Literature Report

Asymmetric Nitrone Synthesis *via* Ligand-Enabled Copper-Catalyzed Cope-Type Hydroamination of Cyclopropene with Oxime

Reporter: Hong-Qiang Shen

Checker: Cong Liu

Date: 2017/10/09

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J. Am. Chem. Soc. **2017**, *139*, 11702-11705.

Contents

CV of Qian Zhang

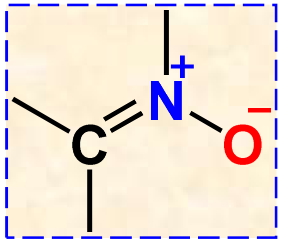
Position: Full Professor

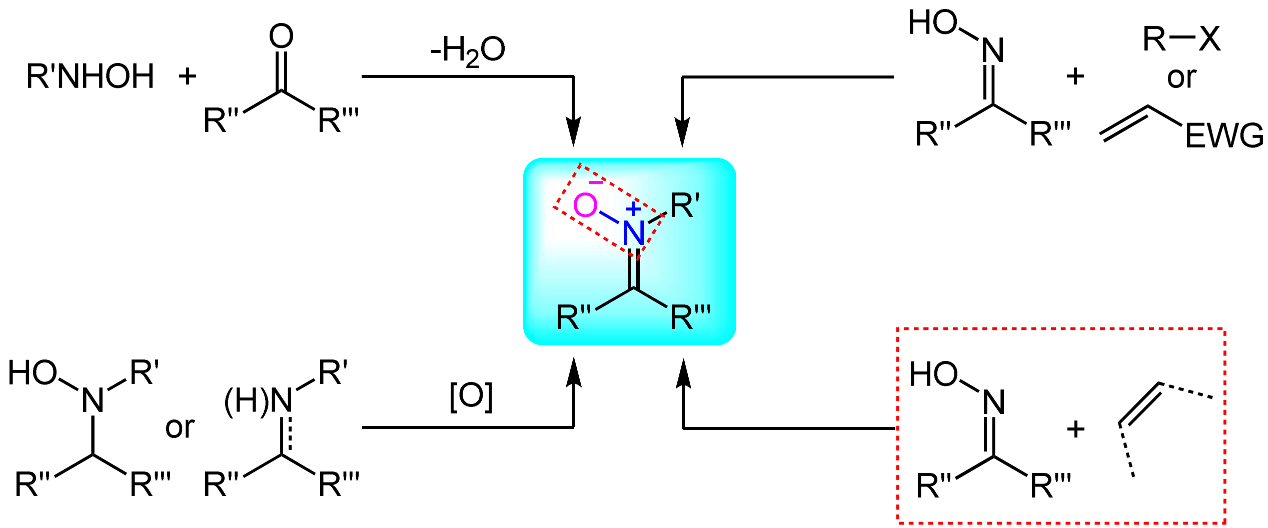
Northeast Normal University

Education:

1989-1993	B. S., Northeast Normal University
1993-1996	M. S., Northeast Normal University
2000-2003	Ph. D., Changchun Institute of Applied Chemistry
2004	Visiting Scholar, The University of Sydney
2004-2010	Associate Professor, Northeast Normal University
2010-	Full Professor, Northeast Normal University

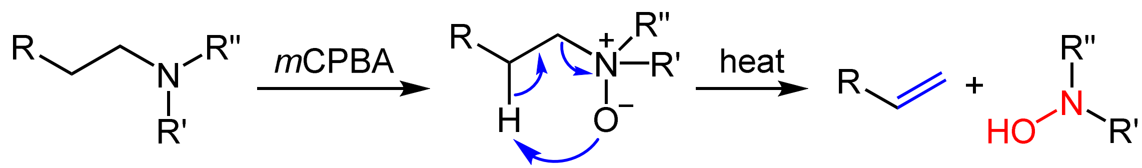
Preparation of Nitrones



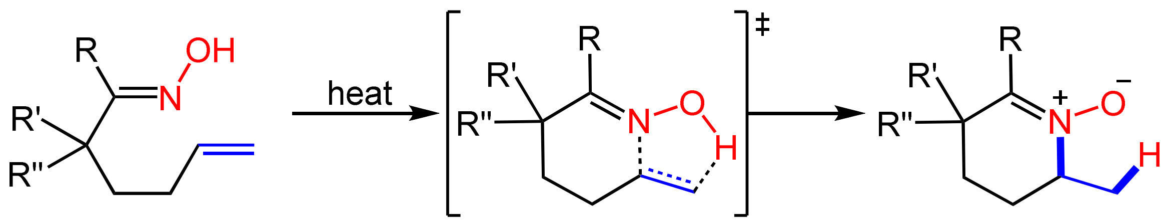


Retro-Cope Hydroamination of Oximes

Cope Elimination:

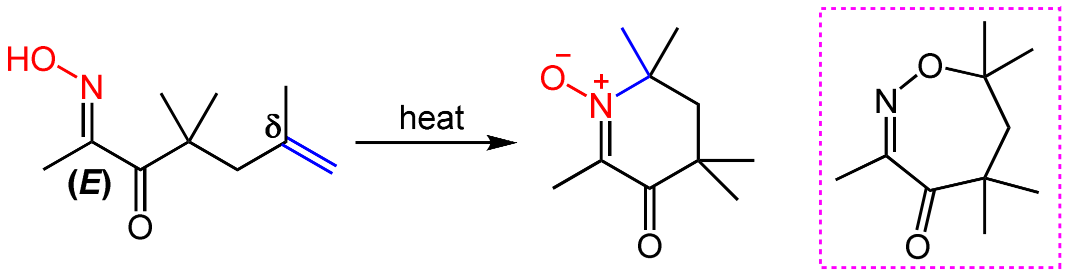


Retro-Cope Hydroamination:

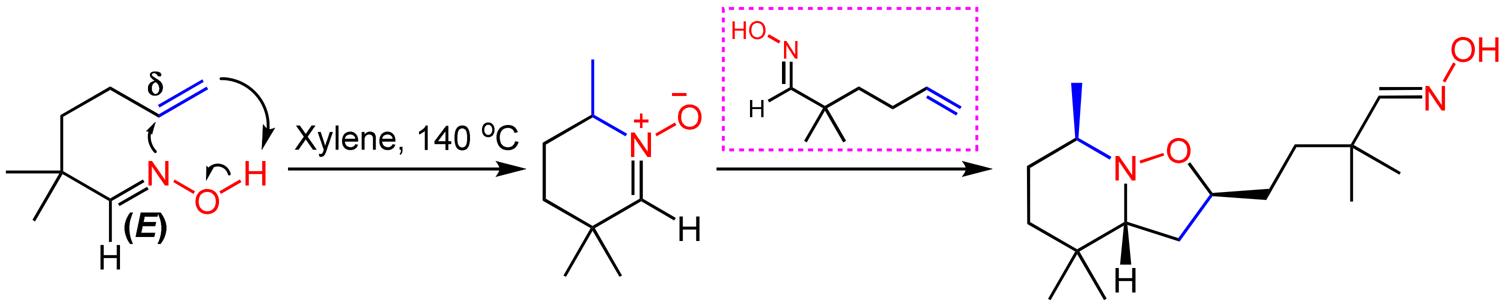


From Wikipedia

Retro-Cope Hydroamination of Oximes

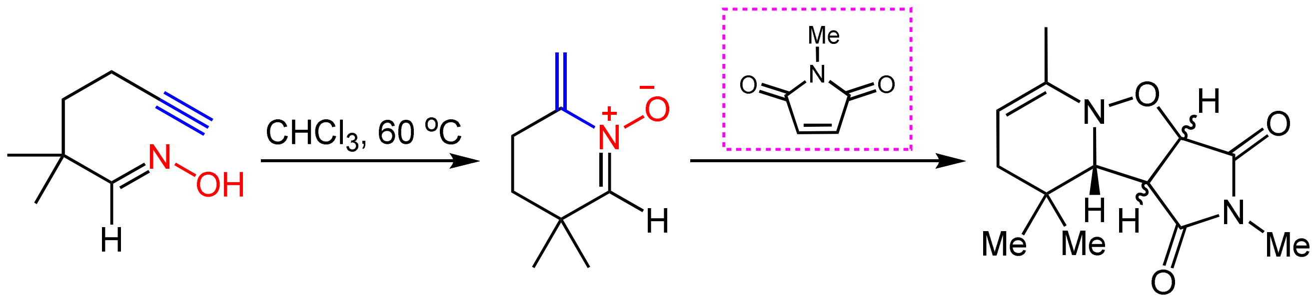


Bishop, R. *et al. Synthesis* **1988**, *1988*, 997.



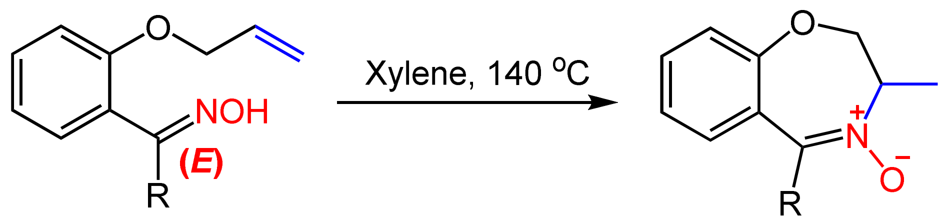
Grigg, R. *et al. Tetrahedron Lett.* **1990**, *31*, 559.

Retro-Cope Hydroamination of Oximes



84% Yield

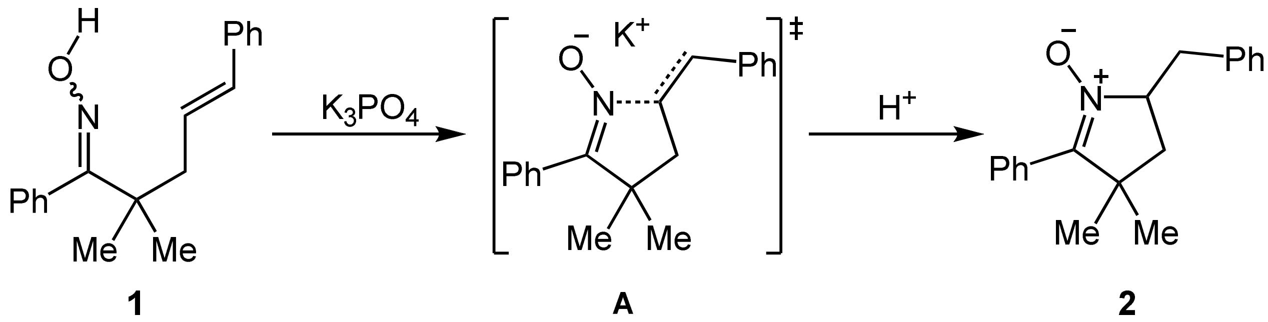
Grigg, R. *et al. J. Chem. Soc., Chem. Commun.* **1993**, 372.



R = Me, >99% Yield
R = Ph, 95% Yield

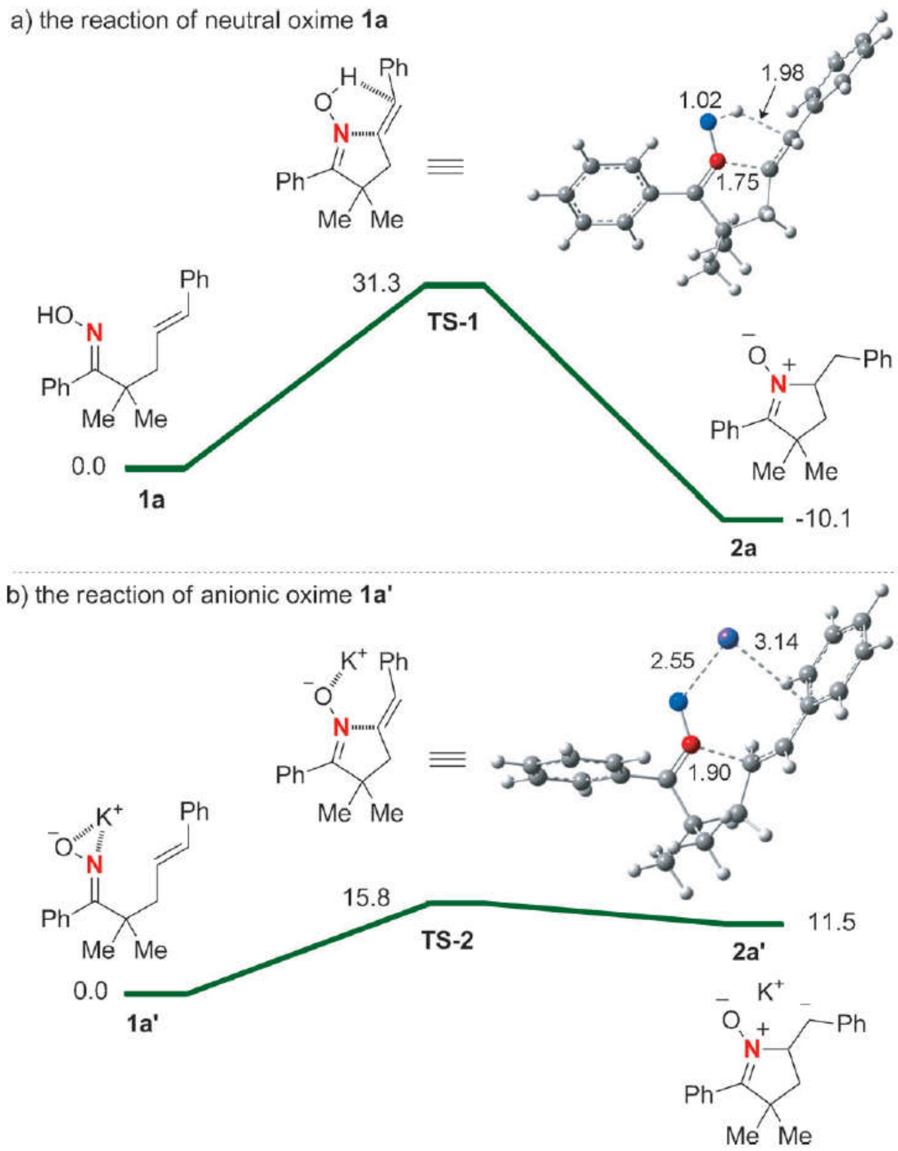
Heaney, F. *et al. Chem. Commun.* **1996**, 167.

Based-Mediated Hydroamination of Oximes

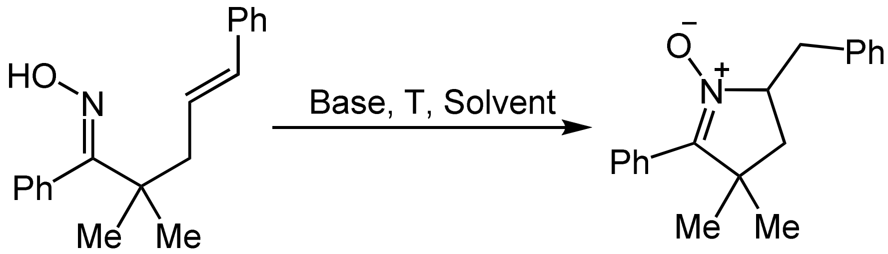


Chiba, S.; Hirao, H. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 1959.

Based-Mediated Hydroamination of Oximes



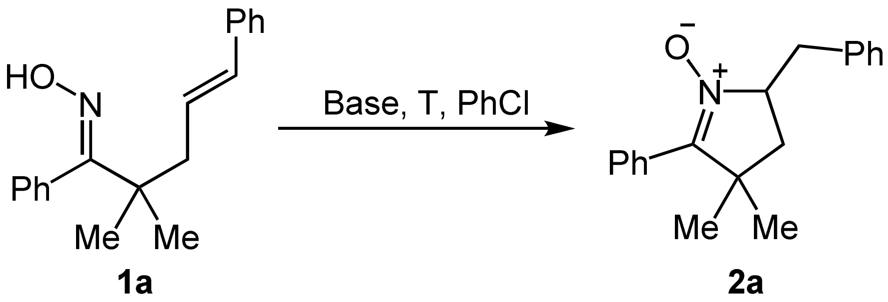
Optimization of the Reaction Parameters



Entry[a]	Base	Solvent	T (°C)	t (h)	Yield (%)[b]
1	none	Toluene	110	24	--
2	none	PhCl	130	24	5
3	none	DMSO	120	24	6
4	K_3PO_4	Toluene	110	12	98
5	K_3PO_4	*o*-Xylene	120	10	98
6	K_3PO_4	PhCl	120	4	98
7	K_3PO_4	DMSO	120	24	59
8	K_3PO_4	DMF	120	24	12

[a] Reaction conditions: **1a** (0.2 mmol), Base (10 mol%), Solvent (2 mL). [b] Isolated yield.

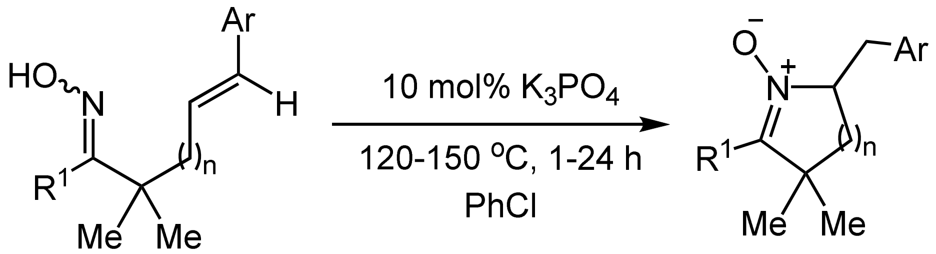
Optimization of the Reaction Parameters



Entry[a]	Base	T (°C)	t (h)	Yield (%)[b]
1	K_3PO_4	120	4	98
2	K_2CO_3	120	24	21
3	KO*t*Bu	120	0.6	96
4	KO*t*Bu	60	20	97
5	NaOMe	120	7	67
6	NaH	120	7	88

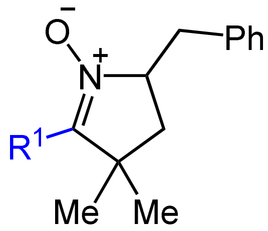
[a] Reaction conditions: **1a** (0.2 mmol), Base (10 mol%), PhCl (2 mL). [b] Isolated yield.

Substrate Scope

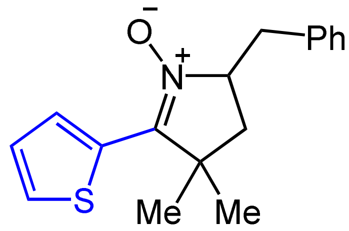


1

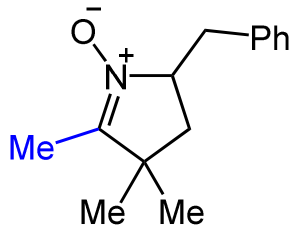
2



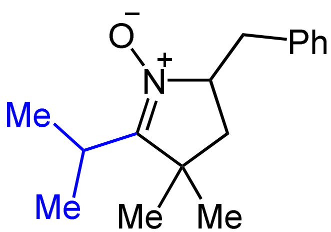
2b: R^1 = 4-$MeOC_6H_4$: 96%
2c: R^1 = 4-$CF_3C_6H_4$: 93%
2d: R^1 = 2-naphthyl: 98%
2e: R^1 = 2-MeC_6H_4: 75%



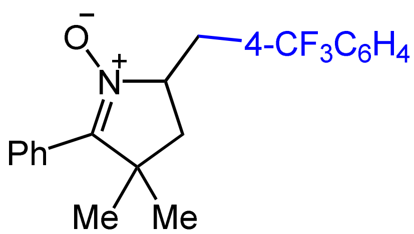
2f: 97%



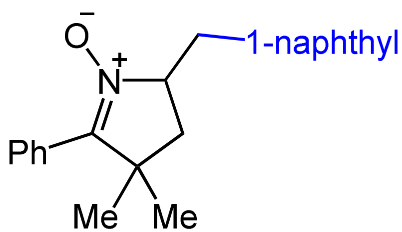
2g: 96%



2h: 91%

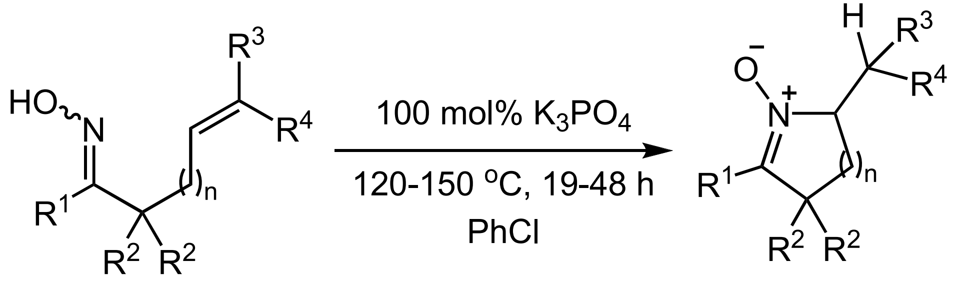


2i: 96%, 1h

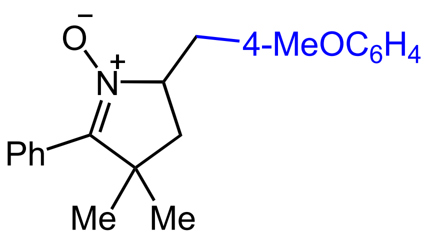


2j: 98%

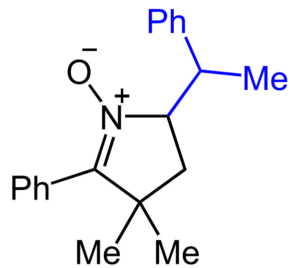
Substrate Scope



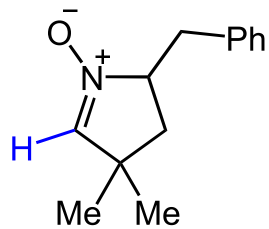
1 **2**



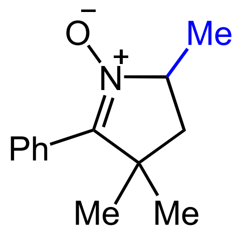
2k[a]: 87%, 48 h



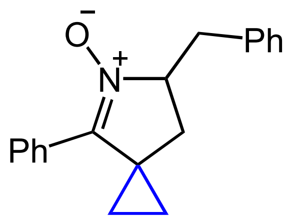
2l: 82%, 1.2:1 d.r.



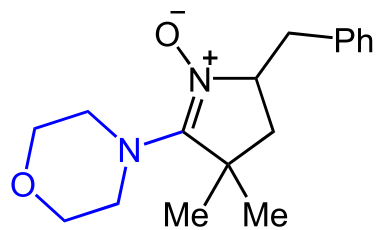
2m: 24%



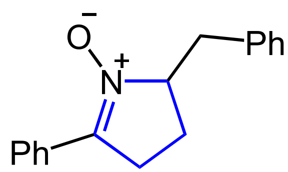
2n: 54%



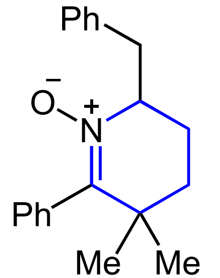
2o: 62%



2p: 89%



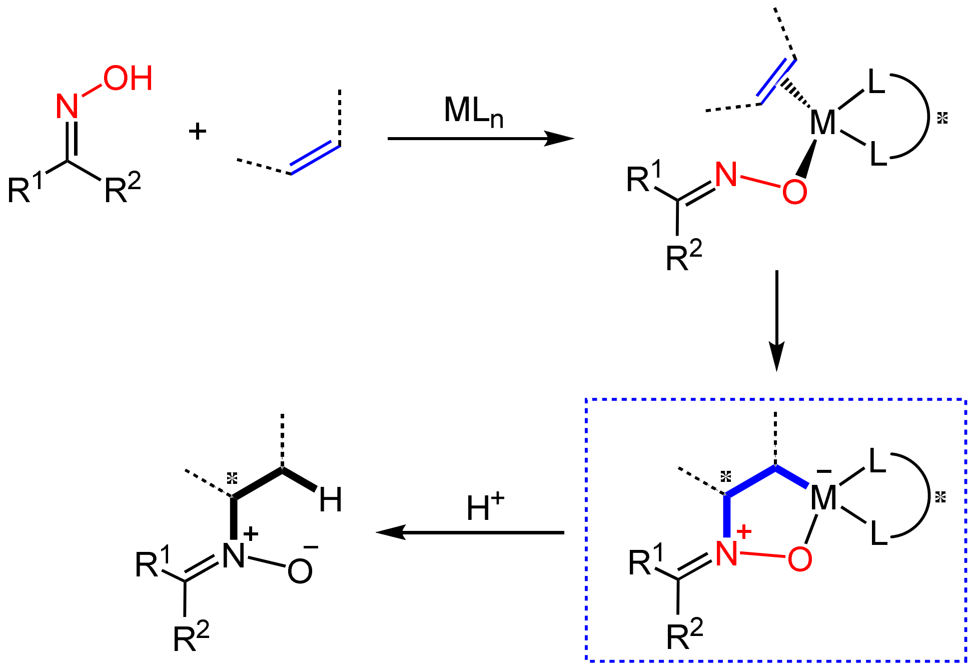
2q: 76%



2r: 65%

[a] 40 mol% K_3PO_4

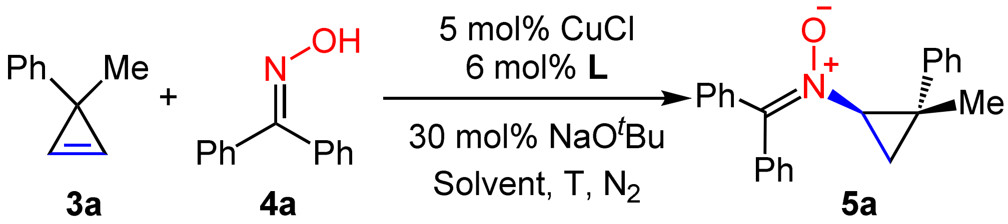
Copper-Catalyzed Hydroamination of Oximes



metalla-retro-Cope intermediate

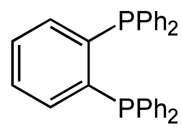
Zhang, Q. *et al. J. Am. Chem. Soc.* **2017**, *139*, 11702.

Optimization of the Reaction Parameters

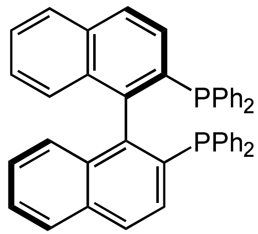


Entry[a]	L	Solvent	Yield (%)[b]	ee (%)[c]
1	--	Toluene	0	--
2	**L1**	Toluene	92	--
3	**L2**	Toluene	69	54
4	**L3**	Toluene	99	56
5	**L4**	Toluene	76	70
6	**L4**	DCE	84	65
7	**L4**	THF	91	76
8[d]	**L4**	THF	84	92
9[e]	**L4**	THF	95	92

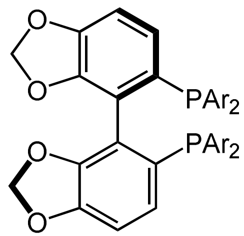
[a] Reaction conditions: **3a** (0.2 mmol), **4a** (0.24 mmol), CuCl (5 mol%), **L** (6 mol%), NaO^{t}Bu (30 mol%), Solvent (2 mL). [b] Isolated yield. [c] Determined by HPLC. [d] -20 °C. [e] -50 °C.



L1

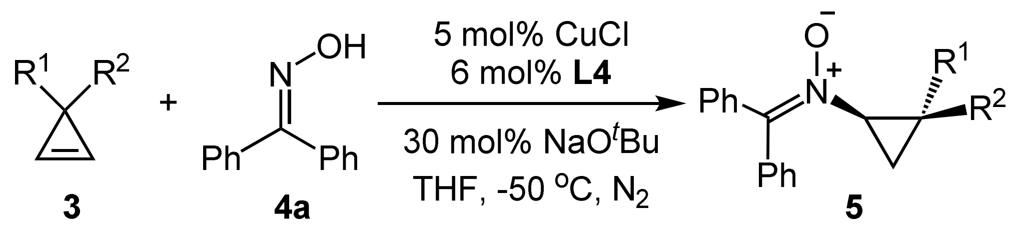


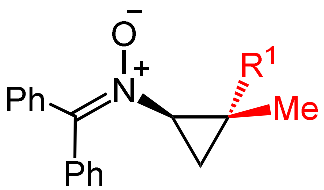
L2



Ar = Ph (**L3**)
Ar = 3,5-(tBu)$_2$-4-MeOC$_6$H$_2$ (**L4**)

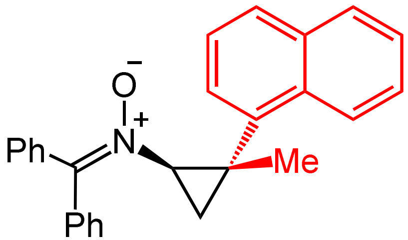
Scope of Cyclopropenes



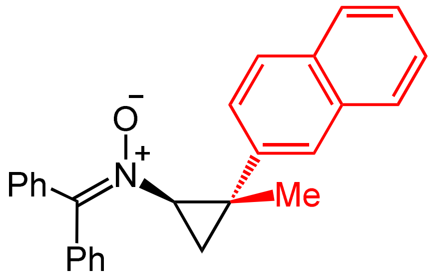


R^1 = 4-MeC_6H_4, **5b**, 89%, 95% ee
4-BrC_6H_4, **5c**, 74%, 94% ee
4-ClC_6H_4, **5d**, 82%, 96% ee
4-$CF_3C_6H_4$, **5e**, 64%, 96% ee
4-$MeOC_6H_4$, **5f**, 71%, 98% ee

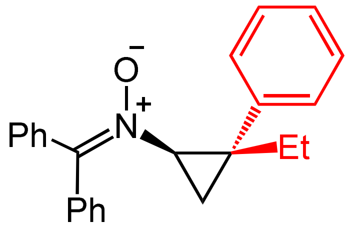
R^1 = 3-MeC_6H_4, **5g**, 76%, 95% ee
3-$MeOC_6H_4$, **5h**, 82%, 95% ee
3-ClC_6H_4, **5i**, 90%, 88% ee
2-MeC_6H_4, **5j**, 66%, 76% ee



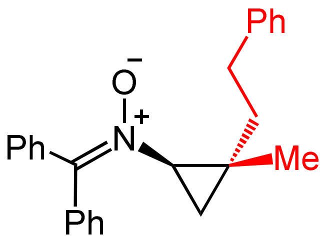
5k, 80%, 82% ee



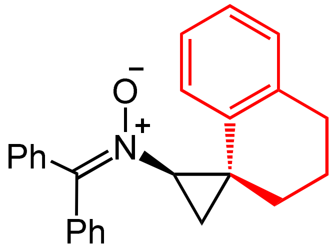
5l, 84%, 95% ee



5m, 67%, 99% ee

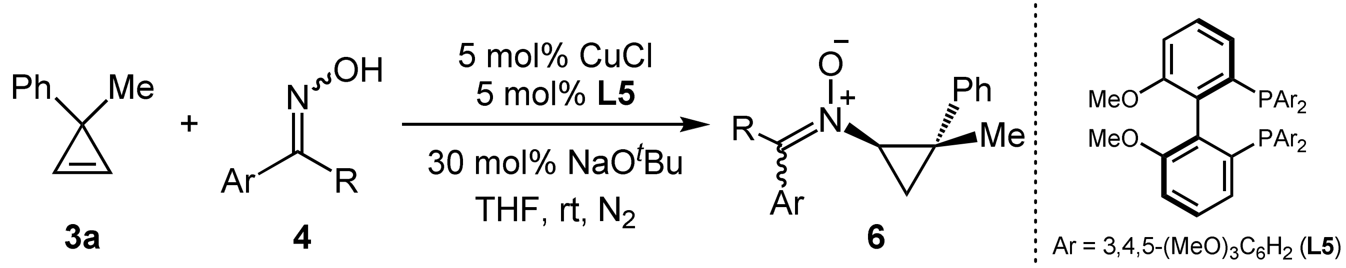


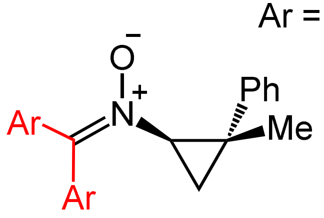
5n, 65%, 96% ee, 18.6/1 d.r.



5o, 83%, 96% ee

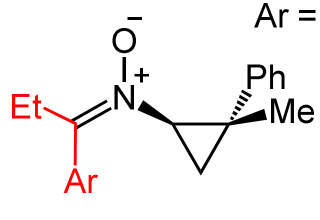
Scope of Ketoximes



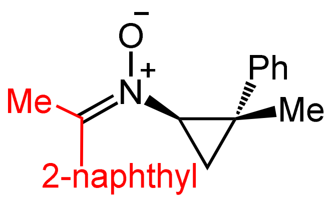


Ar = 4-MeC_6H_4, **6a**, 82%, 90% ee
4-MeOC_6H_4, **6b**, 90%, 90% ee
4-BrC_6H_4, **6c**, 76%, 89% ee
4-ClC_6H_4, **6d**, 90%, 89% ee

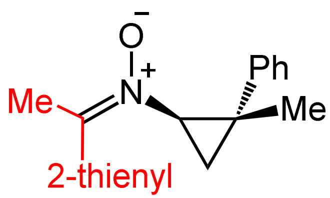
(L4, 0 °C)



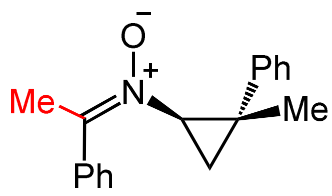
Ar = Ph, **6e**, 99%, 97% ee
4-MeC_6H_4, **6f**, 92%, 97% ee
4-MeOC_6H_4, **6g**, 59%, 95% ee
4-BrC_6H_4, **6h**, 88%, 96% ee
4-ClC_6H_4, **6i**, 88%, 96% ee
4-FC_6H_4, **6j**, 92%, 98% ee



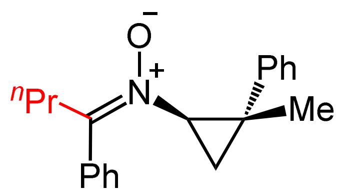
6k, 93%, 98% ee



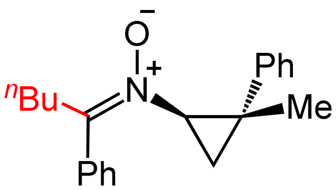
6l, 81%, 66% ee



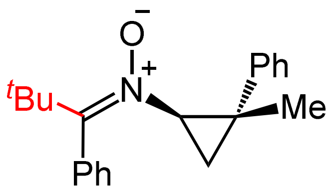
6m, 90%, 94% ee



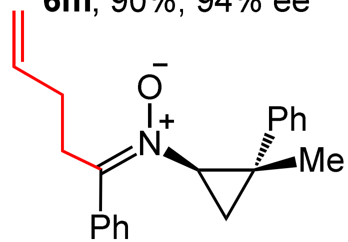
6n, 99%, 98% ee



6o, 96%, 95% ee

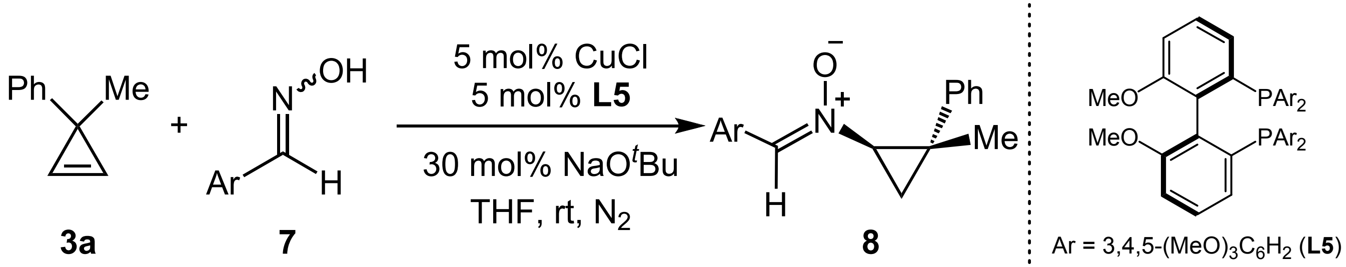


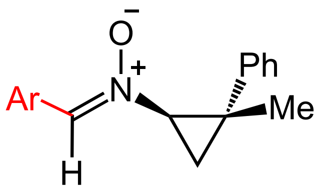
6p, 52%, 77% ee



6q, 80%, 96% ee

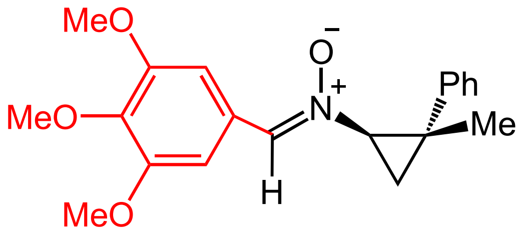
Scope of Aldoximes



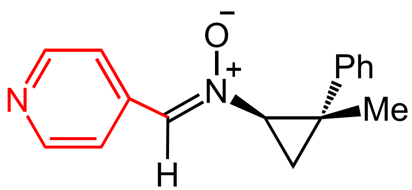


Ar = 4-MeC_6H_4, **8a**, 99%, 92% ee
4-$MeOC_6H_4$, **8b**, 94%, 92% ee
4-$^tBuC_6H_4$, **8c**, 96%, 95% ee
4-ClC_6H_4, **8d**, 89%, 91% ee
4-PhC_6H_4, **8e**, 99%, 92% ee

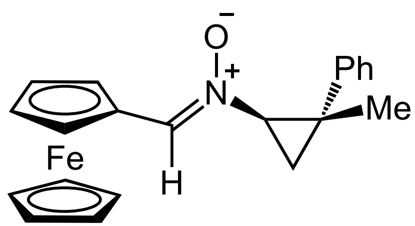
Ar = 4-$O_2NC_6H_4$, **8f**, 90%, 83% ee
3-MeC_6H_4, **8g**, 99%, 99% ee
3-$MeOC_6H_4$, **8h**, 93%, 92% ee
3-BrC_6H_4, **8i**, 95%, 80% ee
3-$CF_3OC_6H_4$, **8j**, 93%, 91% ee



8k, 76%, 93% ee

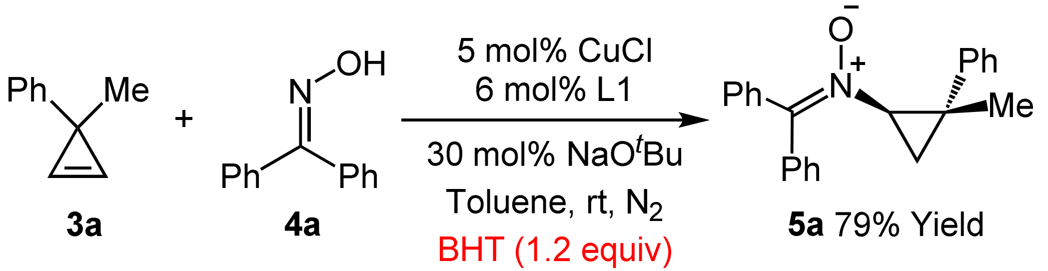


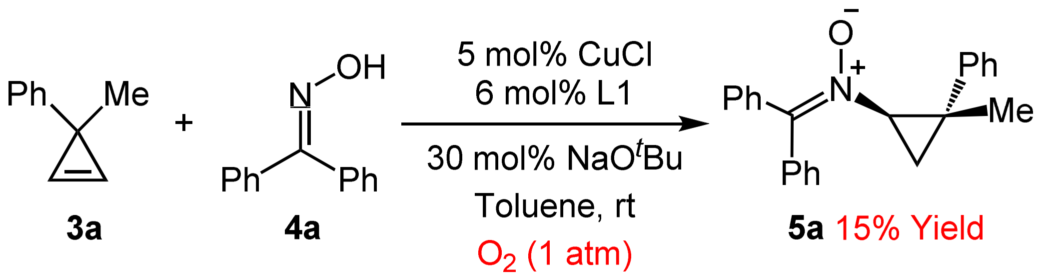
8l, 60%, 84% ee

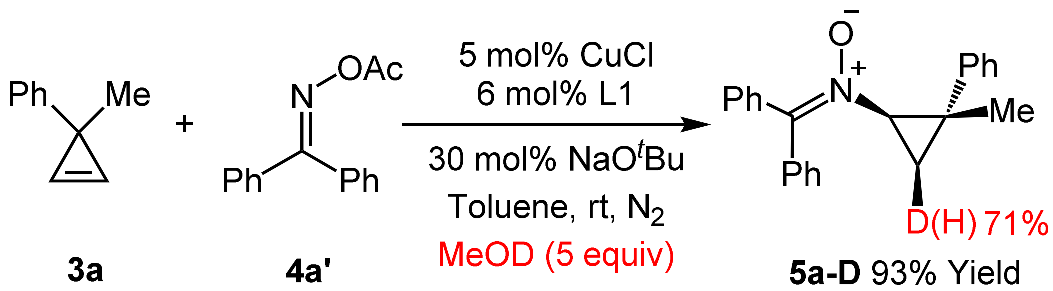


8m, < 5% ee

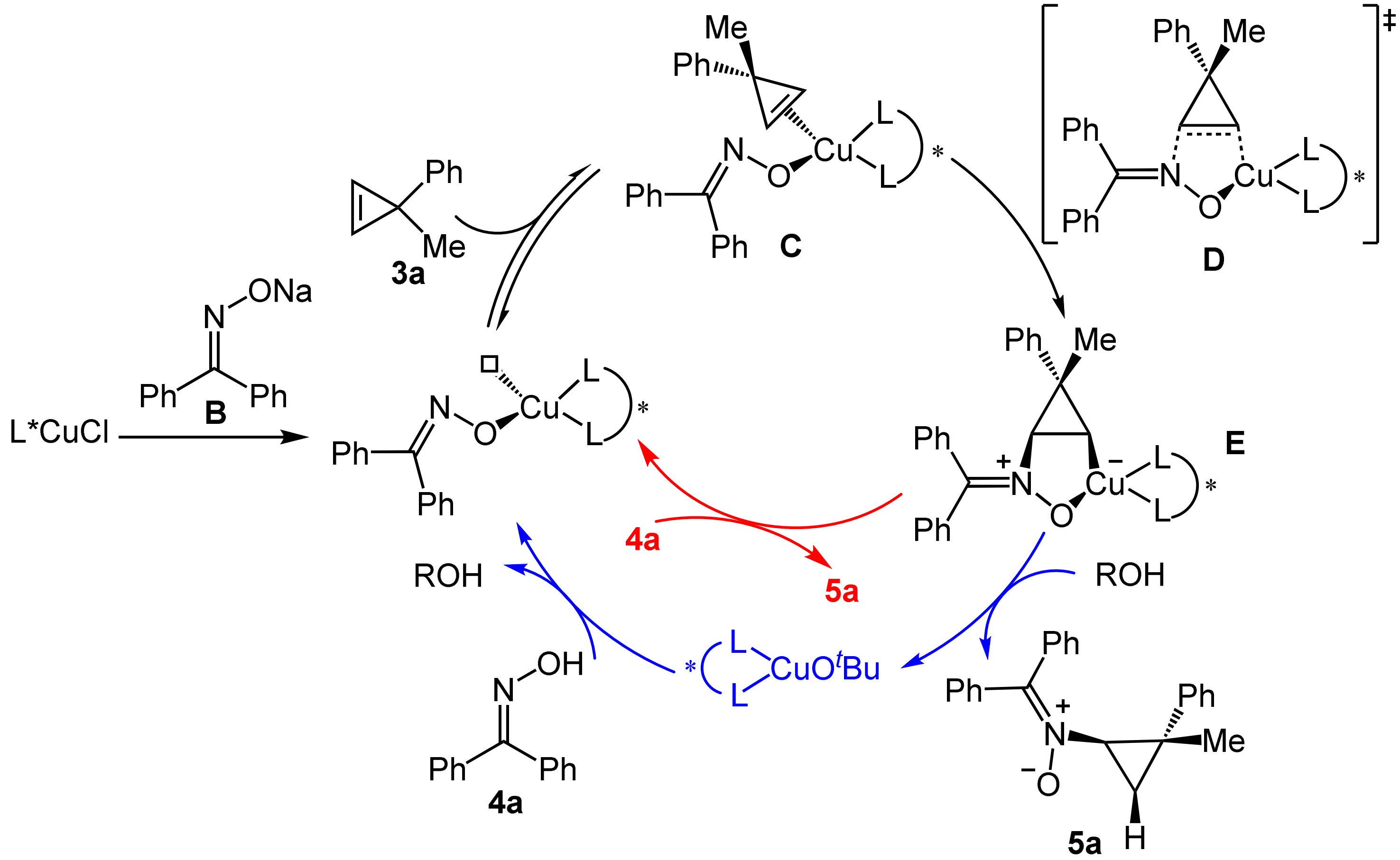
Control Expriments



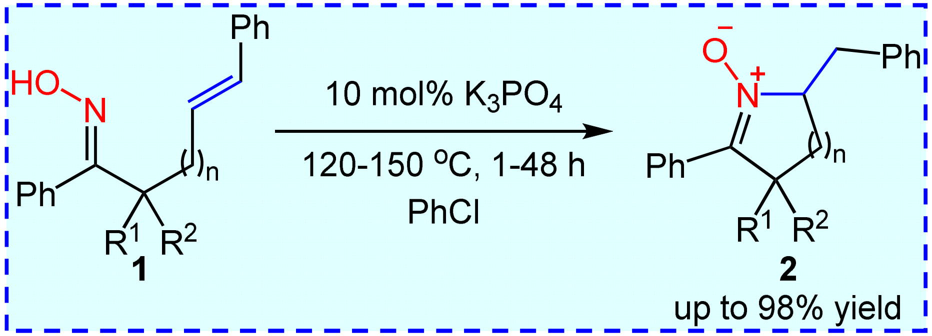




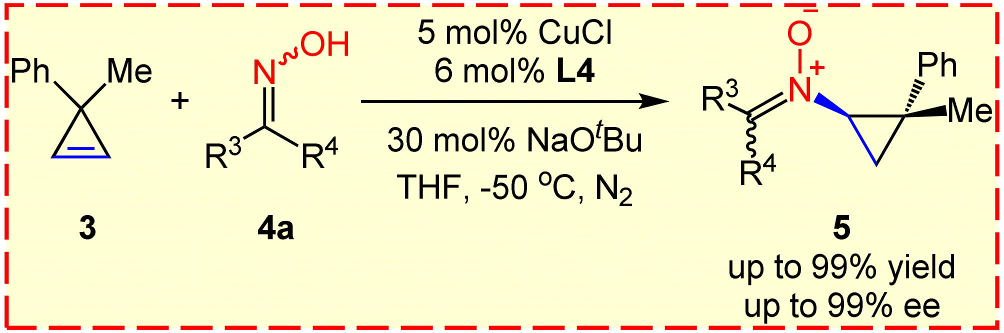
Plausible Mechanism



Summary



Chiba, S.; Hirao, H. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 1959.



Zhang, Q. *et al. J. Am. Chem. Soc.* **2017**, *139*, 11702.

The First Paragraph

As a highly versatile linchpin in synthetic chemistry, nitrone has found widespread applications in 1,3-dipolar cycloaddition for heterocycle and natural product synthesis. Its multifaceted applications as spin trapping agents, bioorthogonal probes and efficacious therapeutic agents also render nitrone a heavily pursued synthetic target. Chiral nitrones also serve as important building blocks in asymmetric synthesis.

The First Paragraph

In stark contrast to their versatile reactivity and prominent roles, routinely employed methods to synthesize nitrones still rely heavily on traditional strategies. Although alternative strategies are emerging at an increasing rate in the past decade, none holds the prospect of enantiocontrol.

The Last Paragraph

We have presented the first example of an intermolecular Cope-type hydroamination process of oximes using catalytic earth-abundant copper salts with the promotion of chiral ligands, allowing for a practical, straightforward access to valuable chiral nitrones in high enantio- and diastereoselectivities from readily available starting materials. The Cu-catalyzed process demonstrated broad scope and remarkable ligand directed stererocontrol, representing the first example of highly enantioselective nitrone formation process. Further developments of the conceptually novel reactivity mode are expected to significantly expedite chiral nitrone synthesis.