Copper-Catalyzed Asymmetric Interrupted Kinugasa Reaction

Reporter: **Bo Wu**
Checker: **Yu-Qing Bai**
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Zhong, X.; Zhou, W.; Cai, Q. *Angew. Chem. Int. Ed.* **2022**, *e202208323*

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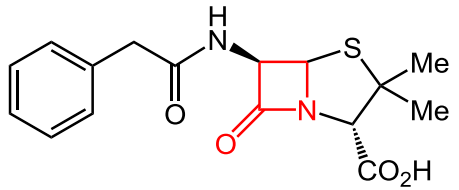
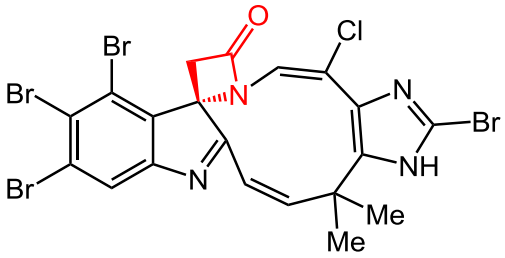
Introduction

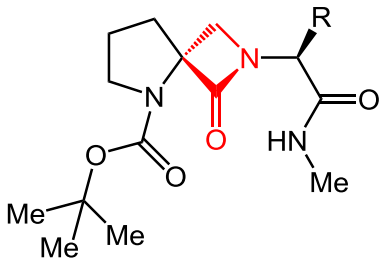
Representative β-Lactam Drugs and Bioactive Compounds



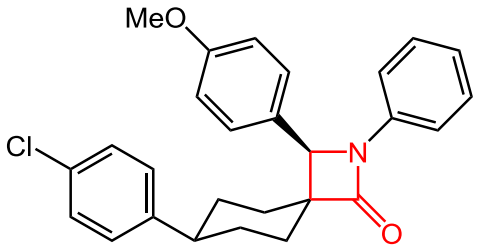
Penicillin



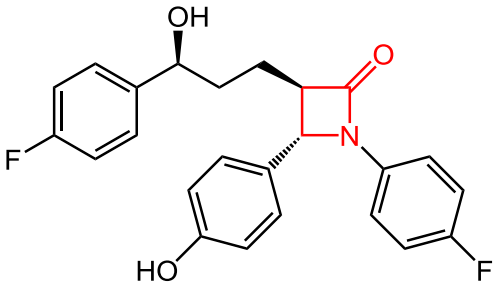
Chartelline A



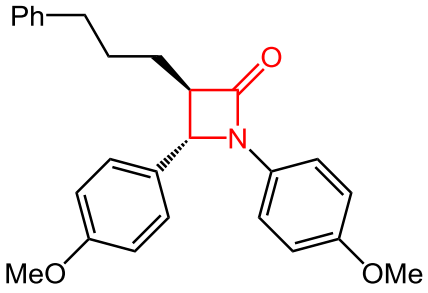
β-Turn nucleators



Cholesterol absorption inhibitor

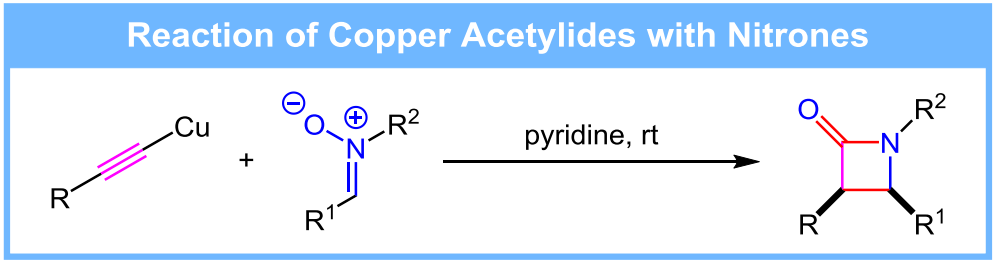


Ezetimibe



(-)-SCH 48461

Kinugasa Reaction



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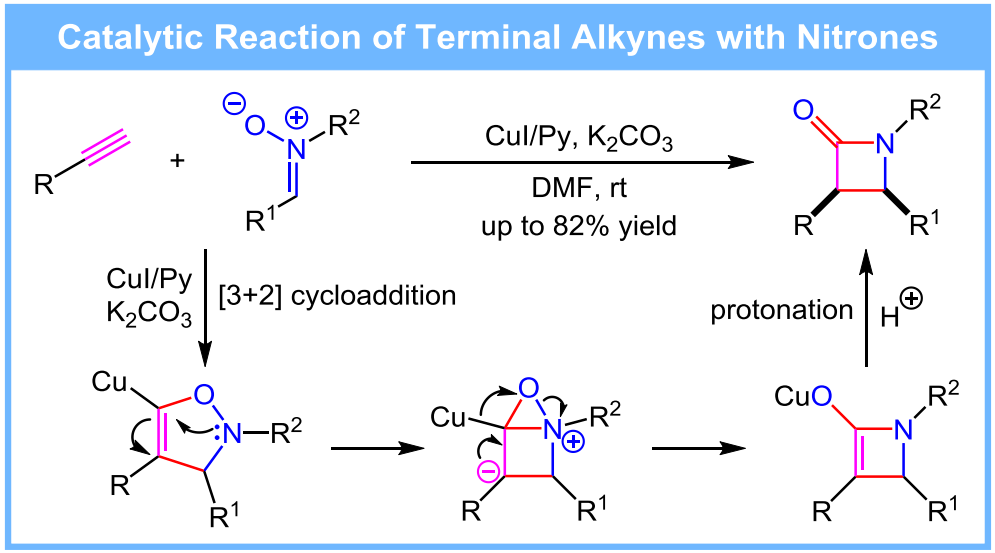

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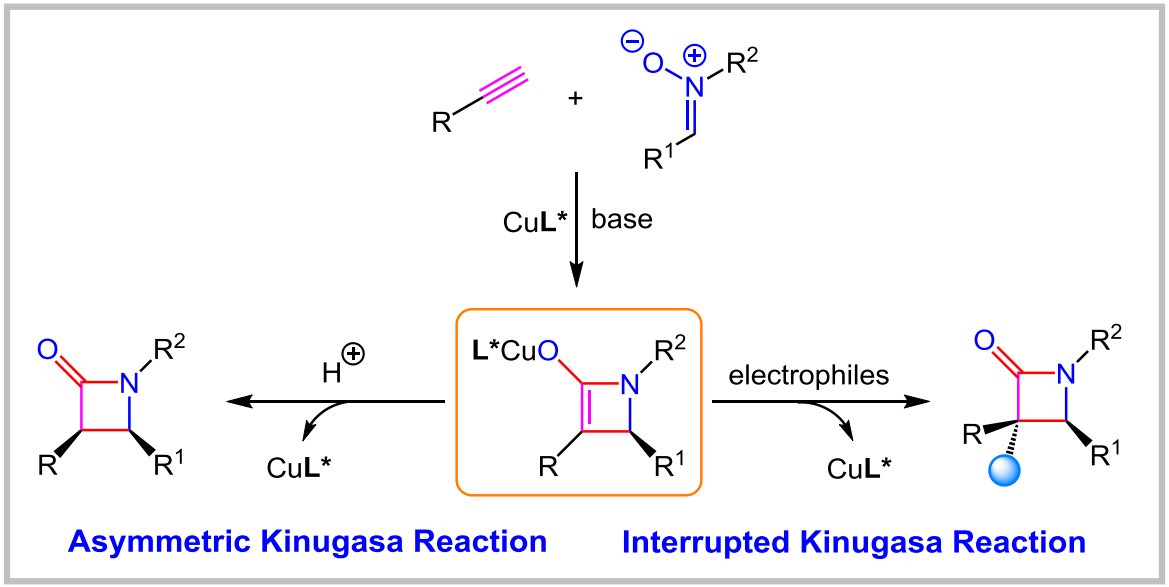
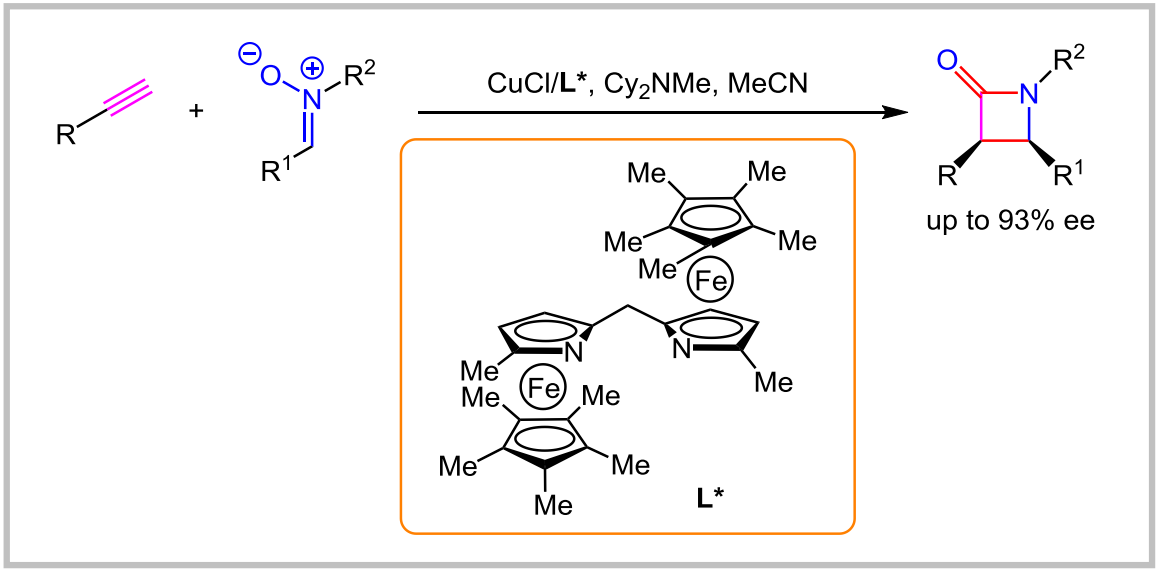
Asymmetric (Interrupted) Kinugasa Reaction



Asymmetric Kinugasa Reaction



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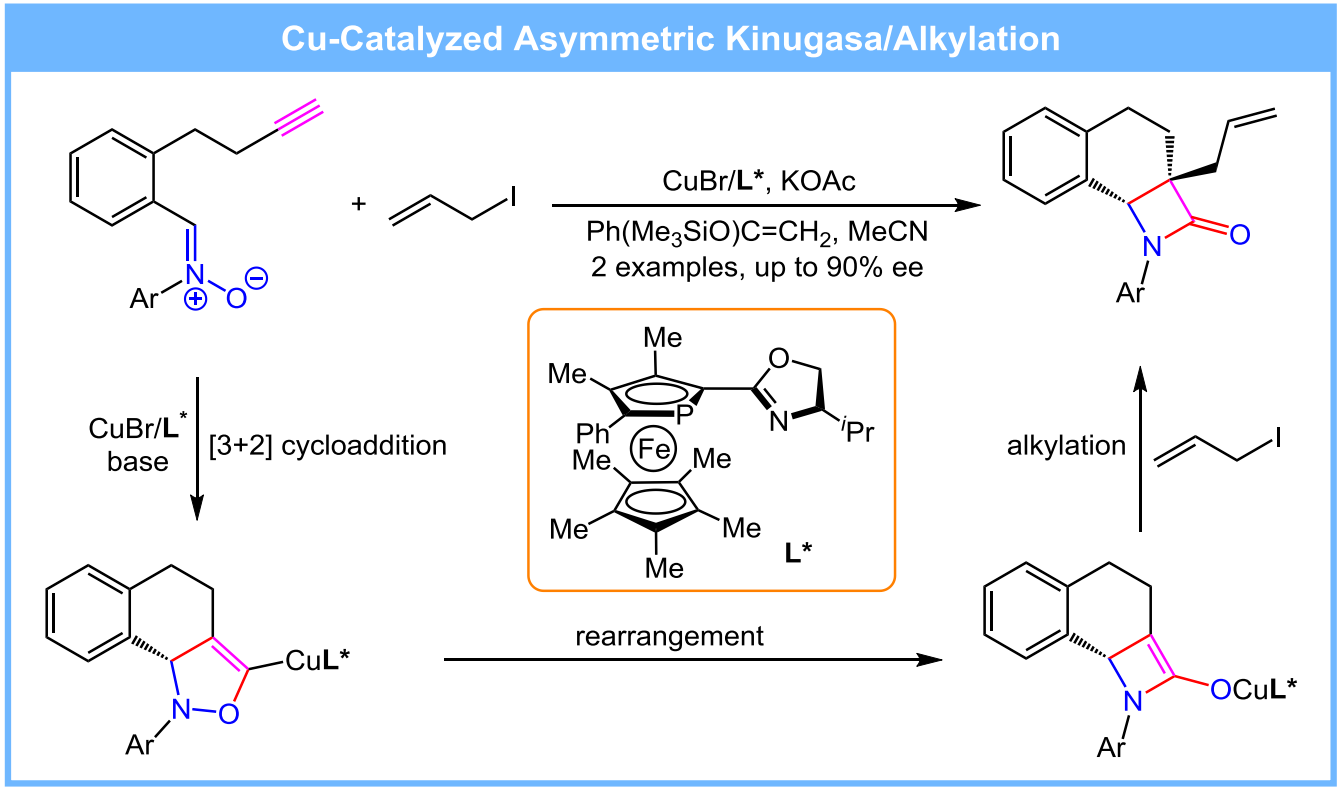
Asymmetric Interrupted Kinugasa Reaction



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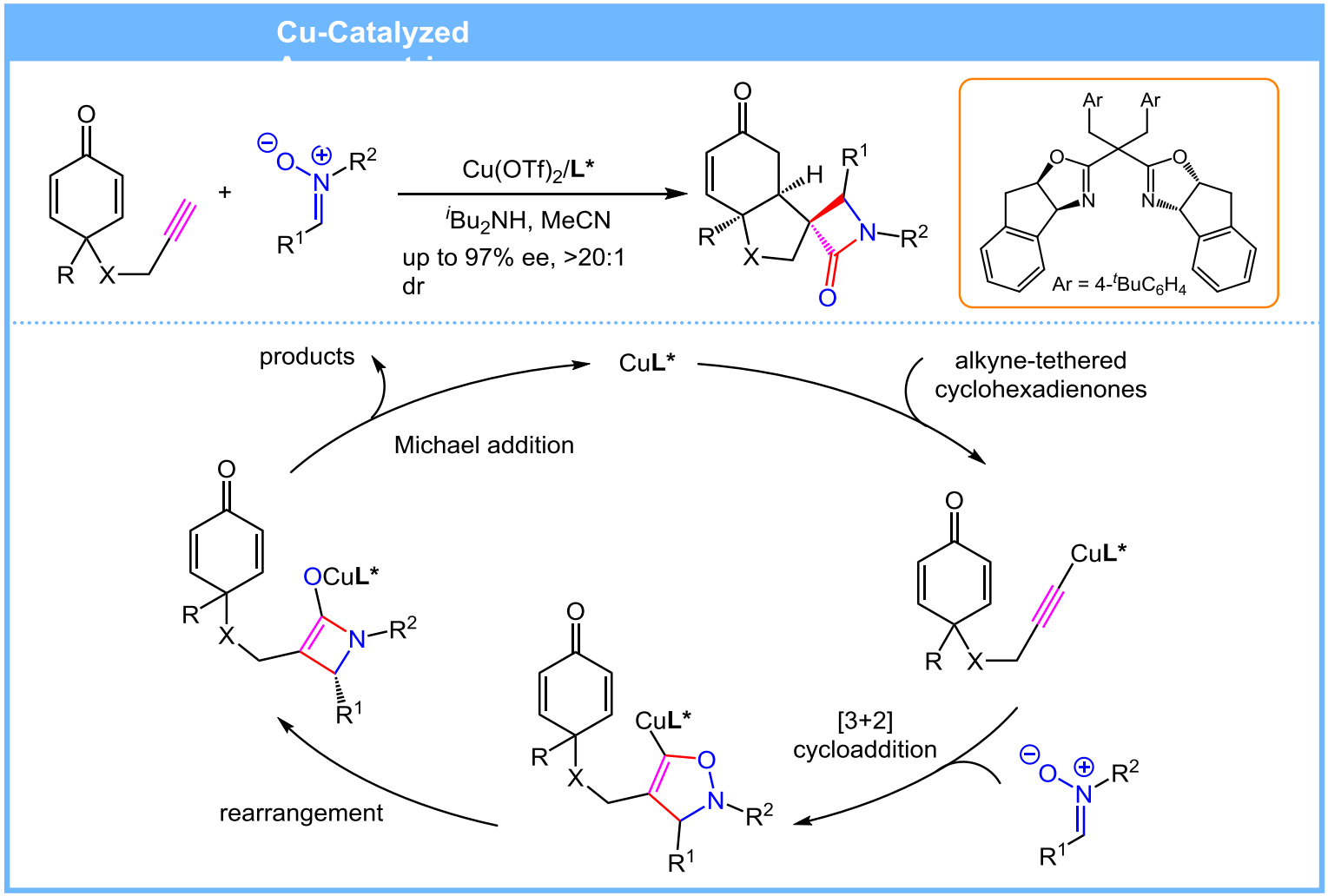
Asymmetric Interrupted Kinugasa Reaction



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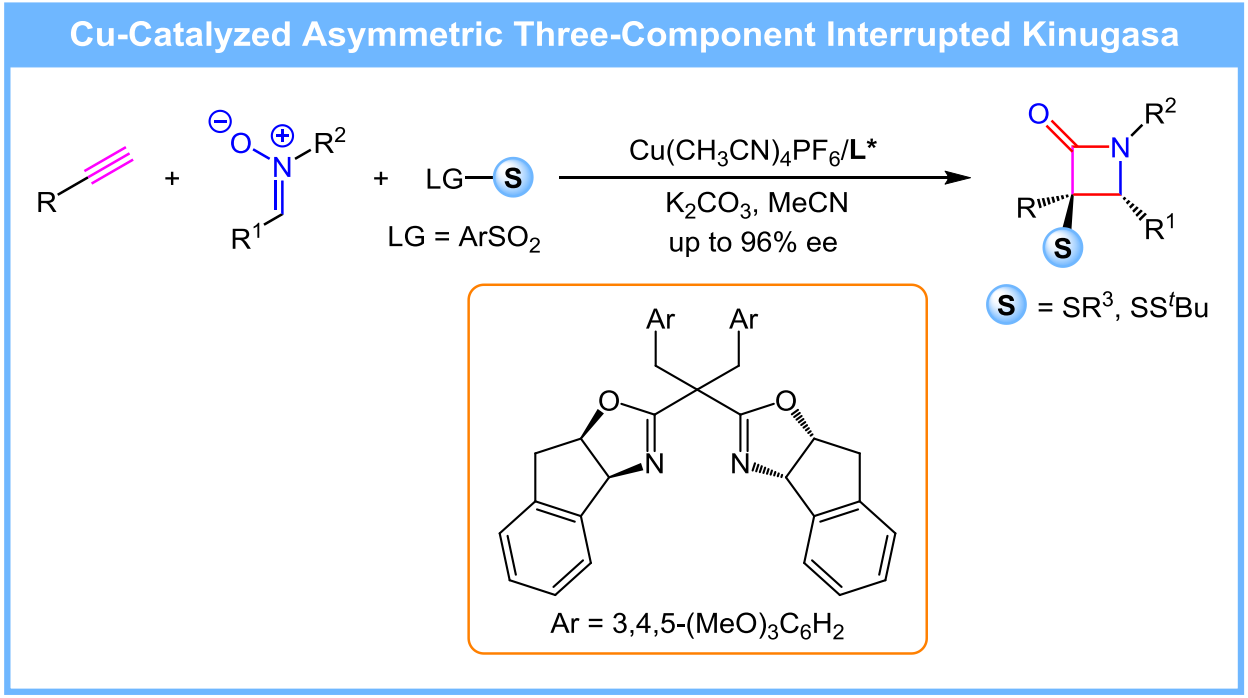
Asymmetric Interrupted Kinugasa Reaction



Qi, J.; Wei, F.; Tung, C.-H.; Xu, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 4561

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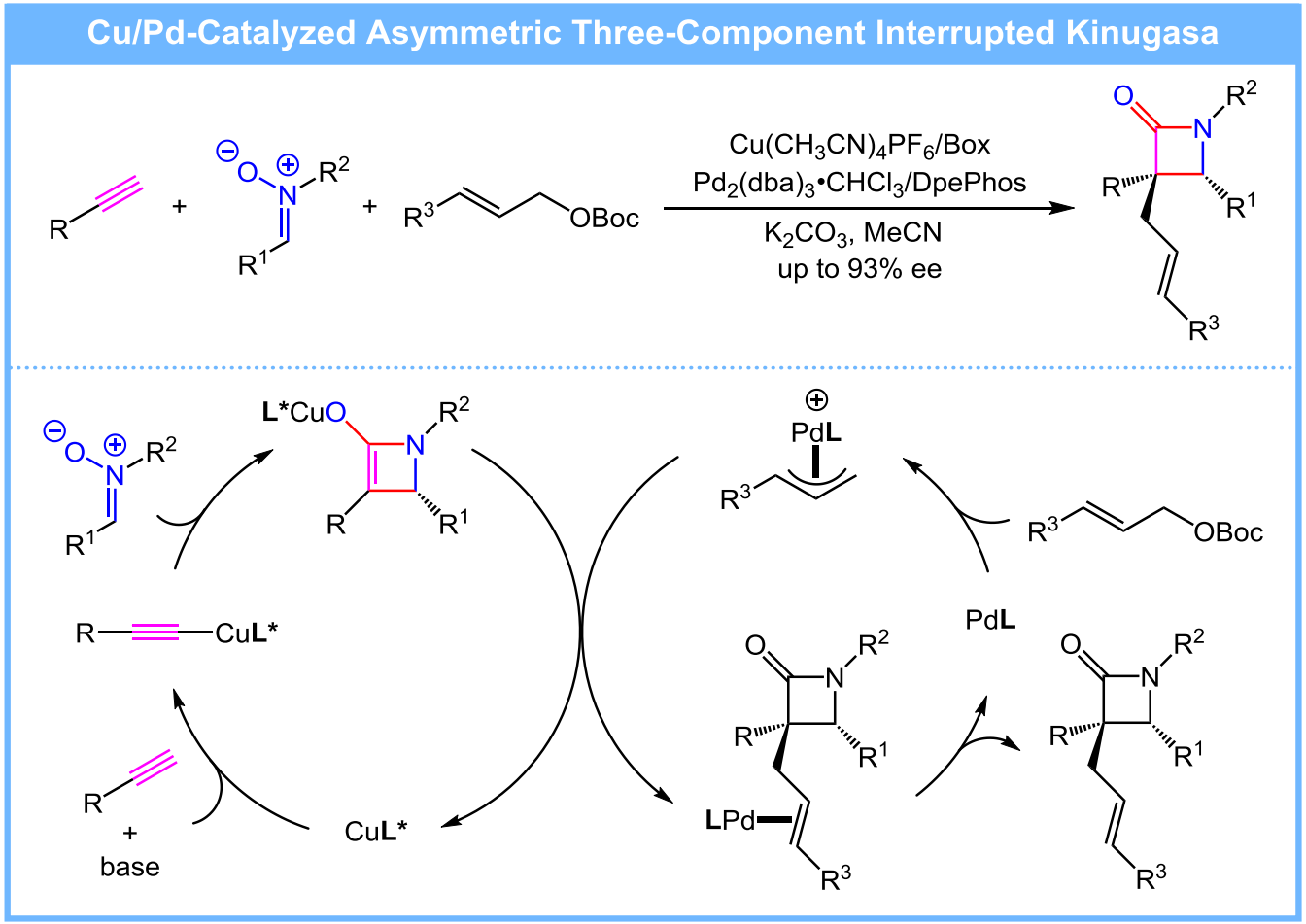
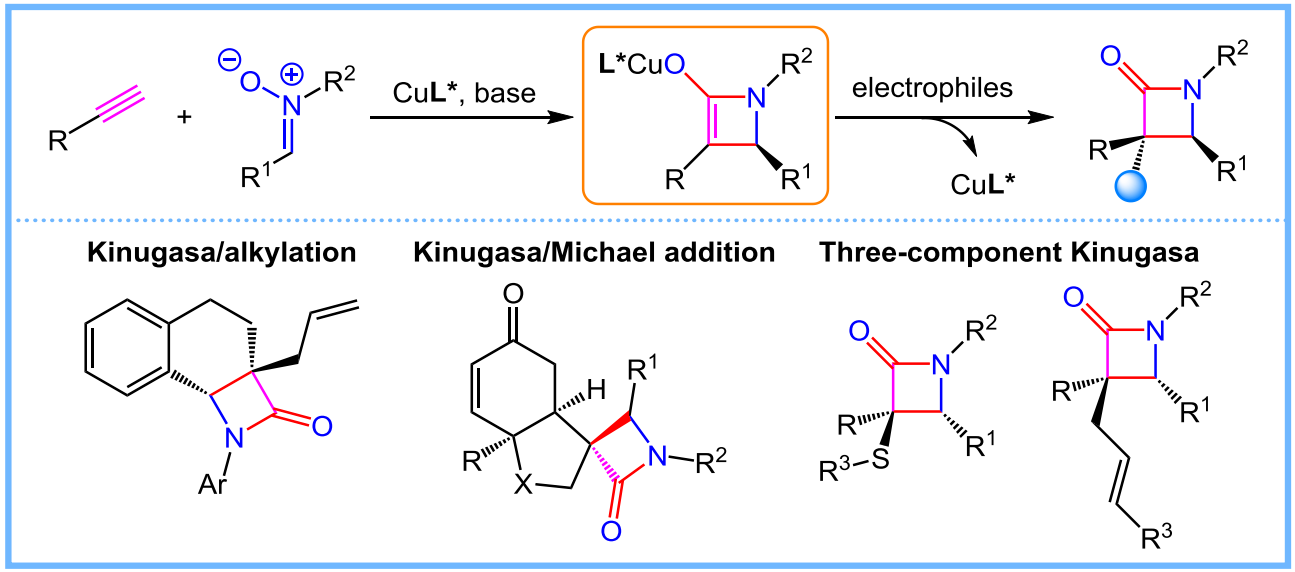
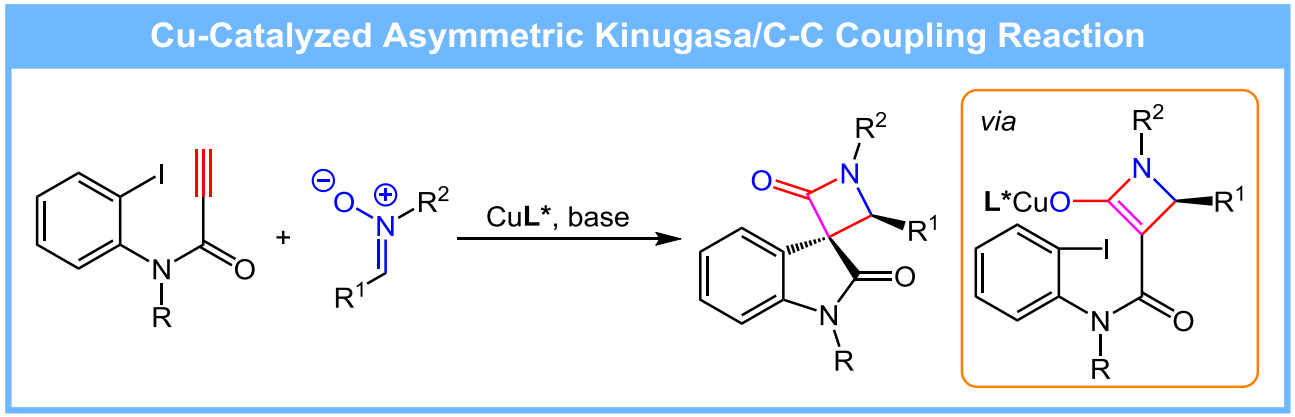


Qi, J.; Wei, F.; Tung, C.-H.; Xu, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 13814

Asymmetric Interrupted Kinugasa Reaction





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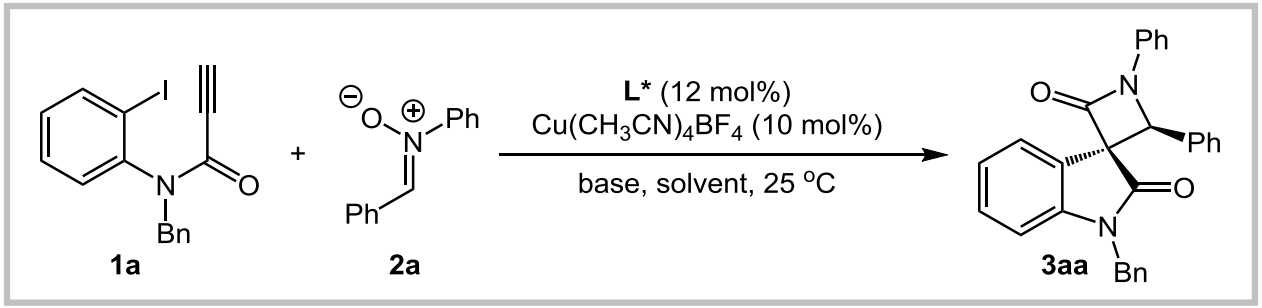
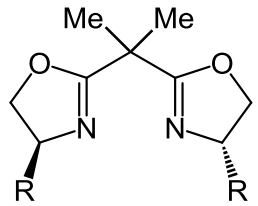
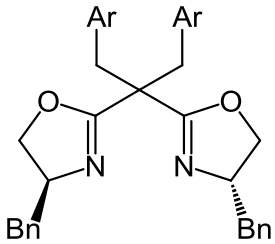
Optimization of Reaction Conditions



Entry	L*	Base	Solvent	Yield (%)	Ee (%)
1	**L1**	LiO^{t}Bu	MeCN	69	26
2	**L2**	LiO^{t}Bu	MeCN	64	6
3	**L3**	LiO^{t}Bu	MeCN	57	10
4	**L4**	LiO^{t}Bu	MeCN	66	80
5	**L5**	LiO^{t}Bu	MeCN	68	84
6	**L6**	**LiO^{t}Bu**	**MeCN**	**76**	**91**
7	**L6**	DIPEA	MeCN	0	--
8	**L6**	KO^{t}Bu	MeCN	14	18
9	**L6**	LiO^{t}Bu	THF	38	44
10	**L6**	LiO^{t}Bu	DMF	60	32



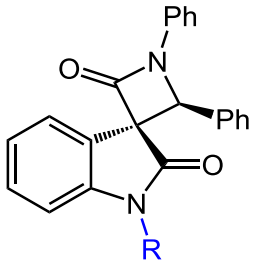
L1: R = Bn
L2: R = ^{t}Bu
L3: R = Ph



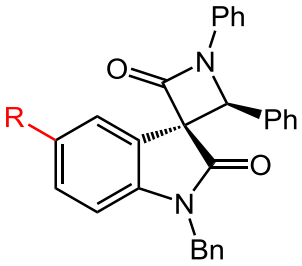
L4: Ar = C_6H_5
L5: Ar = 4-$MeOC_6H_4$
L6: Ar = 4-^{t}BuC_6H_4

Substrate Scope

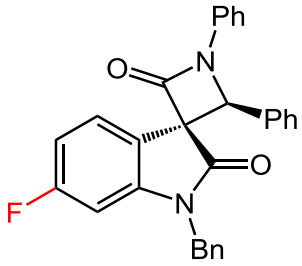
Scope of N-(2-iodoaryl)propiolamides



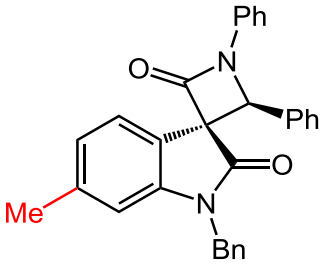
3aa R = Bn, 76%, 91% ee
3ba R = allyl, 72%, 80% ee
3ca R = PMB, 75%, 85% ee



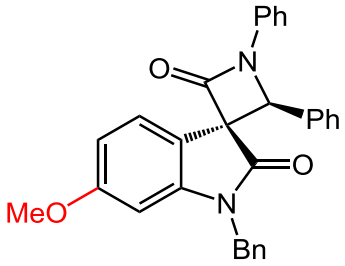
3da R = F, 75%, 92% ee
3ea R = Cl, 78%, 90% ee
3fa R = Br, 75%, 92% ee
3ga R = Me, 72%, 94% ee
3ha R = OMe, 72%, 90% ee



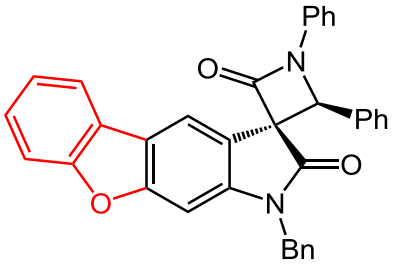
3ia 72%, 91% ee



3ja 56%, 86% ee



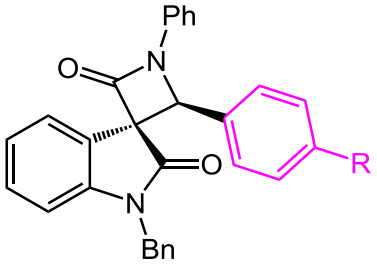
3ka 70%, 87% ee



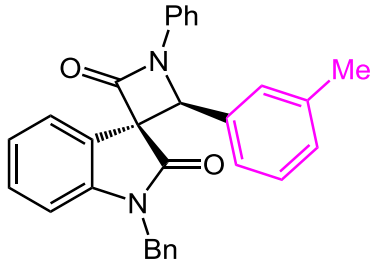
3la 70%, 90% ee

Substrate Scope

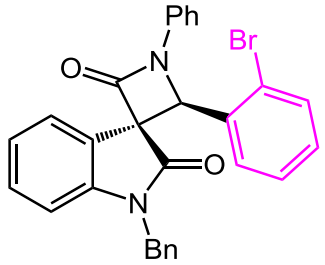
Scope of diarylnitrones



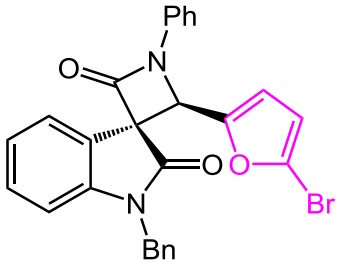
3ab R = F, 71%, 90% ee
3ac R = Cl, 73%, 90% ee
3ad R = Br, 80%, 90% ee
3ae R = CF_3, 75%, 88% ee
3af R = Me, 73%, 92% ee
3ag R = OMe, 68%, 90% ee



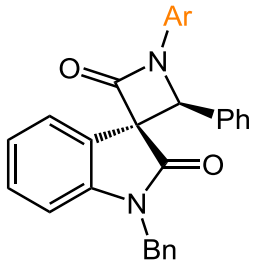
3ah 76%, 90% ee



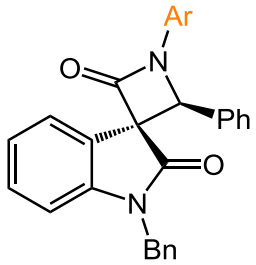
3ai 64%, 81% ee



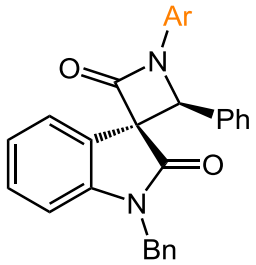
3aj 67%, 80% ee



Ar = 4-FC_6H_4
3ak 78%, 90% ee



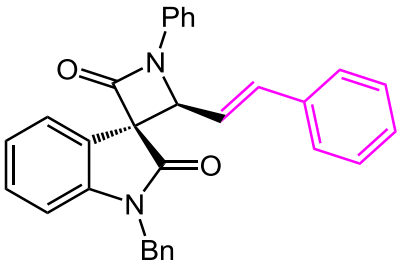
Ar = 4-ClC_6H_4
3al 74%, 90% ee



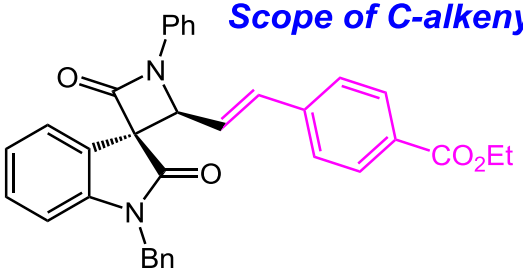
Ar = 4-$MeOC_6H_4$
3am 68%, 91% ee

Substrate Scope

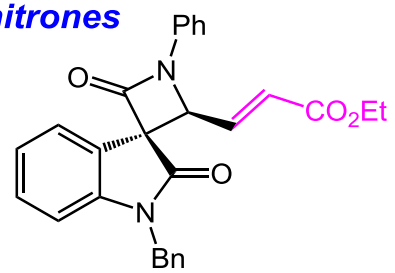
Scope of C-alkenylnitrones



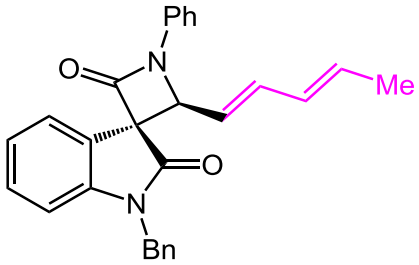
3an 64%, 88% ee



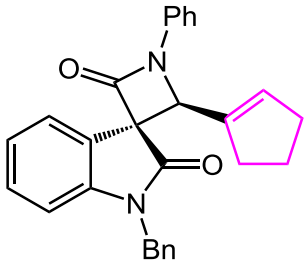
3ao 64%, 94% ee



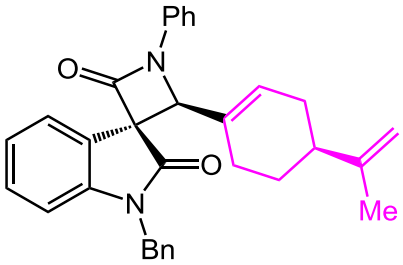
3ap 56%, 90% ee



3aq 50%, 89% ee

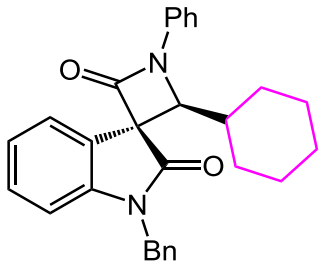


3ar 65%, 92% ee

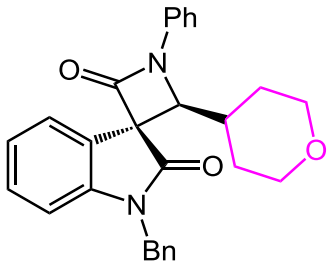


3as 68%, 16:1 dr

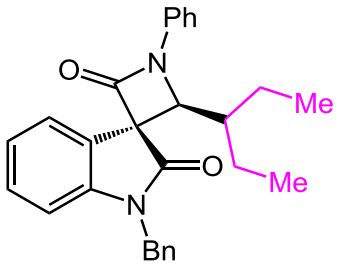
Scope of C-alkylnitrones



3at 67%, 73% ee

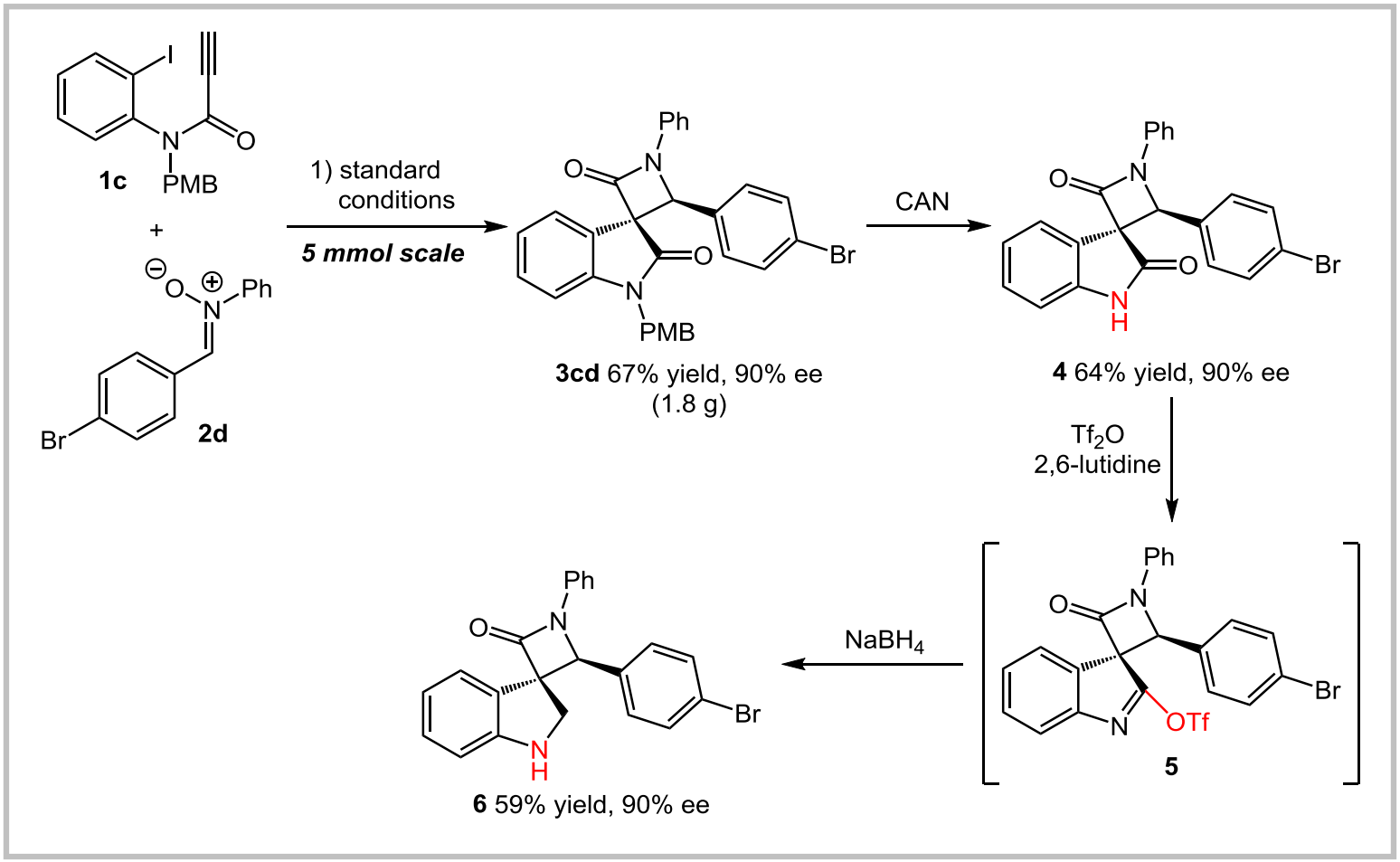


3au 68%, 86% ee

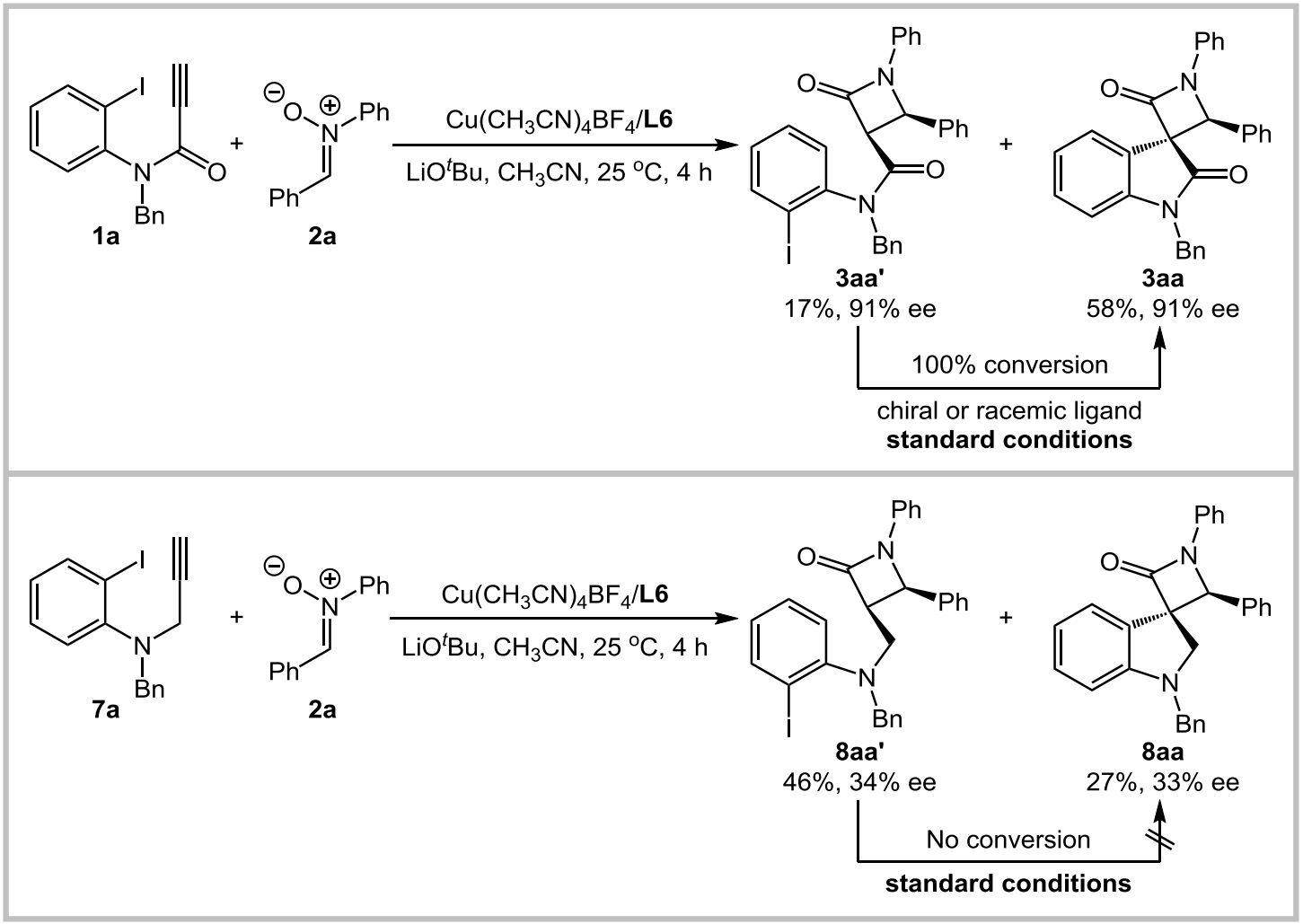


3av 63%, 86% ee

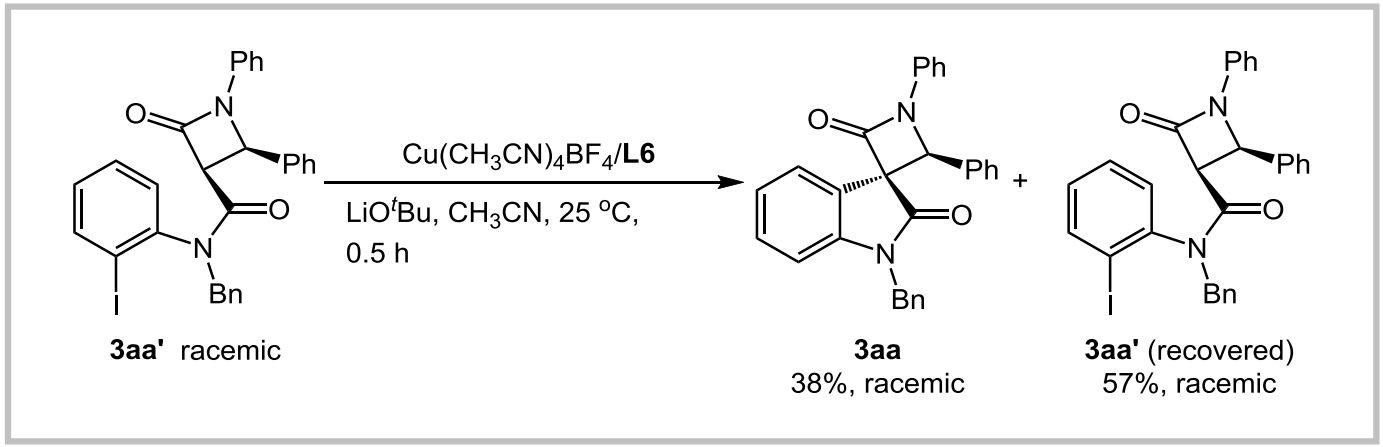
Gram-Scale Reactions and Transformations



Control Experiments



Control Experiments

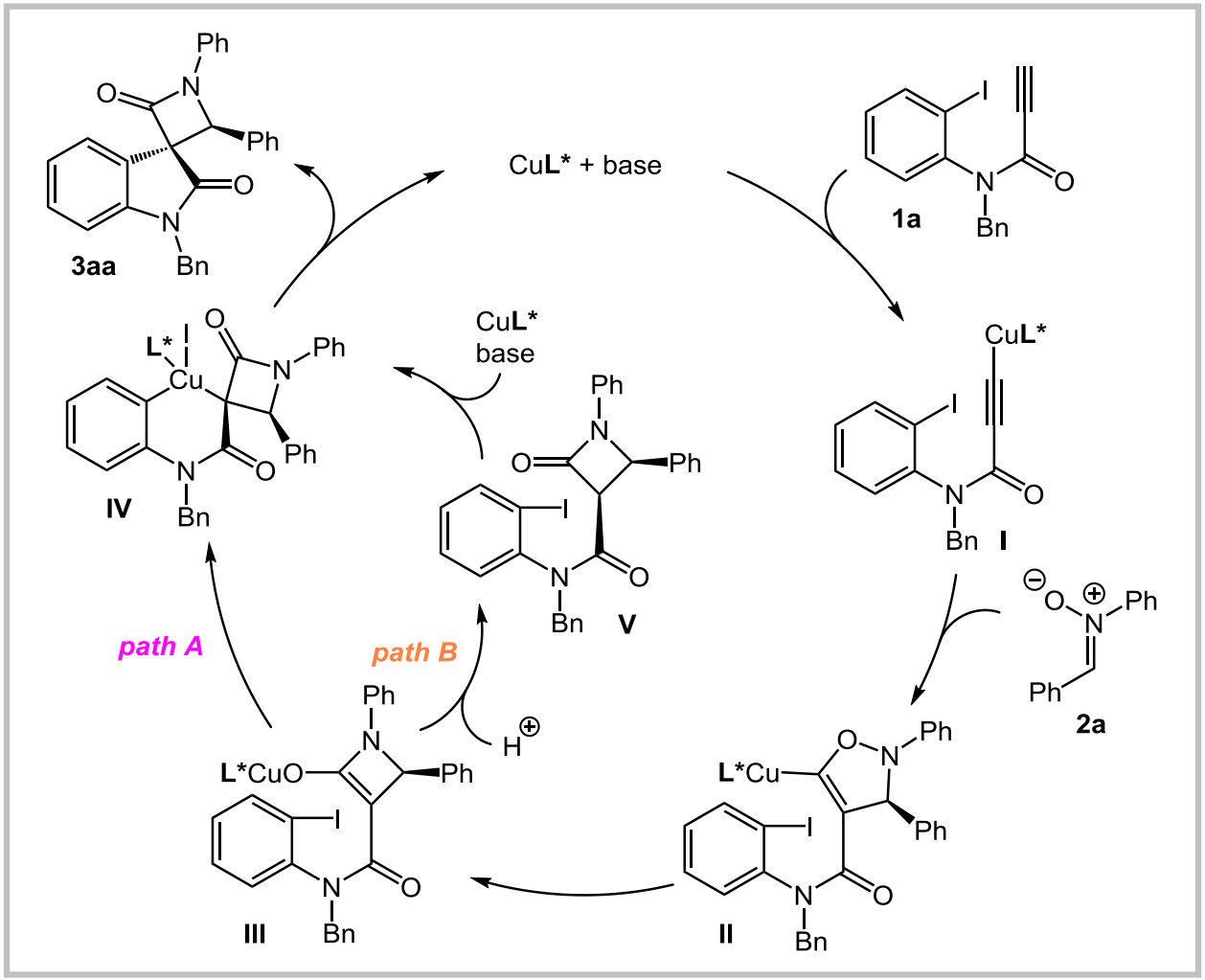


3aa' racemic

3aa
38%, racemic

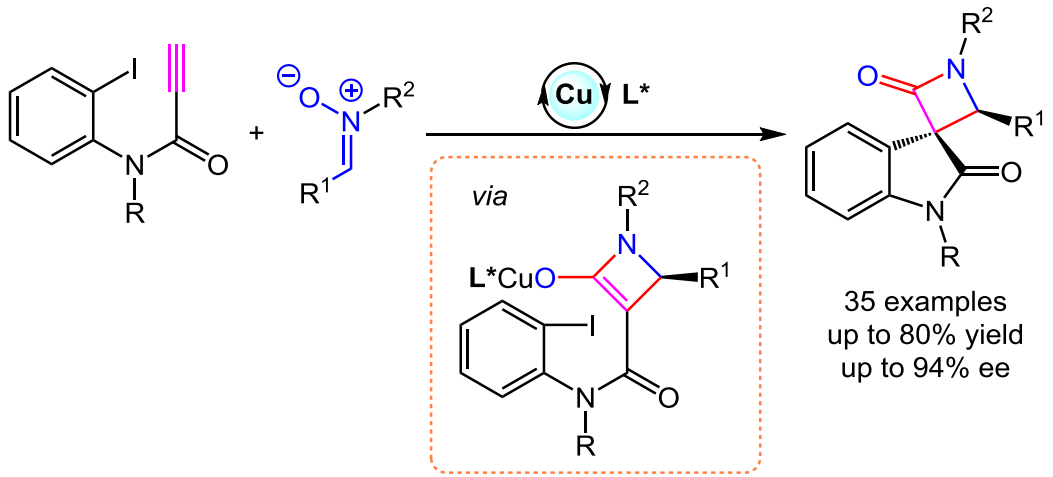
3aa' (recovered)
57%, racemic

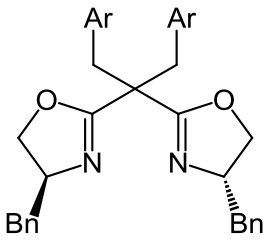
Proposed Mechanism



Summary

Cu-Catalyzed Asymmetric Kinugasa/C-C Coupling Reaction





L* Ar = 4-^{t}BuC$_6$H$_4$

The First Paragraph

Writing Strategy

The importance of spiro[azetidine-indoline] and progress of the synthesis of spiro[azetidine-3,3’-indoline]

The lack of enantioselective synthesis of spiro[azetidine-3,3’-indolines]

The First Paragraph

Azetidine and indoline are privileged heterocyclic skeletons that widely exist in diversified bioactive natural products and pharmaceuticals. Spiro[azetidine-indoline] and analogues, which merge the two unique motifs of azetidine and indoline, have attracted considerable attention from synthetic and medicinal chemists due to the increased structural complexity and the enhanced three dimensionality in space for drug design. A variety of elegant strategies have been developed for diastereo- and enantioselective construction of chiral spiro[azetidine-indolines]. However, most of these efforts have focused on spiro[azetidine-2,3'-indolines]. A similar spiro[azetidine-indoline] skeleton, spiro[azetidine-3,3'-indoline], has been investigated, but only sporadic examples of the racemic synthesis of such structures have been reported to date.

The First Paragraph

In 2012, Tayler et al. demonstrated a copper-catalyzed C-H/Ar-H functionalization method for spirooxindoles, in which a spiro[azetidine-3,3'-indoline]-2,2'-dione product was obtained in low yield. In 2021, Li and co-workers developed an elegant [3+1] cyclization reaction of oxindolyl azaoxylallyl cations with sulfur ylides, which afforded spiro[azetidine-3,3'-indoline]-2,2'-diones in high yields and with excellent diastereoselectivity. Very recently, Bach et al. demonstrated a graceful synthesis of spiro[azetidine-3,3'-indolin]-2-ones or 2,4-diones *via* a visible light-mediated dearomative hydrogen atom abstraction/cyclization cascade reaction of indoles. Despite of these successes, asymmetric synthesis of chiral spiro[azetidine-3,3'-indolines] remains unexplored, and it is highly desirable to develop efficient and practical asymmetric approaches to construct such structures. This will extend the space of spiro[azetidine-indolines] and will provide a great opportunity for the discovery of novel bioactive compounds.

The Last Paragraph

Writing Strategy

Summary of this work

Outlook of this work

The Last Paragraph

In conclusion, we have developed a mild copper-catalyzed asymmetric Kinugasa/*C*-*C* coupling cascade reaction of *N*-(2-iodo-aryl)-propiolamides with nitrones. A set of structurally novel, densely functionalized chiral spiro[azetidine-3,3'-indoline]-2,2'-diones were efficiently constructed in this way as single diastereomers in good yields and with high enantiomeric ratios. Further exploration and applications of this method in the synthesis of chiral spiro heterocycles are currently in progress in our laboratory.

Representative Examples

Spiro[azetidine-indoline] and analogues, which merge the two unique motifs of azetidine and indoline, have attracted considerable attention from synthetic and medicinal chemists due to the increased structural complexity and the enhanced three dimensionality in space for drug design. (阐述合成重要性)

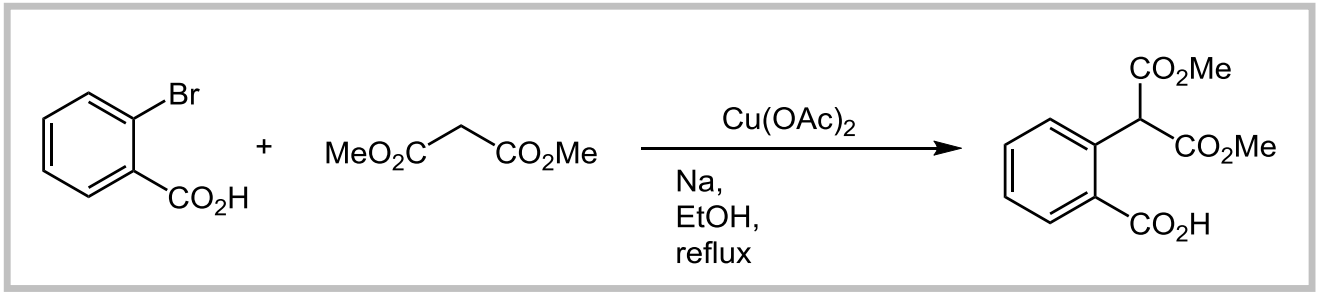
A similar spiro[azetidine-indoline] skeleton, spiro[azetidine-3,3'-indoline], has been investigated, but only sporadic examples of the racemic synthesis of such structures have been reported to date. (阐述现状)

No cascade product was obtained in the presence of organic bases and inferior reaction outcomes were observed with other inorganic bases, such as Cs_2CO_3 and ^{t}BuOK. (条件优化)

Acknowledgement

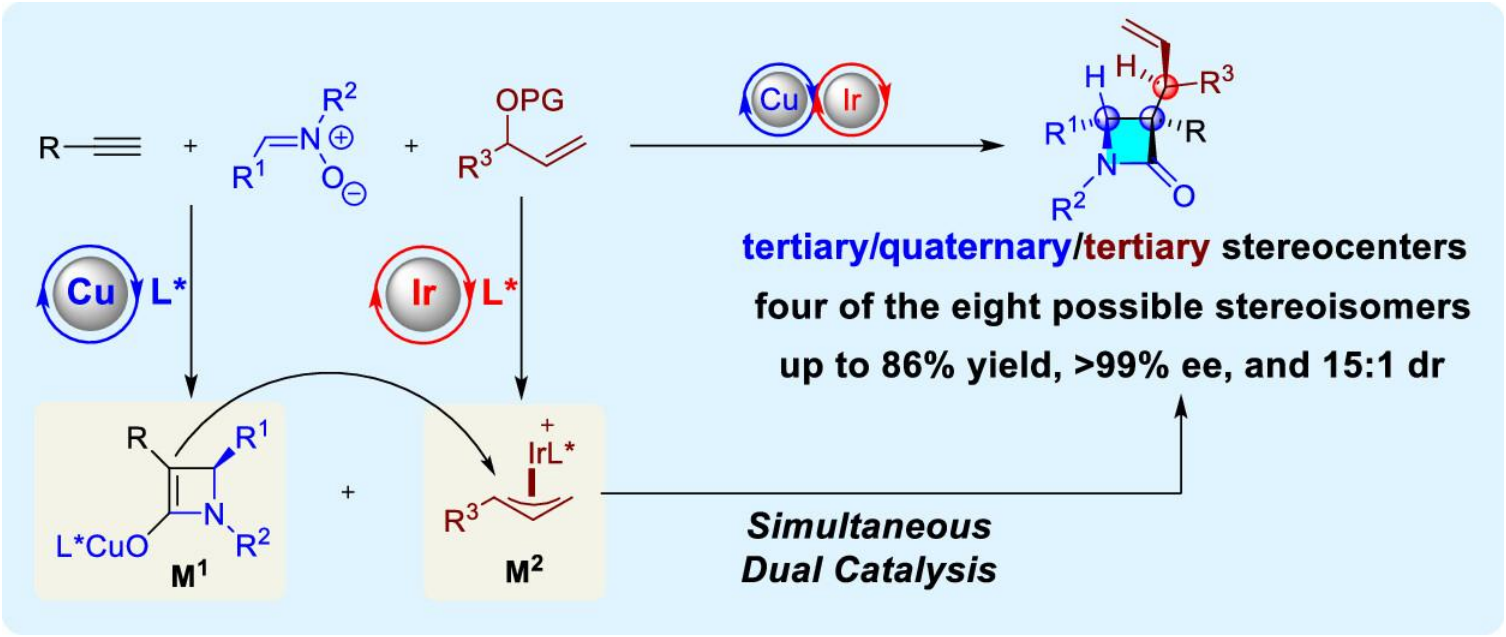
Thanks
for your attention

Hurtly Reaction

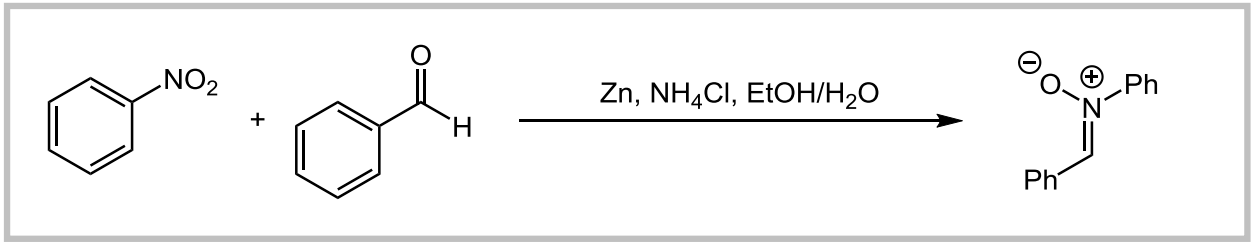


Hurtley, W. R. H. *J. Chem. Soc.* **1929**, *1870*

Asymmetric Three-Component Interrupted Kinugasa



Qi, J.; Song, T.; Yang, Z.; Xu, Z. *ACS Catal.* **2023**, *13,* 2555


NO2
+
O
H
Zn, NH4Cl, EtOH/H2O
O
N
Ph
Ph