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W-Phos Ligand Enables Copper-Catalyzed Enantioselective Alkylation of *N*-Sulfonyl Ketimines with Grignard Reagents

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Cite This: *ACS Catal.* 2023, 13, 8830−8837 Read Online

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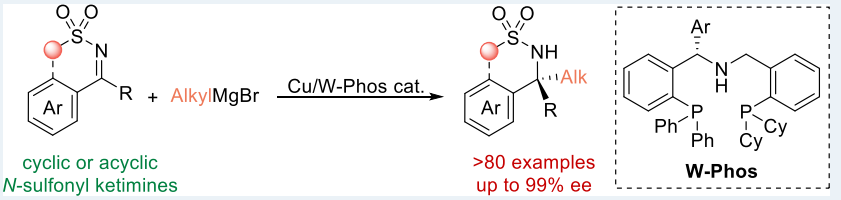


ABSTRACT: Catalytic asymmetric addition of reactive Grignard reagents to ketimines poses a considerable challenge. Herein, a PNP-type **W-Phos** ligand developed recently by our group showed a unique effect toward this end, paving the way to a Cu(I)-catalyzed asymmetric alkylation reaction of *N*-sulfonyl ketimines, delivering optically active α-tertiary amines in high enantioselectivities. This catalytic protocol shows an unprecedented substrate scope with more than 80 examples, not only compatible with benzo five- and six-membered cyclic *N*-sulfonyl ketimines but also suitable for geometrically unstable (*E* or *Z*) acyclic *N*-sulfonyl ketimines. The application potential of the protocol is featured by the extensive presence of α-tertiary amines in natural products and pharmaceutical compounds and also demonstrated by downstream transformations with maintenance of the enantioselectivity.

KEYWORDS: *asymmetric catalysis, alkylation, copper, Grignard reagents, ketimines*

Chiral aza-quaternary stereocenters are known as a class of essential skeletons in biologically active molecules and organic synthons (Scheme 1a, top).[1] Hence, numerous endeavors have been made over the years toward asymmetric synthesis of optically active α-tertiary amines.[2] As a topic of long-standing interest in synthetic chemistry, transition-metal-catalyzed asymmetric addition of organometallic reagents to ketimines represents a straightforward and highly efficient method for constructing optically active aza-quaternary stereocenters. Generally, most advances employed C(sp^2)-organoboron reagents as nucleophiles, and asymmetric arylation,[3] alkenylation,[4] allylation,[5] and propargylation[6] of activated ketimines with the *N*-sulfonyl protecting group have been well established to forge target compounds (Scheme 1b). Despite these significant pioneers, enantioselective alkylation of ketimines using C(sp^3)-organometallic reagents remains hitherto elusive because of the fast β-hydride elimination of alkyl-metal complexes.[7]

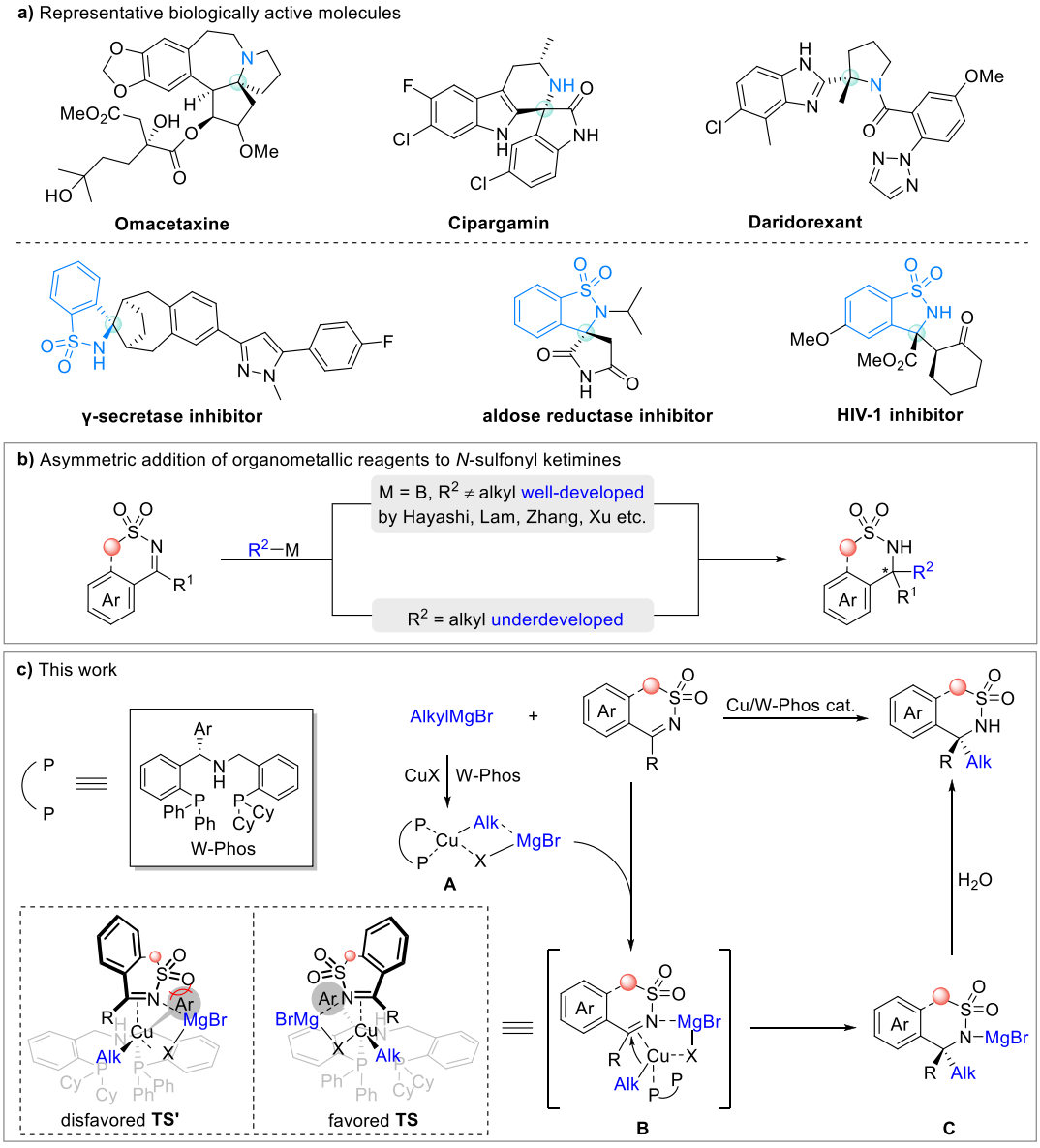
As another classical C(sp^3)-nucleophile, the Grignard reagent is one of the most commonly used alkylating reagents both in laboratory and industry due to its low cost and easy availability.[8] In the past few decades, the asymmetric addition of Grignard reagents to electrophiles such as Michael acceptors,[9] aldehydes,[10] and ketones[11] has been well explored. However, enantioselective alkylation of ketimines with Grignard reagents has rarely been disclosed. The only protocol from Harutyunyan's group capitalized on aryl-alkyl imines as substrates,[12] but not well applicable to aryl-methyl imines, despite the fact that chiral amines bearing methyl groups are vital molecules due to the magic methyl effect.[13] Moreover, enantioselective alkylation of cyclic *N*-sulfonyl ketimines with Grignard reagents are virtually unknown despite the biological activity of the benzosultams products (Scheme 1a, bottom).[14] Therefore, an efficient and general platform for enantioselective alkylation of both cyclic and acyclic *N*-sulfonyl ketimines is still highly desirable.

Recently, our group developed a novel type of **W-Phos** ligands, which enabled Cu-catalyzed asymmetric synthesis of tertiary alcohols through the addition of Grignard reagents to ketones.[15] The unique effect of this ligand was postulated to derive from its conformationally flexible structure, which would temper the reactivity and selectivity in a distinct mechanistic manner. Intrigued by this rewarding entity, we envisioned that the combination of the **W-Phos**/Cu catalyst system and Grignard reagents might pave the way to the enantioselective alkylation of *N*-sulfonyl ketimines for the preparation of chiral α-tertiary amines (Scheme 1c). It was

Received: April 19, 2023
Revised: June 4, 2023
Published: June 20, 2023

https://doi.org/10.1021/acscatal.3c01775
ACS Catal. 2023, 13, 8830−8837

Scheme 1. Representative Biologically Active Molecules and Asymmetric Addition of Organometallic Reagents to *N*-Sulfonyl Ketimines

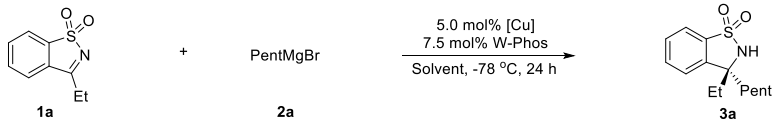


hypothesized that in situ-generated catalytic active species **A** by transmetalation of the Cu precursor with RMgBr would furnish π-Cu(I)-complex **B** with ketimines. A subsequent addition step would thus be facilitated, leading to aza-enolate **C**, followed by hydrolysis to release the final product.[16] The steric hindrance between the sulfonyl moiety of the substrates and the aryl group adjacent to the N-atom of the ligand in complex **B** might force the addition step to proceed in a favorable **TS** to minimize spatial interaction, creating opportunities to produce optically pure products. The easy modifiability on the aryl moiety would provide ample space to achieve high enantioselectivity. Meanwhile, several intrinsic challenges must be addressed: (1) the C═N bond of the ketimines can be easily reduced directly and hydrogenated through Meerwein−Ponndorf−Verley reduction reaction, (2) the high reactivity of Grignard reagents may cause uncatalyzed additions to dominate, and (3) enolization side reaction might occur due to the basicity of Grignard reagents.

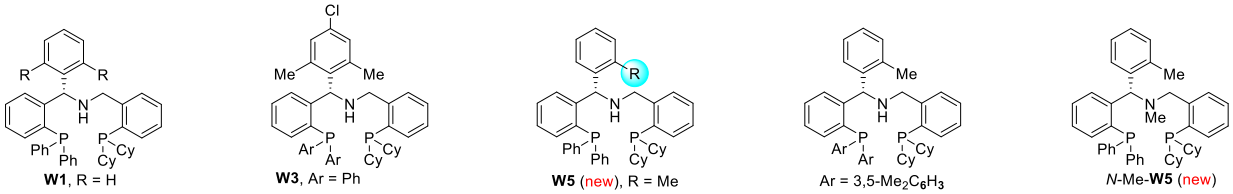
To validate our hypothesis, we initiated our investigation with saccharin-derived cyclic *N*-sulfonyl ketimines **1a** as the pilot substrate and PentMgBr **2a** as an alkylating reagent. Gratifyingly, using CuTc as the precatalyst in an ether solution at −78 °C, the basic version of **W-Phos W1** indeed afforded the desired alkylated product **3a** in 89% yield with 63% ee (Table 1, entry 1). Notably, the reduction product was not observed. This result clearly demonstrates the unique efficacy of **W-Phos** in the catalytic asymmetric alkylation of *N*-sulfonyl ketimines. Encouraged by this outcome, an array of **W-Phos** ligands with modified aryl substituents were tested. Employment of readily obtained ligands **W2**−**W4** markedly improved the enantioselectivities (Table 1, entries 2−4). Excitingly, when removing one methyl group in **W2**, structured as **W5**, the enantiopurity could be significantly increased to 95% ee (Table 1, entry 5). Further increasing the steric hindrance of the aryl substituent at 2-position showed an inferior effect (Table 1, entries 6 and 7). The introduction of methyl groups on the benzene ring of the arylphosphine moiety led to lower

https://doi.org/10.1021/acscatal.3c01775
ACS Catal. 2023, 13, 8830−8837

Table 1. Optimization of the Reaction Conditions



1a 2a 3a



W1, R = H
W2, R = Me
W3, Ar = Ph
W4, Ar = 3,5-$Me_2C_6H_3$
W5 (new), R = Me
W6 (new), R = Et
W7 (new), R = *i*-Pr
Ar = 3,5-$Me_2C_6H_3$ **W8** (new)
N-Me-**W5** (new)

entry[a]	ligand	[Cu]	solvent	yield (%)[b]	ee (%)[c]
1	W1	CuTc	Et_2O	89	63
2	W2	CuTc	Et_2O	72	87
3	W3	CuTc	Et_2O	95	87
4	W4	CuTc	Et_2O	88	88
5	W5	CuTc	Et_2O	90(82)[d]	95
6	W6	CuTc	Et_2O	87	68
7	W7	CuTc	Et_2O	66	56
8	W8	CuTc	Et_2O	71	91
9	N−Me W5	CuTc	Et_2O	58	29
10	W5	CuBr	Et_2O	88	95
11	W5	CuCl	Et_2O	72	93
12	W5	$Cu(CH_3CN)_4BF_4$	Et2O	74	91
13	W5	$Cu(CH_3CN)_4PF_6$	Et2O	84	92
14	W5	CuOAc	Et2O	66	90
15	W5	$Cu(OAc)_2$	Et_2O	73	64
16	W5	CuTc	MTBE	72	61
17	W5	CuTc	CPME	92	65
18	W5	CuTc	THF	n.d[e]	7
19	W5	CuTc	Tol	n.d	26
20	W5	CuTc	DCM	n.d	0
21[f]	W5	CuTc	Et_2O	92	88

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), [Cu] (5.0 mol %), ligand (7.5 mol %), and 3.0 mL of solvent in a Schlenk tube at −78 °C under N_2 for 24 h. [b]Determined by GC using anisole as an internal standard. [c]Determined by HPLC on a chiral stationary phase. [d]Isolated yield in brackets. [e]n.d.: not determined. [f]The reaction was performed at −60 °C.

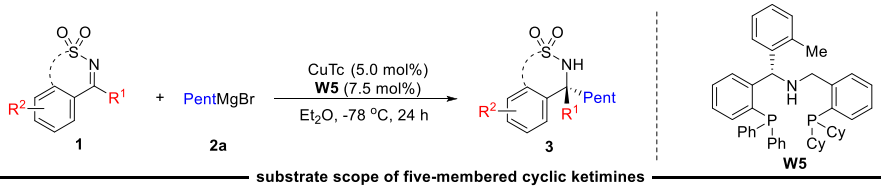
productivity (Table 1, entry 8). Based on our previous experience in research on **Sadphos** ligands, the introduction of substituents on the N-atom might have a dramatic effect on the reactivity.[17] Consequently, ligand **N−Me W5** was examined in the reaction system, and both yield and enantioselectivity decreased significantly (Table 1, entry 9). Noteworthily, other commercially available chiral ligands, including the **Sadphos** ligand kit developed by our group, such as **Ming-Phos**, **Xu-Phos**, **TY-Phos**, **Xiang-Phos**, **Xiao-Phos**, **Wei-Phos**, **PC-Phos**, and **GF-Phos**, were also tested, only leading to inferior results (see Table S1). Subsequent screening of other copper salts as well as solvents gave no better results (Table 1, entries 10−20). Higher temperature was detrimental to the enantioselectivity of the reaction (Table 1, entry 21).

With the optimized conditions in hand, we turned to explore the substrate scope of the reaction. For various 5-membered cyclic ketimines containing alkyl substituents, the reaction proceeded smoothly to afford the products in high yield with excellent enantioselectivities (Scheme 2). When methyl or longer linear alkyl chains were installed, the corresponding products (**3a−3e**) were obtained in moderate to good yields (63−93%) and 90−96% ees. The mild reaction conditions tolerated various α- or β-branches as well as cyclic alkyl groups, affording **3f−3j** in 57−86% yield with 84−92% ees. The enantioselectivities and yields were maintained at a comparable level with the installation of a methyl group at the 5-position of the benzene moiety (**3k** and **3l**). Functional groups such as terminal phenyl, alkene, methoxy, benzyloxy, and acetal motifs remained intact, withstanding the alkylation system smoothly to afford the corresponding products (**3m−3q**: 66−88% yields, 91−97% ees).

Considering the challenges in constructing chiral tertiary α-diarylmethylamines derived from diarylketimines and Grignard reagents,[18] we turned our attention to aryl-substituted 5-membered cyclic *N*-sulfonyl ketimines. Much to our delight, when simple phenyl-substituted ketimine was used as a substrate, the reaction provided **3r** in synthetically useful yield and good ee value. Substrates bearing ortho- and *para*-tolyl substituents were examined, and both the corresponding products **3s** and **3t** were obtained successfully, suggesting the insensitivity to the steric effect. Further substrate exploration suggested that methoxy-substituted aryl substrates were competent ketimines precursors (**3u−3v**). Electron-deficient fluorine-substituted aryl substrates provided the desired

https://doi.org/10.1021/acscatal.3c01775
ACS Catal. 2023, 13, 8830−8837

Scheme 2. Substrate Scope of Cyclic Ketimines[a]



[a]General conditions: **1** (0.2 mmol), **2a** (0.6 mmol), CuTc (5.0 mol %), **W5** (7.5 mol %), and 3.0 mL of Et_2O in a Schlenk tube at −78 °C under N_2 for 24 h. Yields of isolated products are given. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b]**W3** was used as a chiral ligand. [c]1.0 mmol of **2a** was used.

product in 89% yield, albeit with a slight loss of enantioselectivity (**3w**). Disubstituted substrates equipped with both electron-withdrawing and electron-donating aryl groups could be also compatible (**3x**−**3aa**: ≥96% ee). The generality of the reaction was further showcased by the tolerance of the thiophene moiety, as product **3ab** was afforded smoothly. The structure and absolute configuration of the product **3s** were confirmed unambiguously by X-ray crystallographic analysis.[19]

Encouraged by the above results, the asymmetric addition to more challenging and less reactive six-membered cyclic *N*-sulfonyl ketimines was subsequently examined. Gratifyingly, substrates bearing different alkyl groups were all compatible, delivering benzosulfamidates (**3ac**−**3ae**) with remarkable results. The effect of substituents on the aromatic ring was

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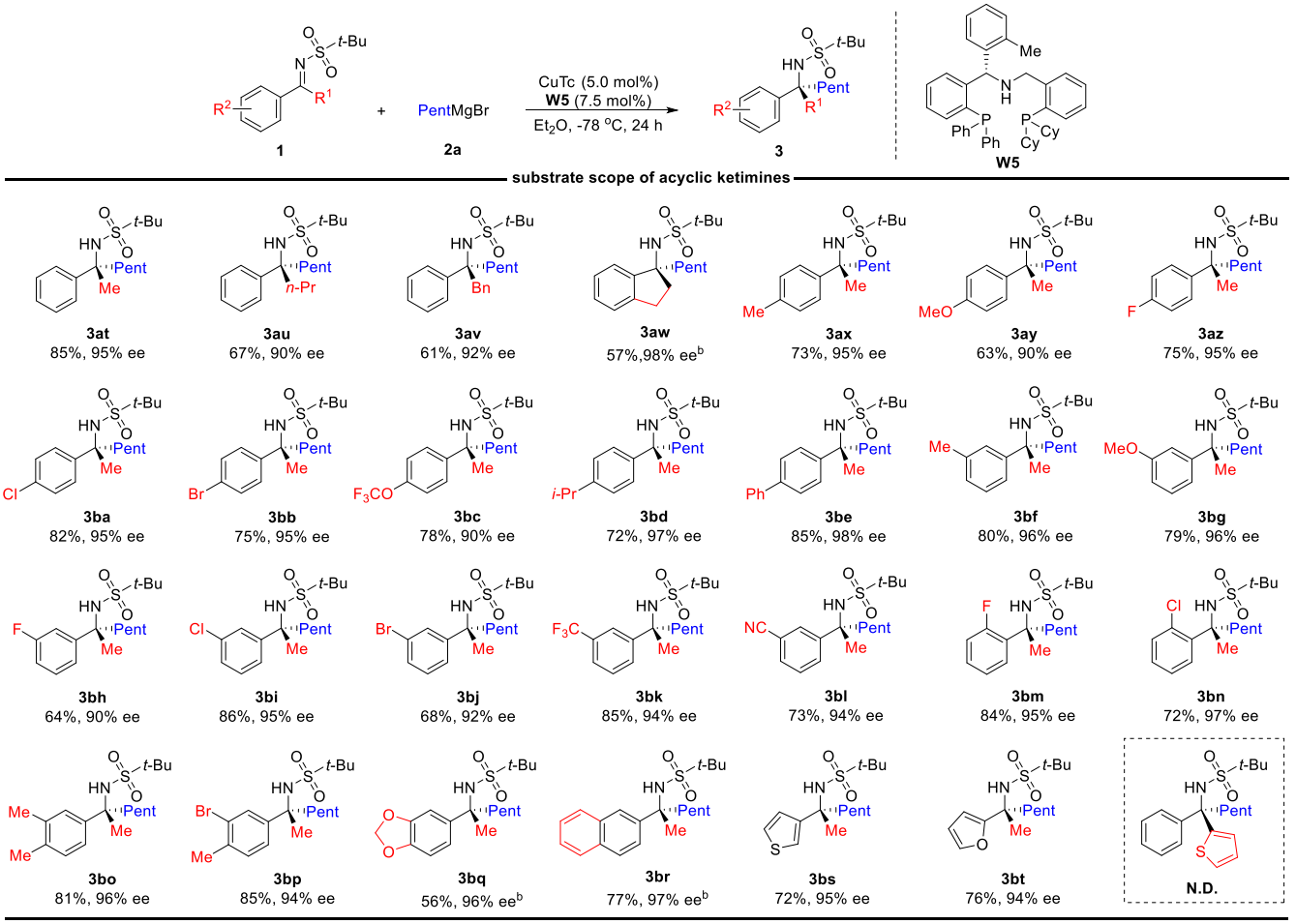
ACS Catal. 2023, 13, 8830−8837

Scheme 3. Substrate Scope of Acyclic Ketimines[a]



[a]General conditions: **1** (0.2 mmol), **2a** (0.6 mmol), CuTc (5.0 mol %), **W5** (7.5 mol %), and 3.0 mL of Et_2O in a Schlenk tube at −78 °C under N_2 for 24 h. Yields of isolated products are given. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b]1.0 mmol of **2a** was used.

further explored. When the electron-donating group (methyl or methoxy) was introduced at C5−C7 positions, the corresponding products (**3af**−**3aj**) were furnished without a hitch in good yields with high ees. Electron-withdrawing group (fluoro, chloro, or bromo)-substituted ketimines were also competent substrates, smoothly affording the desired alkylated products **3ak**−**3aq** with 93−97% ees. The bromo- and chloro-substituents would be useful handles for further manipulations. Notably, naphtho-fused substrates could also be successfully utilized to access **3ar** with 95% ee. Diaryl six-membered cyclic *N*-sulfonyl ketimines were also suitable for the reaction, giving **3as** with 70% yield, albeit with decreased enantioselectivity (71% ee).

Acyclic ketimines are often considered as more challenging substrates because of the unstable geometry (*E* or *Z*) of the ketimines. Indeed, initial attempts with various benzenesulfonamides furnished the desired products in less than 90% enantioselectivities, and non-sulfonyl protecting groups, such as phenyl and benzyl, showed low reactivity (see Table S2). Fortunately, further screening of alkyl sulfonamides led to the identification of ketimine with the bulky *tert*-butylsulfonyl group as an optimal candidate, generating the chiral amine **3at** in 85% yield with 95% ee (Scheme 3). Longer alkyl chains as well as benzyl substituents were both accommodated, leading to the formation of **3au** and **3av** with the same level of enantiomeric purity. The substrate derived from indanone afforded the desired product **3aw** in moderate yield with excellent enantioselectivity (98% ee). Substrates equipped with electron-neutral, -donating, and -withdrawing substituents could all be transformed smoothly, leading to **3ax**−**3bn** in 90−98% ees. Disubstituted amines **3bo**−**3bq** were also obtained in moderate to good yields with excellent enantioselectivities (94−96% ees). Naphthyl and heteroaryl ketimine substrates could be employed as the addition partners with alkyl Grignard reagents to deliver the corresponding products **3br**−**3bt** in good yields and 94−97% ees. Diaryl acyclic *N*-sulfonyl ketimines failed to deliver the desired product under the standard conditions.

The compatibility on Grignard reagents was investigated using ketimines **1b**, **1ac**, and **1at** as substrates (Scheme 4). Linear alkyl groups with different chain lengths could be successfully introduced, furnishing the alkylated α-tertiary amines in moderate to high yields and good ee values (**3bu**−**3bx** and **3cb**−**3cj**). The absolute configuration of the acyclic products was confirmed by the known compound **3ch**.[12] More sterically hindered β-branched Grignard reagents resulted in decreased enantioselectivity (**3by**: 75% ee). Notably, functionalized Grignard reagents bearing terminal phenyl or alkene

https://doi.org/10.1021/acscatal.3c01775
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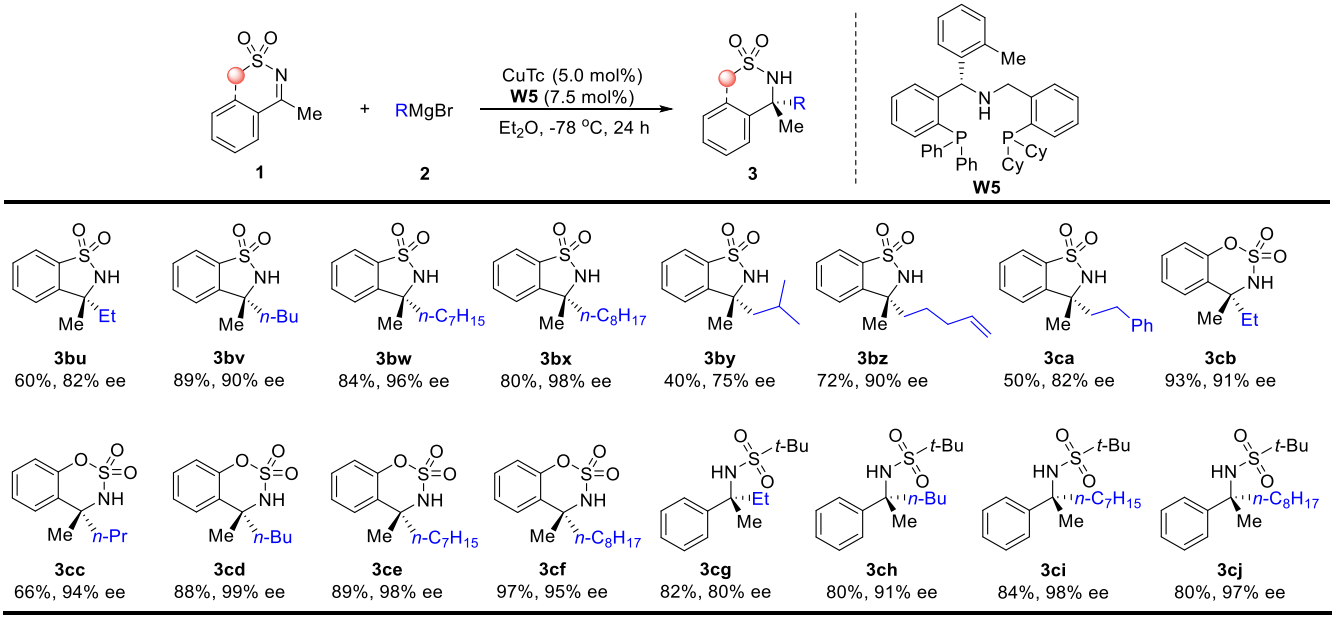
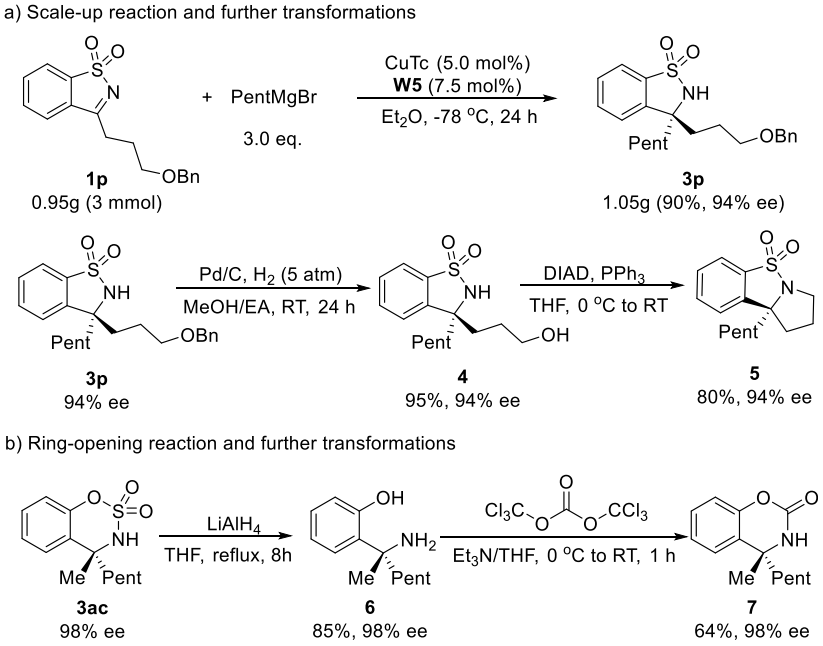
Scheme 4. Substrate Scope of Grignard Reagents[a]



[a]General conditions: **1** (0.2 mmol), **2** (0.6 mmol), CuTc (5.0 mol %), **W5** (7.5 mol %), and 3.0 mL of Et_2O in a Schlenk tube at −78 °C under N_2 for 24 h. Yields of isolated products are given. Enantiomeric excess was determined by HPLC on a chiral stationary phase.

Scheme 5. Scale-Up Reaction and Further Transformations



moieties reacted smoothly under the standard conditions, delivering the adducts in 50−72% yields with 82−90% ees (**3bz** and **3ca**). The asymmetric addition of relatively low reactive MeMgBr has been a long-standing challenge in this field,[9g,11a,12] and our protocol furnished a promising outcome (*ent*-**3bu**: 47% ee, 51% yield, see the Supporting Information for more details). Neither allyl nor phenyl-magnesium bromide was a suitable candidate, and only racemic addition products were formed.

To demonstrate the potential synthetic utility of this protocol, the scale-up reaction of cyclic *N*-sulfonyl ketimines **1p** with pentylmagnesium bromide was carried out, and the product **3p** was isolated in 90% yield with 94% ee (Scheme 5a). The benzosultams **3p** could be further transferred to alcohol **4** through Pd/C hydrogenation-mediated debenzylation. Downstream Mitsunobu cyclization provided the tricyclic product **5** in good yield with complete preservation of enantiopurity. In the presence of $LiAlH_4$, chiral benzosulfamidate **3ac** (98% ee) underwent an efficient ring-opening reaction by the removal of the SO_2 group, successfully leading to the formation of the corresponding 2-hydroxyphenylmethylamine intermediate **6**, which was further treated with triphosgene/Et_3N to produce benzoxazinone derivative **7**

https://doi.org/10.1021/acscatal.3c01775
ACS Catal. 2023, 13, 8830−8837

with the maintenance of the high enantioselectivity (Scheme 5b).

In summary, an efficient catalytic asymmetric alkylation of both cyclic and acyclic *N*-sulfonyl ketimines with alkyl Grignard reagents has been successfully developed. The key to the success was the ancillary of a newly identified PNP-type ligand **W-Phos** and copper catalyst. Both five- and six-membered cyclic and acyclic *N*-sulfonyl ketimines were amenable to this alkylation strategy, affording a wide array of valuable chiral aza-quaternary stereocenters (α-tertiary amines) in good yields with high enantioselectivities. Gram-scale reaction and further derivatization showcased the application potential of this protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c01775.

Experimental details, characterization data, X-ray crystallographic data for **3s** (CCDC 2181586), HPLC spectra, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the funding support of the National Key R&D Program of China (2021YFF0701600), NSFC (22031004, 21901043, and 21921003), and Shanghai Municipal Education Commission (20212308).

■ REFERENCES

(1) Mailyan, A. K.; Eickhoff, J. A.; Minakova, A. S.; Gu, Z.; Lu, P.; Zakarian, A. Cutting-Edge and Time-Honored Strategies for Stereoselective Construction of C−N Bonds in Total Synthesis. *Chem. Rev.* **2016**, *116*, 4441−4557.

(2) For selected reviews, see: (a) Denissova, I.; Barriault, L. Stereoselective Formation of Quaternary Carbon Centers and Related Functions. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Shibasaki, M.; Kanai, M. Asymmetric Synthesis of Tertiary Alcohols and α-Tertiary Amines via Cu-Catalyzed C−C Bond Formation to Ketones and Ketimines. *Chem. Rev.* **2008**, *108*, 2853−2873. (c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. Catalytic Enantioselective Formation of C−C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. *Chem. Rev.* **2011**, *111*, 2626−2704.

(3) (a) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. Rhodium-Catalyzed Asymmetric Arylation of N-Tosyl Ketimines. *J. Am. Chem. Soc.* **2010**, *132*, 13168−13169. (b) Nishimura, T.; Noishiki, A.; Chit Tsui, G.; Hayashi, T. Asymmetric Synthesis of (Triaryl)methylamines by Rhodium-Catalyzed Addition of Arylboroxines to Cyclic *N*-Sulfonyl Ketimines. *J. Am. Chem. Soc.* **2012**, *134*, 5056−5059. (c) Jiang, C.; Lu, Y.; Hayashi, T. High Performance of a Palladium Phosphinooxazoline Catalyst in the Asymmetric Arylation of Cyclic *N*-Sulfonyl Ketimines. *Angew. Chem., Int. Ed.* **2014**, *53*, 9936−9939. (d) Wang, H.; Jiang, T.; Xu, M. H. Simple Branched Sulfur−Olefins as Chiral Ligands for Rh-Catalyzed Asymmetric Arylation of Cyclic Ketimines: Highly Enantioselective Construction of Tetrasubstituted Carbon Stereocenters. *J. Am. Chem. Soc.* **2013**, *135*, 971−974. (e) Jiang, T.; Wang, Z.; Xu, M. H. Rhodium-Catalyzed Asymmetric Arylation of Cyclic *N*-Sulfonyl Aryl Alkyl Ketimines: Efficient Access to Highly Enantioenriched α-Tertiary Amines. *Org. Lett.* **2015**, *17*, 528−531. (f) Yang, G.; Zhang, W. A. A Palladium-Catalyzed Enantioselective Addition of Arylboronic Acids to Cyclic Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540−7544. (g) Kong, J.; McLaughlin, M.; Belyk, K.; Mondschein, R. Enantioselective Rh(I)-Catalyzed Addition of Arylboronic Acids to Cyclic Ketimines. *Org. Lett.* **2015**, *17*, 5520−5523.

(4) (a) Luo, Y.; Carnell, A. J.; Lam, H. W. Enantioselective Rhodium-Catalyzed Addition of Potassium Alkenyltrifluoroborates to Cyclic Imines. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762−6766. (b) Quan, M.; Wang, X.; Wu, L.; Gridnev, I. D.; Yang, G.; Zhang, W. Ni(II)-Catalyzed Asymmetric Alkenylations of Ketimines. *Nat. Commun.* **2018**, *9*, 2258−2268.

(5) (a) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. Enantioselective Rhodium-Catalyzed Nucleophilic Allylation of Cyclic Imines with Allylboron Reagents. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309−8313. (b) Hepburn, H. B.; Lam, H. W. The Isomerization of Allylrhodium Intermediates in the Rhodium-Catalyzed Nucleophilic Allylation of Cyclic Imines. *Angew. Chem., Int. Ed.* **2014**, *53*, 11605−11610. (c) Maciá, E.; Foubelo, F.; Yus, M. Indium-mediated diastereoselective allylation of *N*-tert-butanesulfinyl imines derived from α-ketoesters. *Tetrahedron* **2016**, *72*, 6001−6010. (d) Wu, L.; Shao, Q.; Yang, G.; Zhang, W. Cobalt-Catalyzed Asymmetric Allylation of Cyclic Ketimines. *Chem.—Eur. J.* **2018**, *24*, 1241−1245.

(6) Osborne, C. A.; Endean, T. B.; Jarvo, E. R. Silver-Catalyzed Enantioselective Propargylation Reactions of *N*−Sulfonylketimines. *Org. Lett.* **2015**, *17*, 5340−5343.

(7) (a) Cárdenas, D. J. Towards Efficient and Wide-Scope Metal-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018−3020. (b) Yang, Y.; Tsien, J.; Ben David, A.; Hughes, J. M. E.; Merchant, R. R.; Qin, T. Practical and Modular Construction of C(sp^3)-Rich Alkyl Boron Compounds. *J. Am. Chem. Soc.* **2021**, *143*, 471−480.

(8) (a) Richey, H. G. *Grignard Reagents—New Developments*; Wiley: Chichester, U.K., 2000; pp 165−183. (b) Seyferth, D. The Grignard Reagents. *Organometallics* **2009**, *28*, 1598−1605.

(9) (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. *Chem. Rev.* **2008**, *108*, 2796−2823. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. Catalytic Asymmetric Conjugate Addition and Allylic Alkylation with Grignard Reagents. *Chem. Rev.* **2008**, *108*, 2824−2852. (c) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.;

Alexakis, A. Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers. *J. Am. Chem. Soc.* **2006**, *37*, 8416−8417. (d) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. Cu(I) Tol-BINAP-Catalyzed Enantioselective Michael Reactions of Grignard Reagents and Unsaturated Esters. *J. Am. Chem. Soc.* **2007**, *129*, 276−277. (e) Hénon, H.; Mauduit, M.; Alexakis, A. Regiodivergent 1,4 Versus 1,6 Asymmetric Copper−Catalyzed Conjugate Addition. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122−9124. (f) Fañanás-Mastral, M.; Feringa, B. L. Copper-Catalyzed Regio- and Enantioselective Synthesis of Chiral Enol Acetates and β-Substituted Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 13152−13153. (g) Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R. Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic *N*-Heterocycles. *Science* **2016**, *352*, 433−437. (h) Jumde, R. P.; Lanza, F.; Pellegrini, T.; Harutyunyan, S. R. Highly Enantioselective Catalytic Synthesis of Chiral Pyridines. *Nat. Commun.* **2017**, *8*, 2058−2067. (i) Rodríguez-Fernández, M.; Yan, X.; Collados, J. F.; White, P. B.; Harutyunyan, S. R. Lewis Acid Enabled Copper-Catalyzed Asymmetric Synthesis of Chiral β-Substituted Amides. *J. Am. Chem. Soc.* **2017**, *139*, 14224−14231. (j) Guo, Y.; Kootstra, J.; Harutyunyan, S. R. Catalytic Regio- and Enantioselective Alkylation of Conjugated Dienyl Amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 13547−13550. (k) Guo, Y.; Harutyunyan, S. R. Highly Enantioselective Catalytic Addition of Grignard Reagents to *N*-Heterocyclic Acceptors. *Angew. Chem., Int. Ed.* **2019**, *58*, 12950−12954. (l) Yan, X.; Harutyunyan, S. R. Catalytic Enantioselective Addition of Organometallics to Unprotected Carboxylic Acids. *Nat. Commun.* **2019**, *10*, 3402−3411. (m) Yan, X.; Ge, L.; Castiñeira Reis, M.; Harutyunyan, S. R. Nucleophilic Dearomatization of *N*-Heteroaromatics Enabled by Lewis Acids and Copper Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 20247−20256.

(10) (a) Muramatsu, Y.; Harada, T. Catalytic Asymmetric Alkylation of Aldehydes with Grignard Reagents. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088−1090. (b) Muramatsu, Y.; Harada, T. Catalytic Asymmetric Aryl Transfer Reactions to Aldehydes with Grignard Reagents as the Aryl Source. *Chem.—Eur. J.* **2008**, *14*, 10560−10563. (c) Da, C.-S.; Wang, J.-R.; Yin, X.-G.; Fan, X.-Y.; Liu, Y.; Yu, S.-L. Highly Catalytic Asymmetric Addition of Deactivated Alkyl Grignard Reagents to Aldehydes. *Org. Lett.* **2009**, *11*, 5578−5581. (d) Fernández-Mateos, E.; Maciá, B.; Yus, M. Catalytic Enantioselective Addition of Alkyl Grignard Reagents to Aliphatic Aldehydes. *Adv. Synth. Catal.* **2013**, *355*, 1249−1254.

(11) (a) Madduri, A. V.; Harutyunyan, S. R.; Minnaard, A. J. Asymmetric Copper-Catalyzed Addition of Grignard Reagents to Aryl Alkyl Ketones. *Angew Chem. Int. Ed. Engl.* **2012**, *51*, 3164−3167. (b) Rong, J.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R. Catalytic Asymmetric Alkylation of Acylsilanes. *Angew Chem. Int. Ed. Engl.* **2015**, *54*, 3038−3042. (c) Bieszczad, B.; Gilheany, D. G. Asymmetric Grignard Synthesis of Tertiary Alcohols through Rational Ligand Design. *Angew. Chem., Int. Ed.* **2017**, *56*, 4272−4276. (d) Monasterolo, C.; Müller-Bunz, H.; Gilheany, D. G. Very Short Highly Enantioselective Grignard Synthesis of 2,2-Disubstituted Tetrahydrofurans and Tetrahydropyrans. *Chem. Sci.* **2019**, *10*, 6531−6538. (e) Kavanagh, S. E.; Gilheany, D. G. Harnessing the Power of the Asymmetric Grignard Synthesis of Tertiary Alcohols: Ligand Development and Improved Scope Exemplified by One-Step Gossonorol Synthesis. *Org. Lett.* **2020**, *22*, 8198−8203. (f) Monasterolo, C.; O'Gara, R.; Kavanagh, S. E.; Byrne, S. E.; Bieszczad, B.; Murray, O.; Wiesinger, M.; Lynch, R. A.; Nikitin, K.; Gilheany, D. G. Asymmetric Addition of Grignard Reagents to Ketones: Culmination of the Ligand-Mediated Methodology Allows Modular Construction of Chiral Tertiary Alcohols. *Chem. Sci.* **2022**, *13*, 6262−6269.

(12) Ortiz, P.; Collados, J. F.; Jumde, R. P.; Otten, E.; Harutyunyan, S. R. Copper−Catalyzed Enantioselective Alkylation of Enolizable Ketimines with Organomagnesium Reagents. *Angew. Chem., Int. Ed.* **2017**, *56*, 3041−3044.

(13) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246.

(14) (a) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. Novel Spirosuccinimides with Incorporated Isoindolone and Benzisothiazole 1,1-Dioxide Moieties as Aldose Reductase Inhibitors and Antihyperglycemic Agents. *J. Med. Chem.* **1992**, *35*, 4613−4627. (b) Supuran, C. T.; Casini, A.; Scozzafava, A. Protease Inhibitors of the Sulfonamide Type: Anticancer, Antiinflammatory, and Antiviral Agents. *Med. Res. Rev.* **2003**, *23*, 535−558. (c) Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R. Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. Sultam Hydroxamates as Novel Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **2004**, *47*, 2981−2983. (d) Kiefer, L.; Gorojankina, T.; Dauban, P.; Faure, H.; Ruat, M.; Dodd, R. H. Design and Synthesis of Cyclic Sulfonamides and Sulfamates as New Calcium Sensing Receptor Agonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7483−7487. (e) Lad, N. P.; Kulkarni, S.; Sharma, R.; Mascarenhas, M.; Kulkarni, M. R.; Pandit, S. S. Piperlongumine Derived Cyclic Sulfonamides (Sultams): Synthesis and in Vitro Exploration for Therapeutic Potential Against HeLa Cancer Cell Lines. *Eur. J. Med. Chem.* **2017**, *126*, 870−878.

(15) Luo, W.; Zhang, L.-M.; Zhang, Z.-M.; Zhang, J. Synthesis of W−Phos Ligand and Its Application in the Copper-Catalyzed Enantioselective Addition of Linear Grignard Reagents to Ketones. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202204443.

(16) (a) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to α, β-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2006**, *128*, 9103−9118. (b) Rong, J.; Pellegrini, T.; Harutyunyan, S. R. Synthesis of Chiral Tertiary Alcohols by Cu^{I}-Catalyzed Enantioselective Addition of Organomagnesium Reagents to Ketones. *Chem.—Eur. J.* **2016**, *22*, 3558−3570. (c) Collados, J. F.; Solà, R.; Harutyunyan, S. R.; Maciá, B. Catalytic Synthesis of Enantiopure Chiral Alcohols via Addition of Grignard Reagents to Carbonyl Compounds. *ACS Catal.* **2016**, *6*, 1952−1970.

(17) (a) Zhu, C.; Chu, H.; Li, G.; Ma, S.; Zhang, J. Pd-Catalyzed Enantioselective Heck Reaction of Aryl Triflates and Alkynes. *J. Am. Chem. Soc.* **2019**, *141*, 19246−19251. (b) Pan, Z.; Li, W.; Zhu, S.; Liu, F.; Wu, H. H.; Zhang, J. Palladium/TY-Phos-Catalyzed Asymmetric Intermolecular α-Arylation of Aldehydes with Aryl Bromides. *Angew. Chem., Int. Ed.* **2021**, *60*, 18542−18546. (c) Wang, Y.; Wang, L.; Chen, M.; Tu, Y.; Liu, Y.; Zhang, J. Palladium/Xu-Phos-Catalyzed Asymmetric Carboamination towards Isoxazolidines and Pyrrolidines. *Chem. Sci.* **2021**, *12*, 8241−8245. (d) Xu, B.; Ji, D.; Wu, L.; Zhou, L.; Liu, Y.; Zhang, Z.-M.; Zhang, J. Palladium/Xu-Phos-Catalyzed Enantioselective Cascade Heck/Remote C(sp^2)-H Alkylation Reaction. *Chem* **2022**, *8*, 836−849.

(18) Desmarchelier, A.; Ortiz, P.; Harutyunyan, S. R. Tertiary α-Diarylmethylamines Derived from Diarylketimines and Organomagnesium Reagents. *Chem. Commun.* **2015**, *51*, 703−706.

(19) CCDC 2181596 (**3s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

https://doi.org/10.1021/acscatal.3c01775
ACS Catal. 2023, 13, 8830−8837