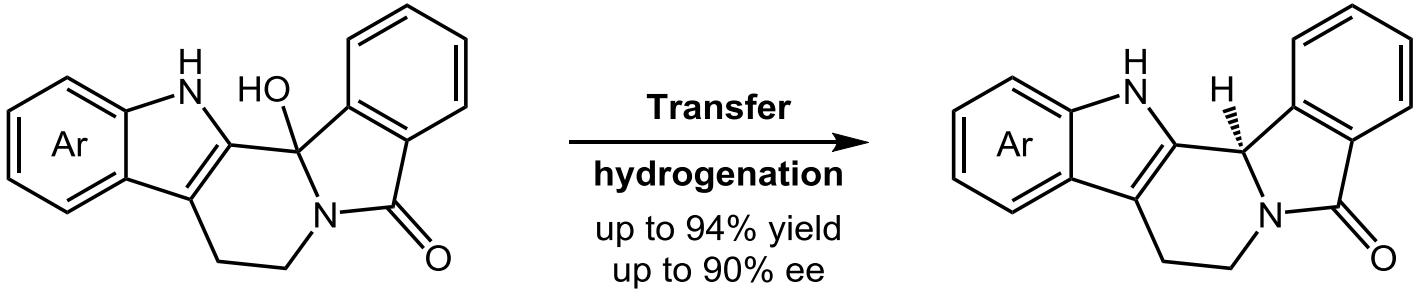
Strategy 3: Enantioselective hydrogenolysis of lactam hemiaminals.



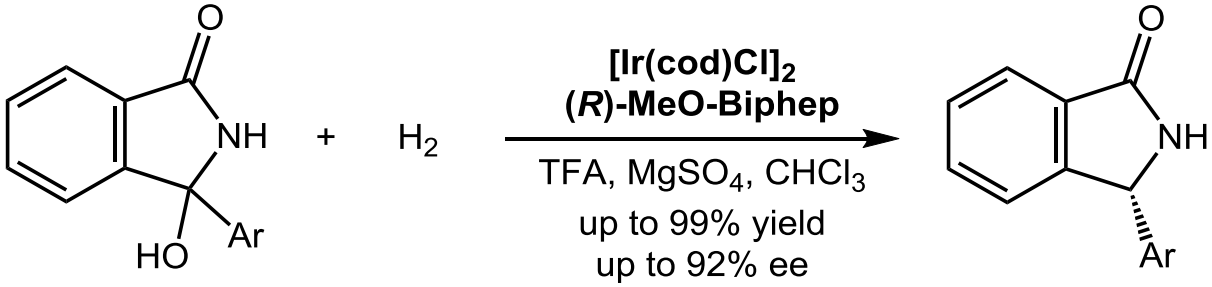


Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; **Zhou, Y.-G.** *Chem. Commun.* **2012**, *48*, 1698.

Catalytic Synthesis of Chiral Isoindolinones



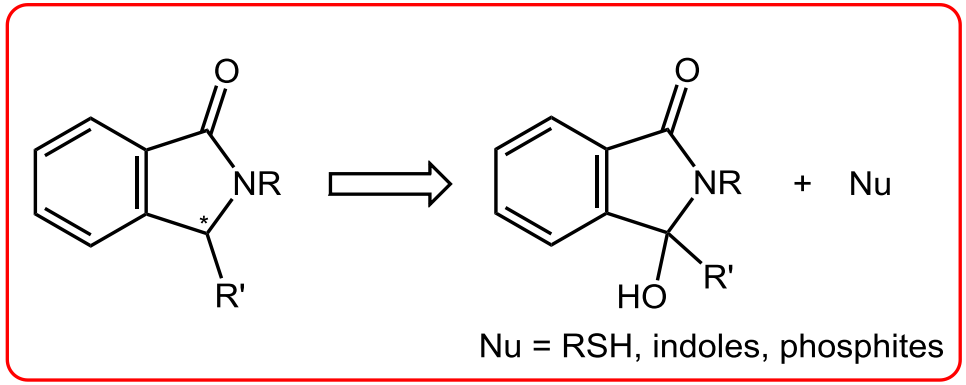
Yin, Q.; Wang, S.-G.; **You, S.-L.** *Org. Lett.* **2013**, *15,* 2688.

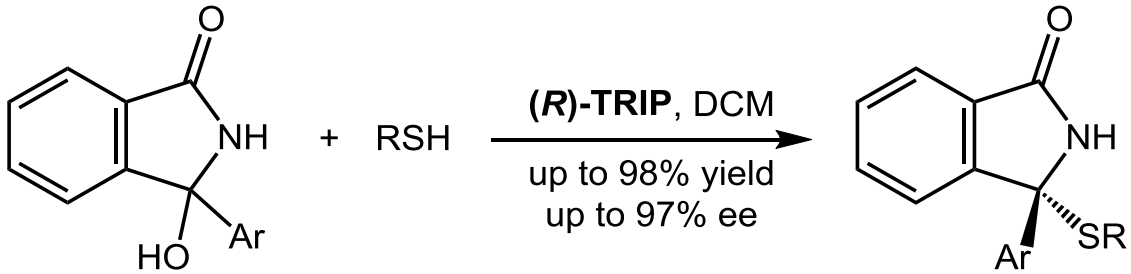


Ge, C.; Liang, R.-X.; Liu, R.-R.; Xiang, B.; **Jia, Y.-X.** *Tetrahedron Lett.* **2017**, *58,* 142.

Catalytic Synthesis of Chiral Isoindolinones

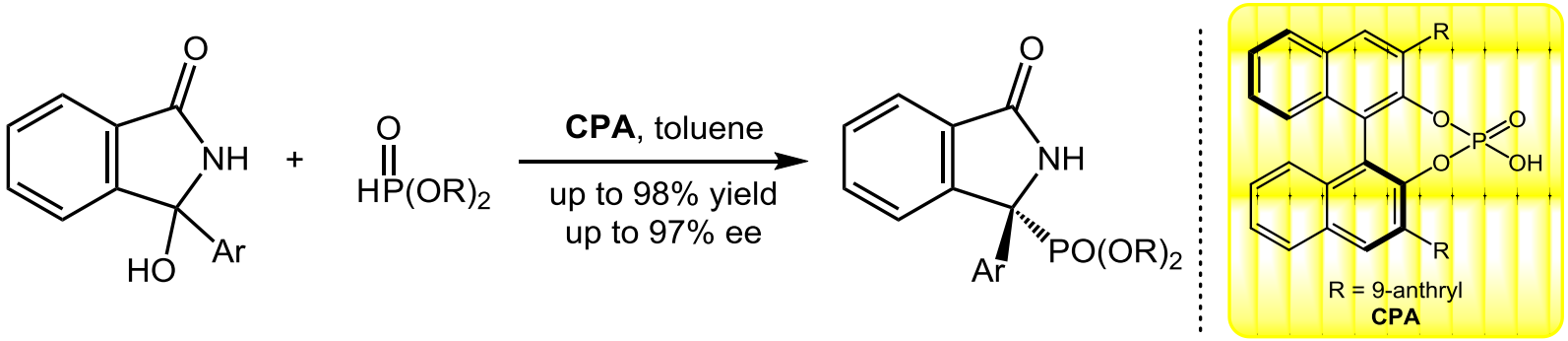
Strategy 4: Enantioselective addition to lactam hemiaminals.



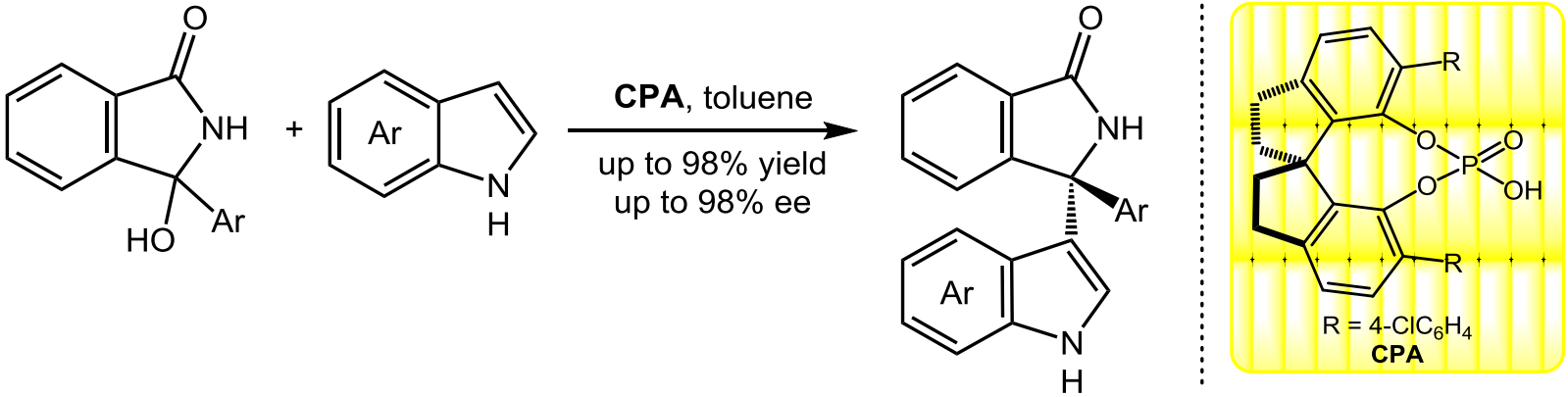


Suć, J.; Dokli, I.; **Gredičak, M.** *Chem. Commun.* **2016**, *52*, 2071.

Catalytic Synthesis of Chiral Isoindolinones

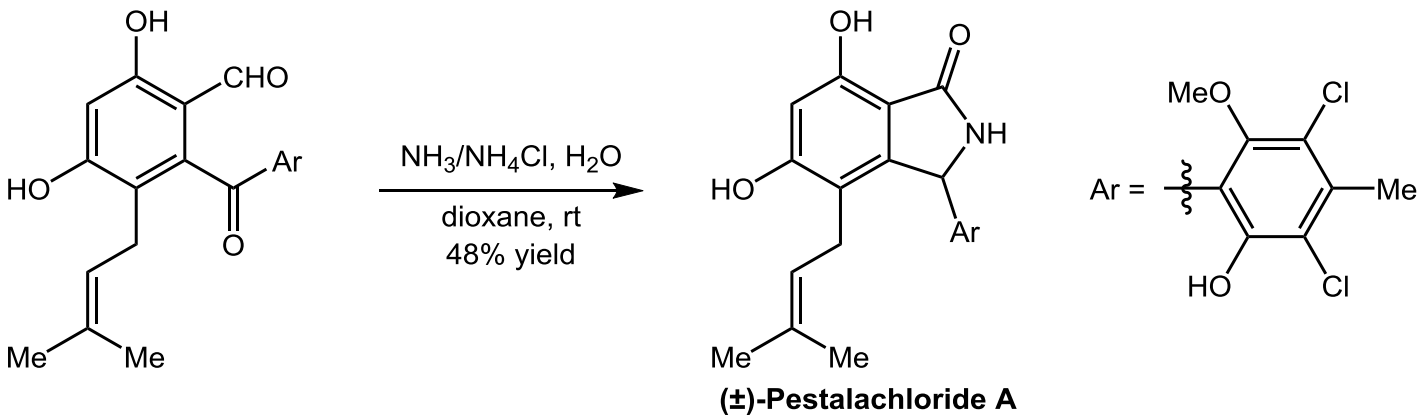


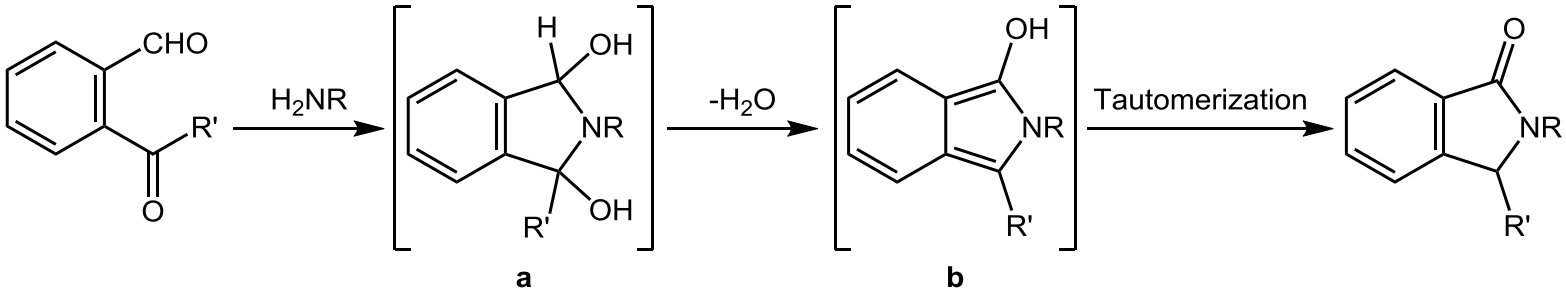
Suneja, A.; Unhale, R. A.; **Singh, V. K.** *Org. Lett.* **2017**, *19*, 476.



Glavač, D.; Zheng, C.; Dokli, I.; **You, S.-L.; Gredičak, M.** *J. Org. Chem.* **2017**, *82*, 8752.

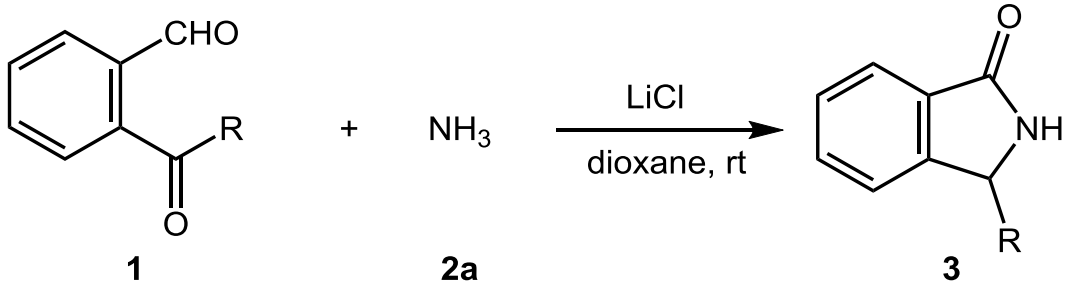
Biomimetic Synthesis of Isoindolinones





Slavov, N.; Cvengroš, J.; **Schmalz, H.-G.** *Angew. Chem. Int. Ed.* **2010**, *49*, 7588.

Formation of Isoindolinones

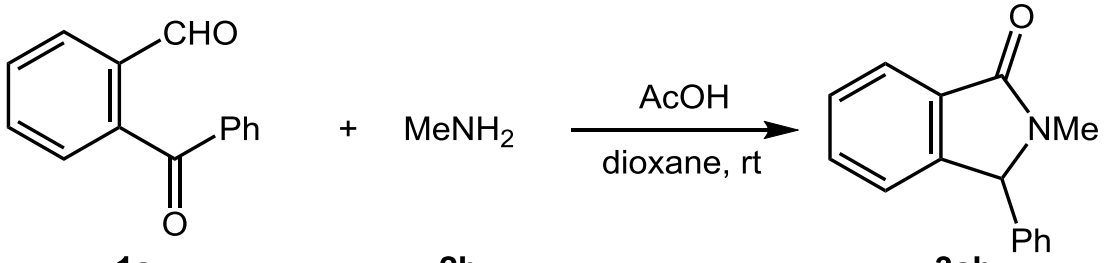


Entry[a]	R	Product	Yield (%)
1	C_6H_5	**3aa**	74
2	2-HOC_6H_4	**3ba**	63
3	4-$O_2NC_6H_4$	**3ca**	0
4	4-$MeOC_6H_4$	**3da**	50
5	Pyridin-4-yl	**3ea**	0
6	C_2H_5	**3fa**	0

[a] Reaction condition: **1** (0.5 mmol), **2a** (2.0 eq.), LiCl (1.0 eq.), dioxane (2.0 mL), rt, 5 h.

Augner, D.; Gerbino, D. C.; Slavov, N.; **Schmalz, H.-G.** *Org. Lett.* **2011**, *13,* 5374.

Optimization of the Reaction Conditions

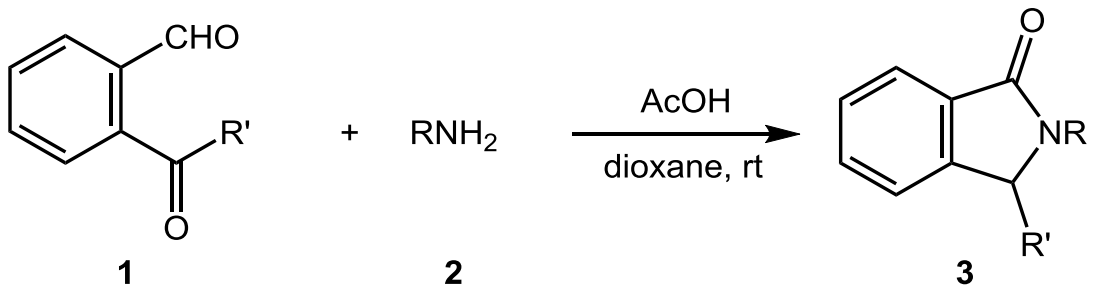


1a **2b** **3ab**

Entry[a]	$MeNH_2$ (eq.)	AcOH (eq.)	Time	Yield (%)
1	10.0	1.0	3.5 h	14
2	5.0	0.4	5.0 h	19
3	5.0	1.0	25 min	24
4	5.0	2.0	25 min	36
5	2.0	2.3	1 min	99
6	1.1	1.1	1 min	77

[a] Reaction condition: **1a** (0.5 mmol), dioxane (2.0 mL), rt.

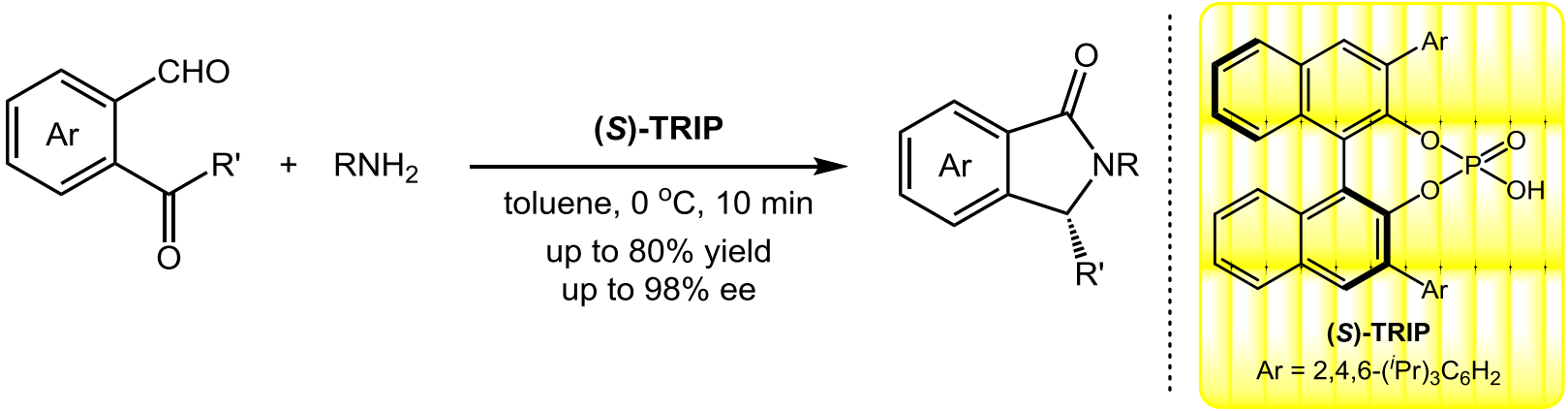
Substrate Scope



Entry[a]	R’	R	Product	Yield (%)
1	C_6H_5	Me	**3ab**	99
2	2-HOC_6H_4	Me	**3bb**	93
3	4-$O_2NC_6H_4$	Me	**3cb**	69
4	4-$MeOC_6H_4$	Me	**3db**	82
5	Pyridin-4-yl	Me	**3eb**	72
6	C_2H_5	Me	**3fb**	43
7	C_6H_5	Bn	**3fc**	92

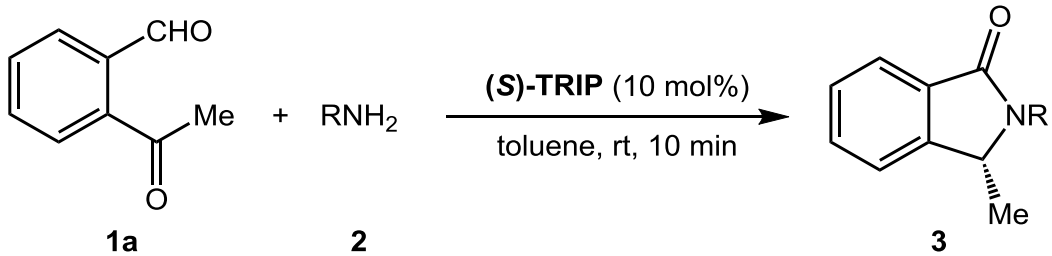
[a] Reaction condition: **1** (0.5 mmol), **2** (2.0 eq.), AcOH (2.3 eq.), dioxane (2.0 mL), rt.

Biomimetic Synthesis of Chiral Isoindolinones



Min, C.; Lin, Y.; **Seidel, D.** *Angew. Chem. Int. Ed.* **2017**, *56*, 15353.

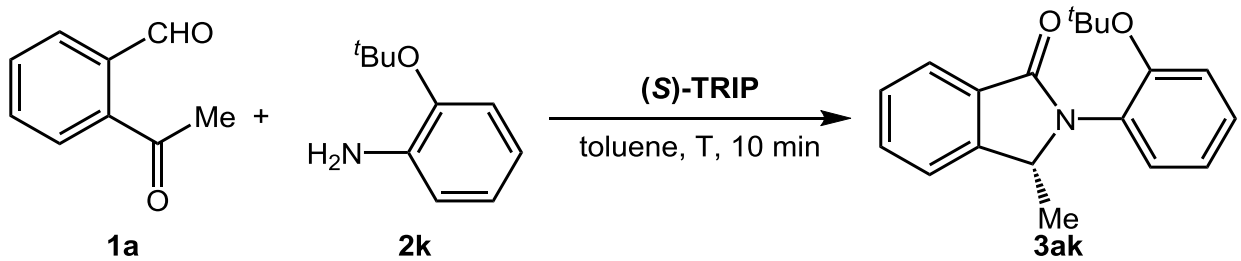
Evaluation of the Amine 2



Entry[a]	R	Product	Yield (%)	Ee (%)
1	Cbz	**3aa**	NR	--
2	^{t}Bu	**3ab**	NR	--
3	Bn	**3ac**	44	13
4	Ph	**3ad**	trace	--
5	4-$MeOC_6H_4$	**3ae**	54	0
6	2-$MeOC_6H_4$	**3af**	49	10
7	2,4-$(MeO)_2C_6H_3$	**3ag**	66	49
8	2,6-$(MeO)_2C_6H_3$	**3ah**	67	65
9	2,6-$(Me)_2C_6H_3$	**3ai**	88	11
10	3,4,5-$(MeO)_3C_6H_2$	**3aj**	70	19
11	2-^{t}$BuOC_6H_4$	**3ak**	71	83

[a] Reaction condition: **1a** (0.1 mmol), **2** (2.0 eq.), **(*S*)-TRIP** (10 mol%), toluene (1.0 mL), rt.

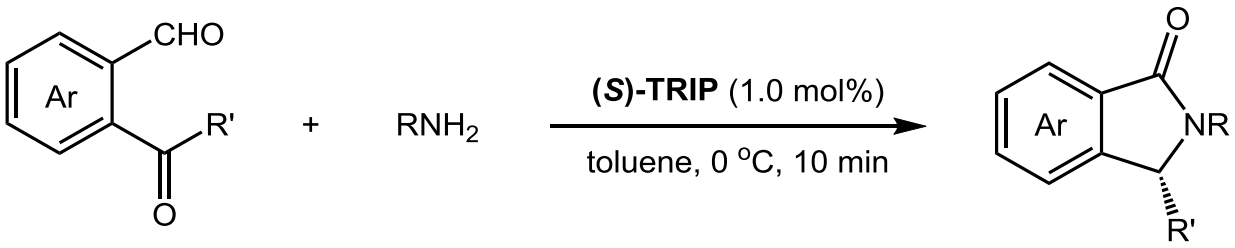
Optimization of Reaction Parameters



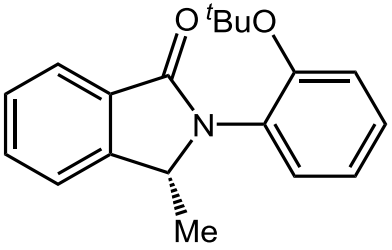
Entry[a]	T (°C)	**(*S*)-TRIP** (mol%)	C (M)	Yield (%)	Ee (%)
1	RT	10	0.1	71	83
2[b]	RT	10	0.1	54	49
3	0	10	0.1	75	97
4	-20	10	0.1	65	93
5	0	1	0.1	71	97
6[c]	0	1	0.1	72	97
7	0	0.1	0.1	55	92
8[d]	0	1	0.1	74	97
9[e]	0	1	0.1	61	94
10	0	1	0.2	74	96
11	0	1	0.05	68	97

[a] Reaction condition: **1a** (0.1 mmol), **2k** (2.0 eq.), toluene (1.0 mL). [b] 4 Å MS was added. [c] H_2O (5.0 eq.) was added. [d] **2k** (4.0 eq.) was added. [e] **2k** (1.2 eq.) was added.

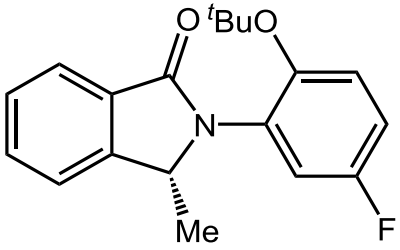
Substrate Scope



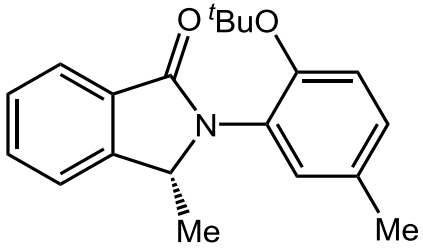
1 **2** **3**



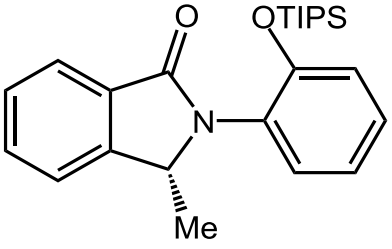
3ak
71% yield, 97% ee



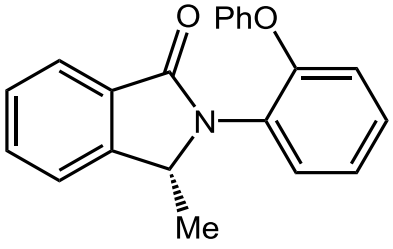
3al
50% yield, 94% ee



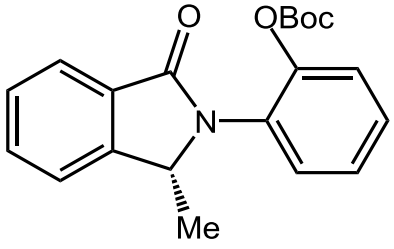
3am
70% yield, 94% ee



3ao
52% yield, 96% ee

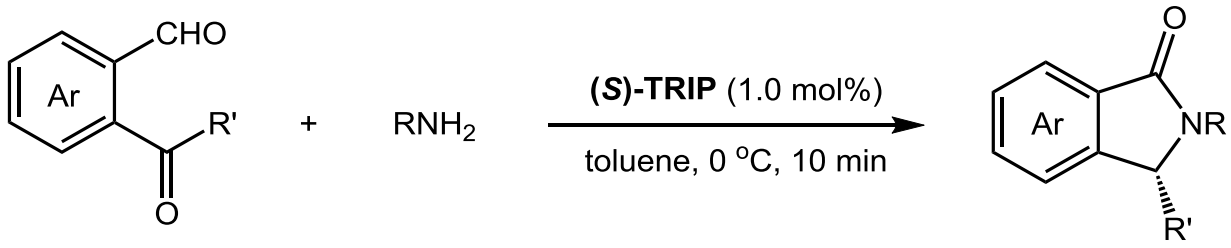


3ap
80% yield, 83% ee

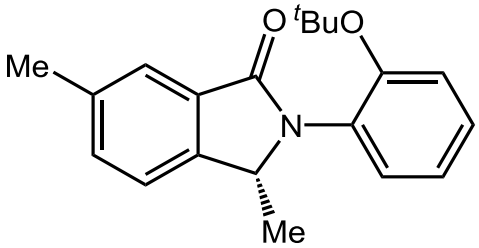


3aq
61% yield, 86% ee

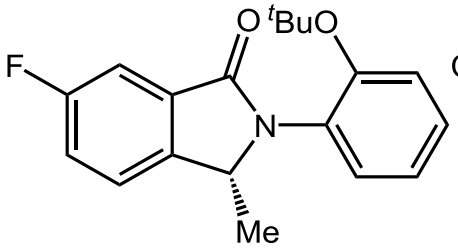
Substrate Scope



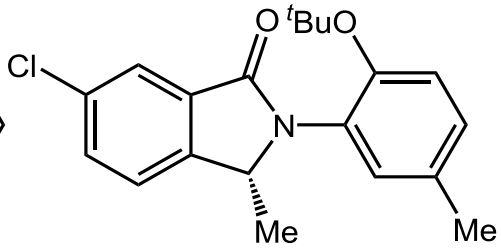
1 **2** **3**



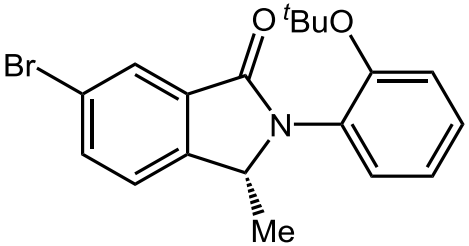
3bk
74% yield, 86% ee



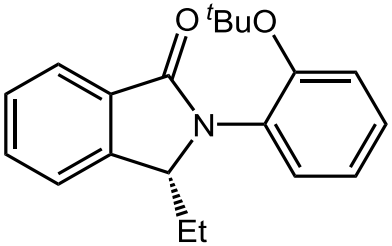
3ck
64% yield, 94% ee



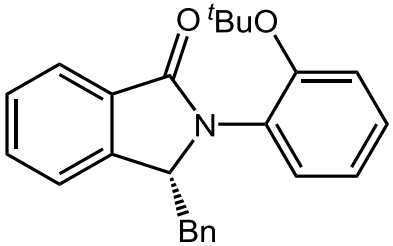
3dk
53% yield, 98% ee



3ek
49% yield, 90% ee

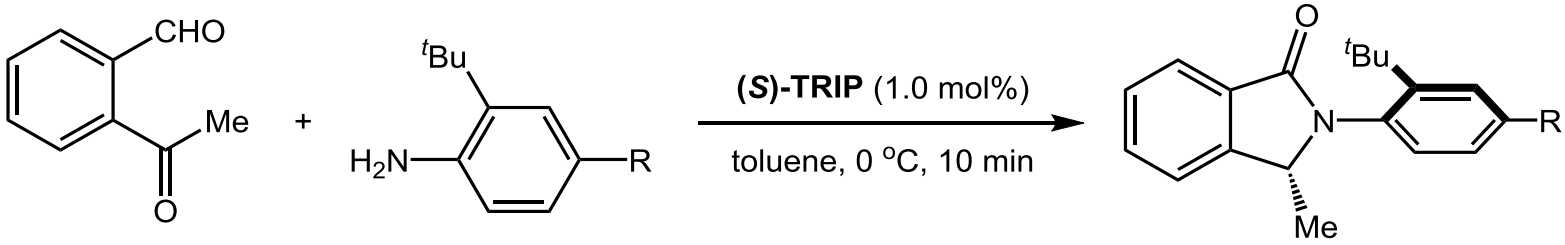


3fk
70% yield, 85% ee

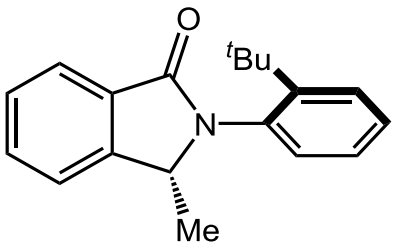


3gk
52% yield, 71% ee

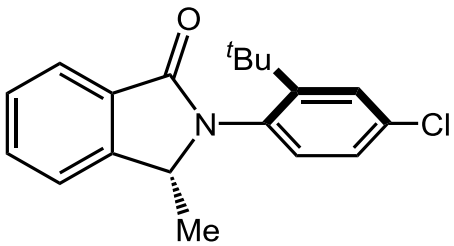
Substrate Scope



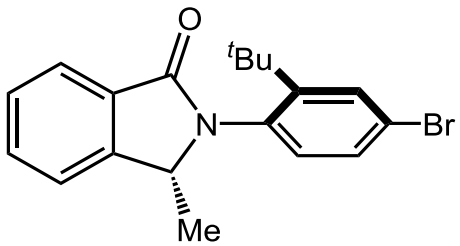
1a **2** **3**



3ar
75% yield, dr = 7.5:1
93% ee (major)

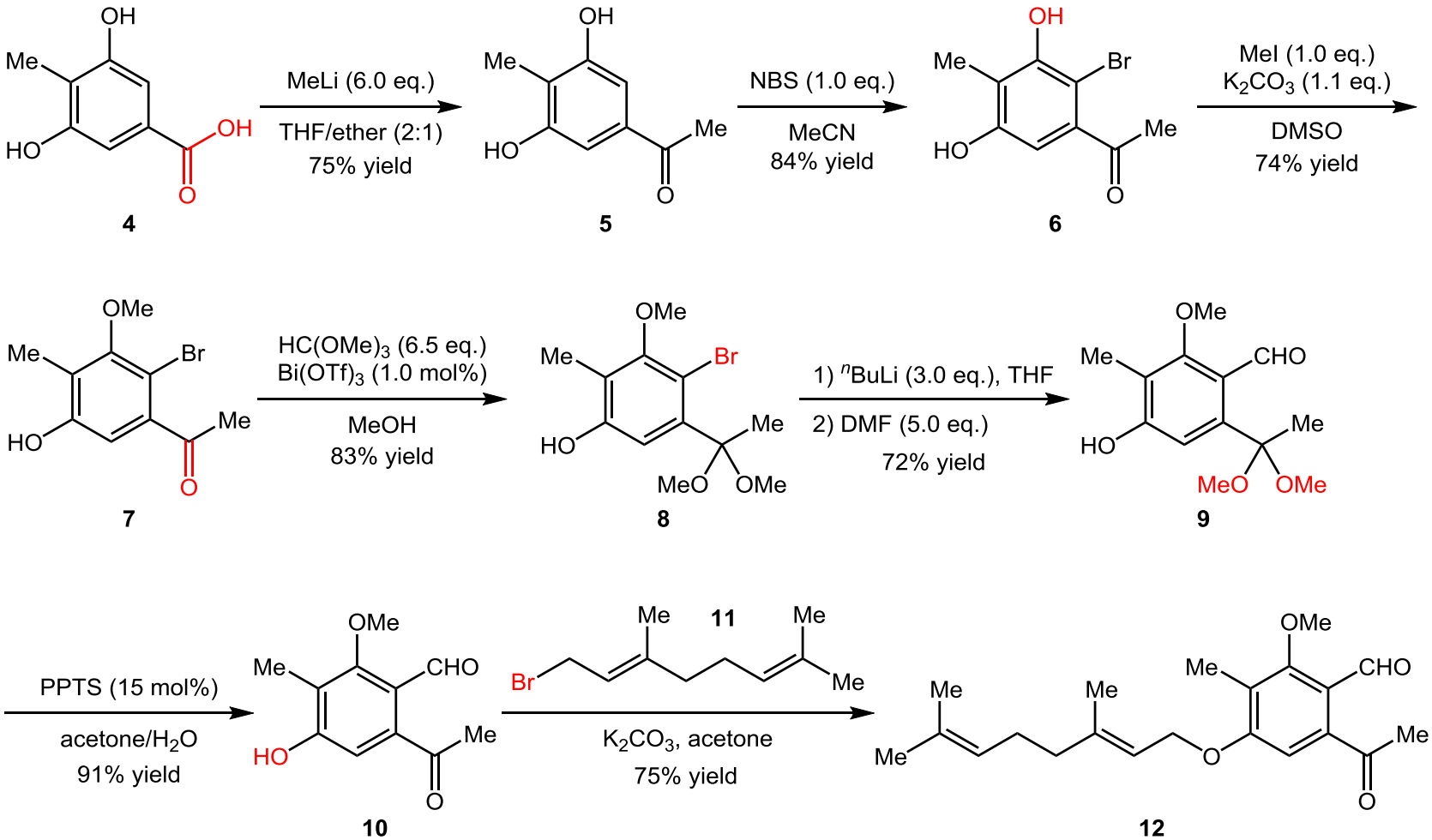


3as
73% yield, dr = 6:1
90% ee (major)

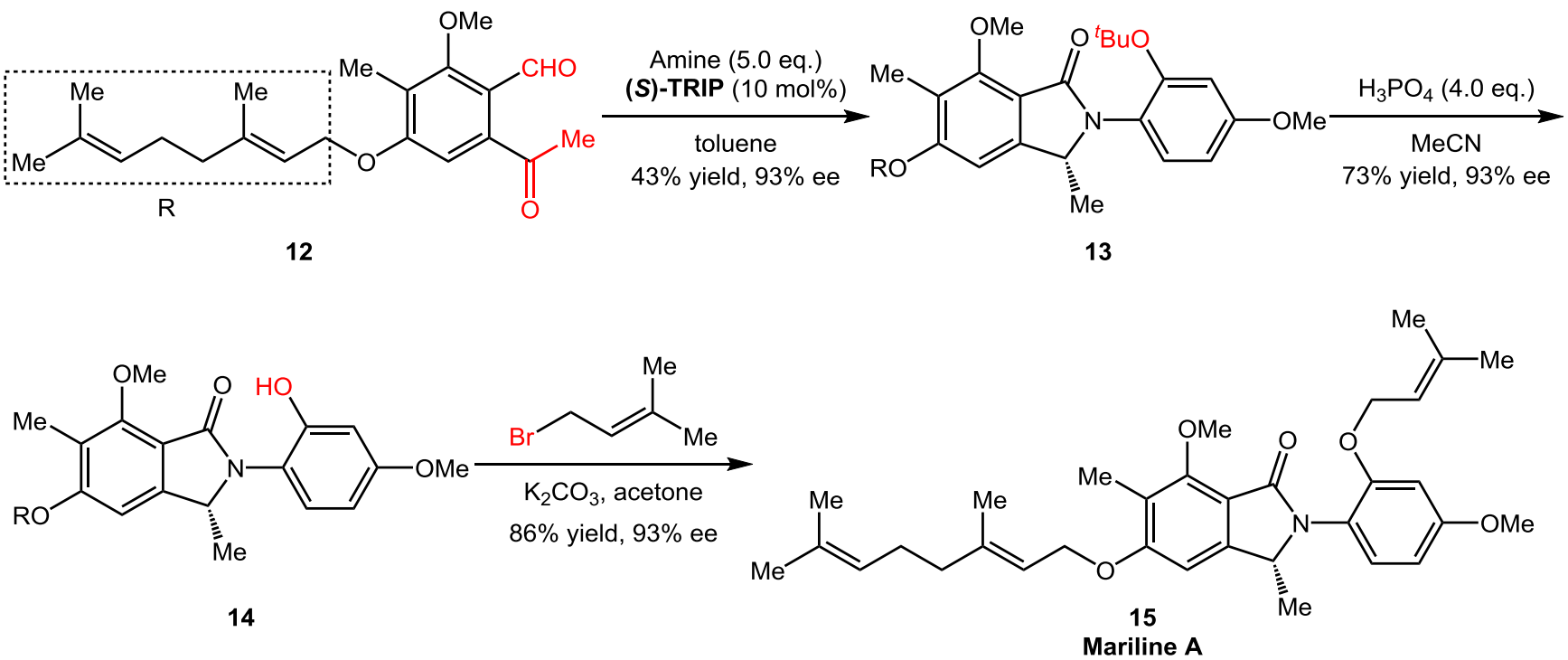


3at
63% yield, dr = 7:1
90% ee (major)

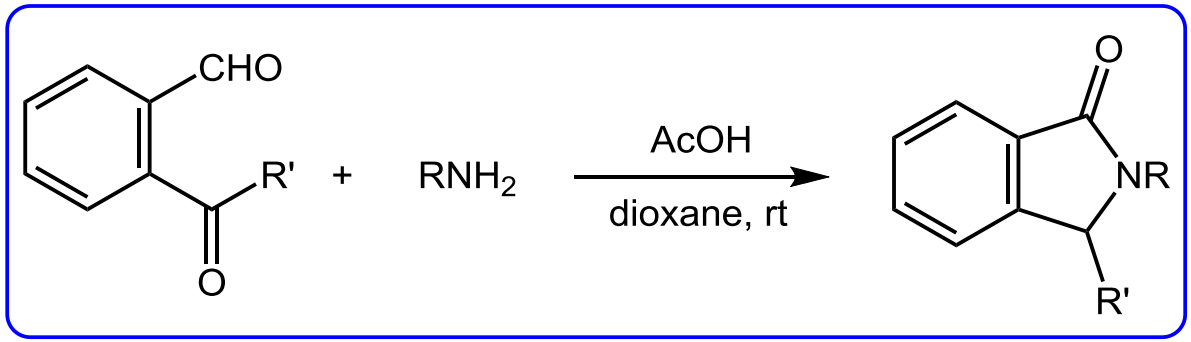
Enantioselective Synthesis of Mariline A



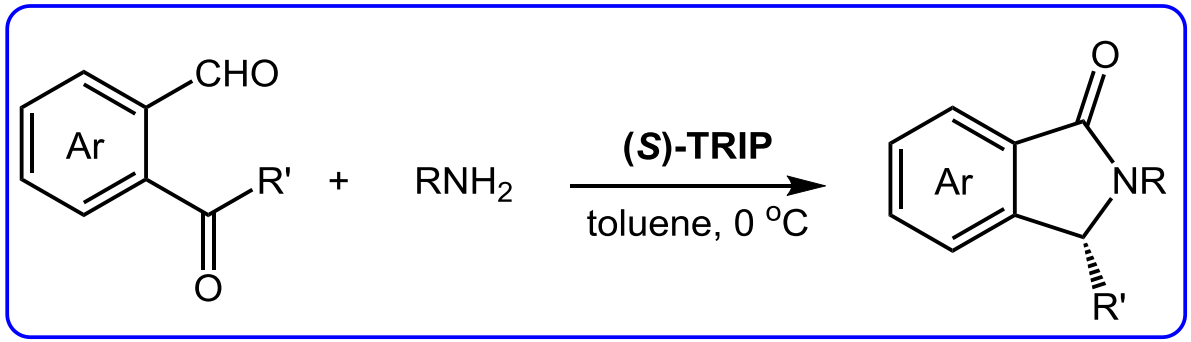
Enantioselective Synthesis of Mariline A



Summary



Augner, D.; Gerbino, D. C.; Slavov, N.; **Schmalz, H.-G.** *Org. Lett.* **2011**, *13*, 5374.



Min, C.; Lin, Y.; **Seidel, D.** *Angew. Chem. Int. Ed.* **2017**, *56*, 15353.

The First Paragraph

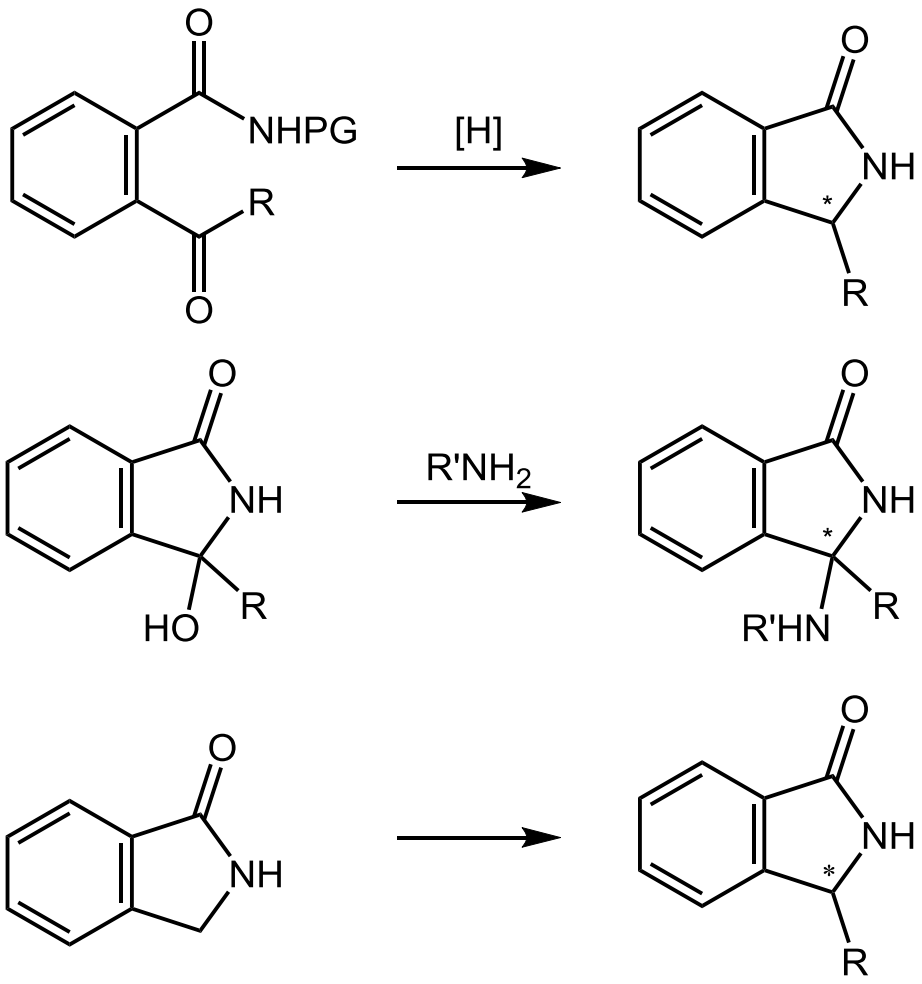
Isoindolinones are important pharmacophores and form the core of a range of natural products. Largely due to their manifold biological activities, there has been a long-standing interest in the asymmetric synthesis of chiral isoindolinones. However, catalytic enantioselective methods remain underdeveloped. Previous approaches have focused on constructing the lactam moiety through 1,2-addition of nucleophiles to ortho-formylbenzoate-derived imines, with subsequent amide-bond-forming ring closure. Intramolecular additions of benzamides to ortho olefins, including conjugate additions and an asymmetric aza-Wacker-type cyclization, have also been disclosed.

The First Paragraph

Other approaches are known, including catalytic enantio-selective reduction or addition to lactam hemiaminals. A particularly attractive approach to chiral isoindolinones was recently reported by Schmalz and co-workers, who showed that the marine antibiotic pestalone undergoes facile conversion to pestalachloride A upon exposure to ammonia/ammonium chloride in aqueous dioxane. The same group later showed that this type of reaction is general for a range of amines and 2-acyl-benzaldehydes. Herein, we report the first catalytic enantioselective version of this valuable transformation.

The Last Paragraph

In summary, we have achieved the catalytic enantio-selective synthesis of 3-alkyl isoindolinones through a biomimetic condensation approach, utilizing 2-acyl-benz-aldehydes and 2-substituted anilines as starting materials. This method enabled the first enantioselective synthesis of mariline A.


O
NHPG
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R'NH2
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R'HN
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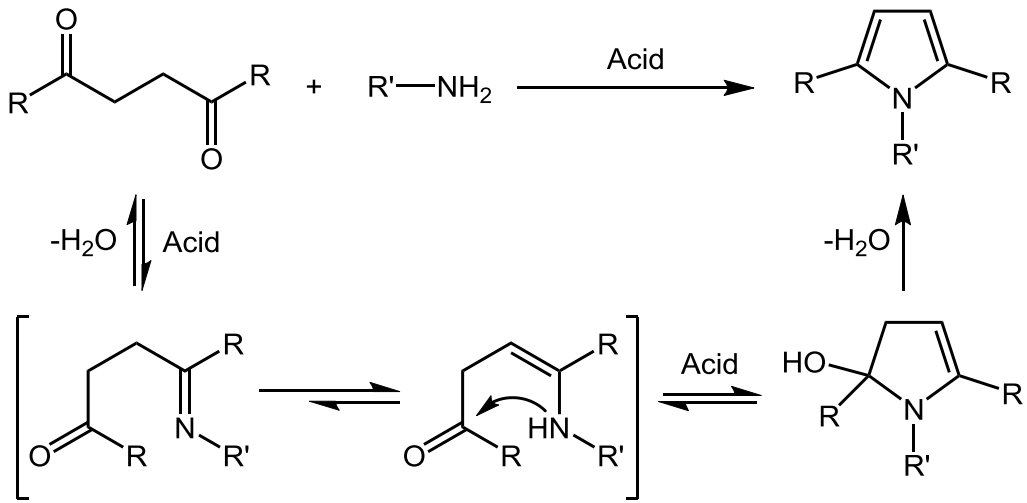
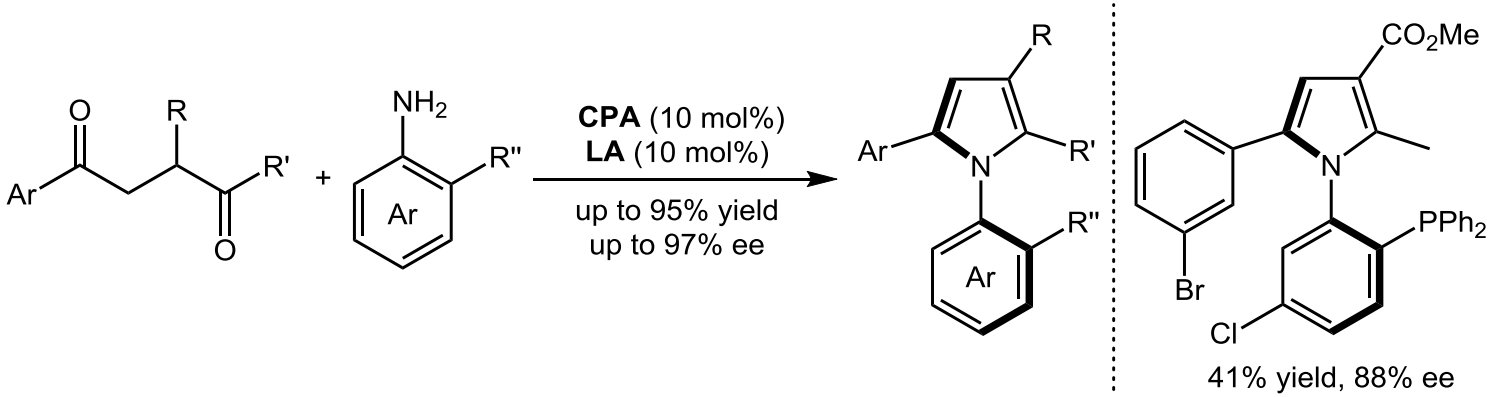
*
R

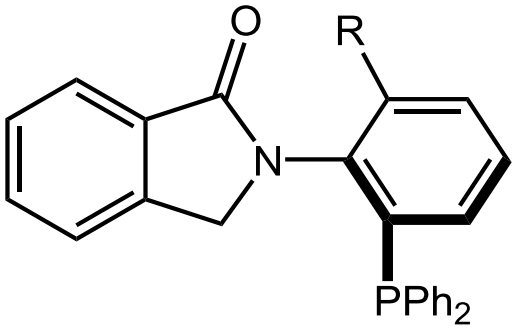
Asymmetric Paal-Knorr Reaction

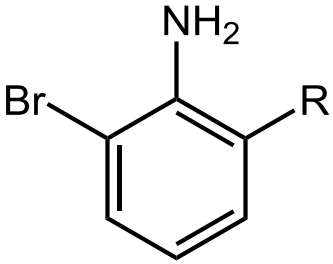
Paal-Knorr reaction

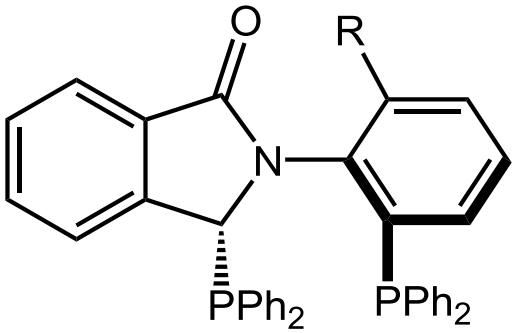


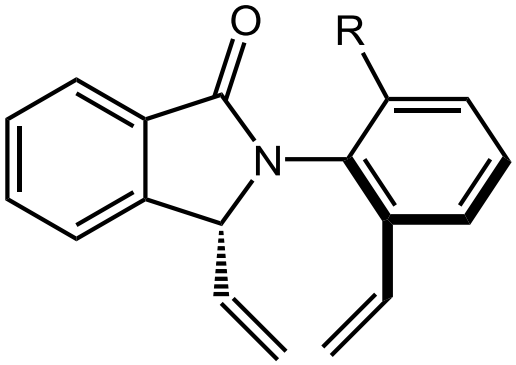


Zhang, L.; Zhang, J.; Ma, J.; **Tan, B.** *J. Am. Chem. Soc*. **2017**, *139*, 1714.


O
R
N
PPh2


NH2
Br
R


O
R
N
PPh2
PPh2


O
R
N