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Copper(I)-Catalyzed Asymmetric Vinylogous Aldol-Type Reaction of Allylazaarenes

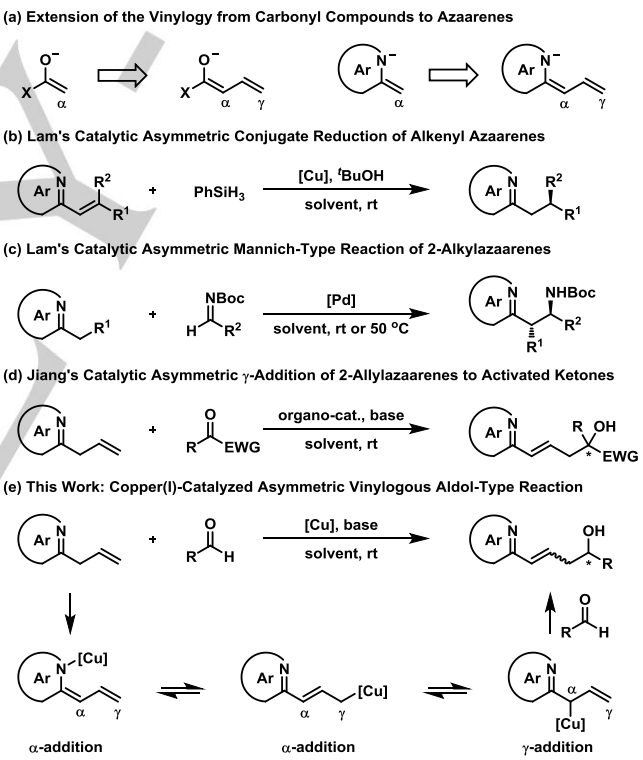
Si-Qing Wang,[+] Zong-Ci Liu,[+] Wen-Jun Yue,[+] and Liang Yin*

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry (SIOC)

Abstract: *A vinylogous aldol-type reaction of allylazaarenes and aldehydes is disclosed, which affords a series of chiral γ-hydroxyl-α,β-unsaturated azaarenes in moderate to excellent yields with high to excellent regio- and enantioselectivities. With (R,R_P)-TANIAPHOS and (R,R)-QUINOXP* as the ligand, the carbon-carbon double bond in the products is generated in (E)-form. With (R)-DTBM-SEGPHOS as the ligand, (Z)-form carbon-carbon double bond is formed in the major product. In this vinylogous reaction, aromatic, α,β-unsaturated, and aliphatic aldehydes are competent substrates. Moreover, a variety of azaarenes, such as pyrimidine, pyridine, pyrazine, quinoline, quinoxaline, quinazoline, and benzo[d]imidazole are well tolerated. At last, the chiral vinylogous product is demonstrated as a suitable Michael acceptor towards CuI-catalyzed nucleophilic addition with organomagnesium reagents.*

The vinylogous principle in organic chemistry defines the transmission of the nucleophilicity of a functional group to distal positions through interposed conjugated carbon-carbon double bonds in a molecule.[1] Usually, the functional group is a carbonyl moiety, including aldehyde, ketone, ester, and amide. Due to the synthetic versatility of the vinylogous product, which contains a carbonyl group, a conjugated carbon-carbon double bond, and a secondary alcohol (vinylogous aldol reaction), an amine/amide (vinylogous Mannich reaction), or an additional carbonyl group (vinylogous Michael reaction), vinylogous reactivity is frequently employed in the efficient asymmetric synthesis of complex natural products and pharmaceutically active compounds.[2] Since azaarenes are analogues of carbonyl compounds, it is envisioned that the vinylogy on carbonyl compounds would be extended to azaarenes (Scheme 1a). Thus, the nucleophilicity of α-position of the anion generated from unsaturated azaarenes would be transmitted to γ-position, which leads to new vinylogous reactions.

In the vinylogous aldol reaction of linear unsaturated nucleophiles, there are two challenging issues. One is the control of the regioselectivity as α-addition is favored in many cases.[3,4] For example, in the copper(I)-catalyzed aldol reaction of α-vinyl thioamides and α-vinyl 7-azaindoline amide, α-addition dominated the aldol reaction.[4d,4e] The other is the control of the geometry of the conjugated carbon-carbon double bond in the vinylogous aldol products. For example, in the copper(I)-catalyzed asymmetric vinylogous aldol reaction of dienolsilanes and aldehydes, the products were obtained as a mixture of (*E*)-form and lactone derived from (*Z*)-form.[5] Such a tendency was also observed in the copper(I)-catalyzed direct vinylogous aldol reaction of aldehydes and ester of but-3-enoic acid.[6] Fortunately, a one-pot strategy including vinylogous aldol reaction, Ph_2PMe-promoted isomerization of (*E*)-form to (*Z*)-form, and intramolecular transesterification, could be employed to afford lactone as the only product.[6] However, the above two issues remain as concerns in the vinylogous aldol reaction.



Scheme 1. Introduction and Our Work in the Catalytic Asymmetric Vinylogous Aldol-Type Reaction of Allylazaarenes.

Azaarenes are common structural units in bioactive alkaloids and medicinal molecules,[7] which act through coordination of the nitrogen atoms to the active sites of biomolecules, such as enzymes.[8] Thus there is a growing interest in the asymmetric synthesis of chiral molecules containing azaarenes.[9] Previously, azaarenes served as nonparticipating bystanders in organic reactions. Recently, it has been disclosed that azaarenes worked as electron-deficient functional groups,[10] which led to an array of appealing catalytic asymmetric reactions.[11-15] For example, α,β-unsaturated azaarenes were employed by the Lam

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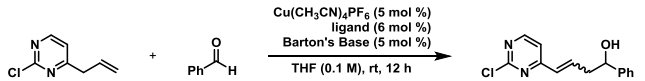
group as efficient Michael acceptors towards copper(I)-catalyzed asymmetric conjugate reduction (Scheme 1b).[11a] Later, the same group disclosed palladium(II)-catalyzed asymmetric additions of 2-alkylazaarenes bearing strong electron-withdrawing groups to *N*-Boc aldimines and nitroalkenes (Scheme 1c).[11d] Generally speaking, hydrogens at the α-position of azaarenes are weakly acidic and thus the azaarenes are very reluctant to react with electrophiles except at high temperatures.[16] Therefore, it is envisioned that the α-protons of allylazaarenes would be more acidic, which would allow facile deprotonation by an organic base and thus enable catalytic asymmetric vinylogous nucleophilic addition to electrophiles.[17] Jiang and co-workers reported a leading enantioselective γ-selective addition of 2-allylazaarenes to activated ketones with powerful bifunctional organocatalysts (Scheme 1d).[18]



entry	ligand	yield[b]	*E*/*Z*[b]	ee of *E* (%)[c]	ee of *Z* (%)[c]
1	(*R*)-BINAP	80	8/1	31	-
2	(*R*)-Tol-BINAP	86	5/1	44	-
3	(*R*)-SEGPHOS	72	12/1	55	-
4	(*R*)-DTBM-SEGPHOS	64	1/5	55	94
5	(*R*,*R*)-Ph-BPE	78	4/1	56	-
6	(*R*,*R*)-QUINOXP*	78	20/1	68	-
7	(*R*)-(*S*)-JOSIPHOS	81	>20/1	-47	-
8	(*R*,R_P)-TANIAPHOS	60	>20/1	-81	-
9[d]	(*R*,R_P)-TANIAPHOS	71	>20/1	-81	-
10[d,e]	(*R*,R_P)-TANIAPHOS	93	>20/1	-92	-
11[d,e]	(*R*)-DTBM-SEGPHOS	84	1/9	-	94
12[d,f]	(*R*)-DTBM-SEGPHOS	22	1/7	-	95
13[g]	-	trace	-	-	-

[a] **1a**: 0.6 mmol, **2a**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis of reaction crude mixture using CH_3NO_2 as an internal standard. [c] Determined by chiral-stationary-phase HPLC analysis. [d] 5 mol % $Cu(CH_3CN)_4BF_4$ used. [e] 0 °C. 24h. [f] -20 °C. 24 h. α-Adducts were generated in 36% yield. [g] The reation was performed without copper(I) salt and ligand. Barton's Base = 2-^{t}Butyl-1,1,3,3-tetramethylguanidine.

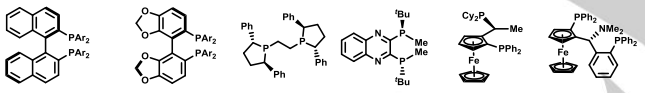
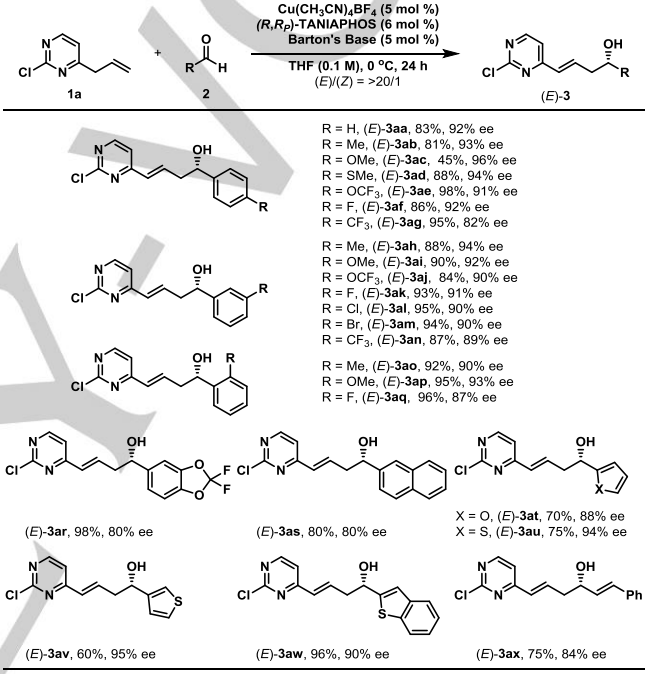


Table 1. Optimization of Reaction Conditions.[a]

Actually, the coordinating nature of the azaarenes would potentially deactivate the transition metal catalysts as stoichiometric amount of starting materials or products containing azaarene moiety are present in the catalytic reaction.[19] Moreover, there are also worrying issues in the catalytic asymmetric addition of allylazaarenes to electrophiles, such as aldehydes. The first is the regioselectivity issue. Is it possible to achieve a copper(I)-catalyzed asymmetric vinylogous aldol reaction in high regioselectivity (γ-addition *vs* α-addition)? The second is the geometry issue of the carbon-carbon double bond in vinylogous products. Is it possible to achieve both (*E*)-form and (*Z*)-form vinylogous products? With these questions in mind, we targeted aldehydes as the electrophiles and attempted to develop a copper(I)-catalyzed asymmetric vinylogous aldol-type reaction of allylazaarenes and aldehydes (Scheme 1e).

The reaction between 4-allyl-2-chloropyrimidine (**1a**) and benzaldehyde (**2a**) was investigated for the optimized reaction conditions in the presence of 5 mol % copper(I)-bisphosphine complex and 5 mol % Barton's Base. With (*R*)-BINAP as the ligand, the vinylogous addition occurred smoothly to afford product **3aa** in 80% yield with 8/1 (*E*)/(*Z*) ratio and 31% ee for the (*E*)-isomer. Switching to (*R*)-Tol-BINAP led to slight increases in both yield and enantioselectivity. However, the (*E*)/(*Z*) ratio decreased to 5/1. The reaction with (*R*)-SEGPHOS gave better (*E*)/(*Z*) ratio and enantioselectivity. Notably, the reaction with (*R*)-DTBM-SEGPHOS furnished (*Z*)-**3aa** as the major isomer and 94% ee was obtained for (*Z*)-**3aa**. (*R*,*R*)-Ph-BPE did not give improved results.



[a] **1**: 0.6 mmol, **2**: 0.2 mmol. Isolated yield. The enantioselectivity was determined by chiral-stationary-phase HPLC analysis.

Table 2. Substrate Scope of Aromatic Aldehydes.[a]

Fortunately, (*E*)-**3aa** was generated in 20/1 (*E*)/(*Z*) ratio with 68% ee in the reaction with (*R*,*R*)-QUINOXP*. Utilization of (*R*)-(*S*)-JOSIPHOS and (*R*,R_P)-TANIAPHOS further enhanced the (*E*)/(*Z*) ratio. In the case of (*R*,R_P)-TANIAPHOS, (*E*)-**3aa** was produced in 81% ee. The reaction with $Cu(CH_3CN)_4BF_4$ resulted in higher yield than the one with $Cu(CH_3CN)_4PF_6$. Performing the reaction with $Cu(CH_3CN)_4BF_4$ at 0 °C further enhanced both yield and enantioselectivity (93%, 92% ee). The (*Z*)-selective reaction with (*R*)-DTBM-SEGPHOS was set up at 0 °C, which provided (*Z*)-**3aa** in 84% yield with 9/1 (*Z*)/(*E*) ratio and 94% ee. Further lowering the reaction temperature to -20 °C was not fruitful as α-products were generated in 36% yield. Without copper(I)-complex, the vinylogous addition proceeded reluctantly as only trace **3aa** was detected. Moreover, the reaction with (*R*,R_P)-TANIAPHOS and **1a** less than 3 equiv delivered (*E*)-**3aa** in reduced yield with maintained enantioselectivity (for the details, see SI).

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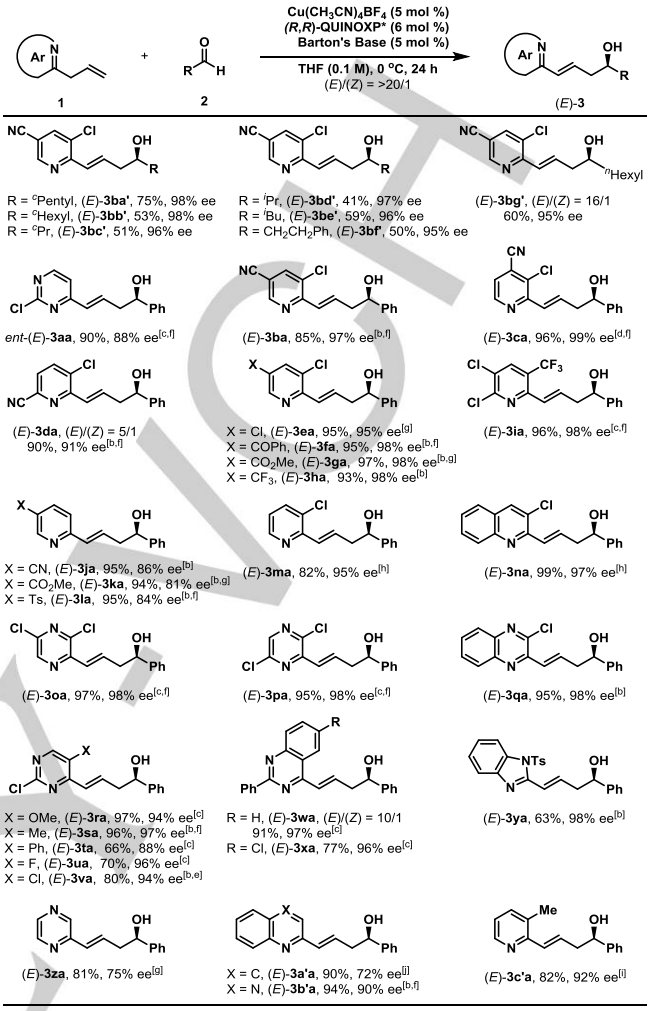
Under the optimized reaction conditions, the substrate scope of aromatic aldehydes in the (*E*)-selective addition was studied as shown in Table 2. At the *para*-position of the phenyl group, strong electron-donating group (such as methoxyl) led to slightly higher enantioselectivity but significantly attenuated yield ((*E*)-**3ac**, 45%, 96% ee). Strong electron-withdrawing group (such as trifluoromethyl) led to higher yield but decreased enantioselectivity ((*E*)-**3ag**, 95%, 82% ee). At the *meta*-position, the substituents were well tolerated with desirable results ((*E*)-**3ah**-(*E*)-**3an**, 84%-95%, 89-94% ee). The aldehydes containing an *ortho*-group were competent substrates to provide the corresponding products in satisfactory results ((*E*)-**3ao**-(*E*)-**3aq**, 92%-96%, 87%-93% ee). Disubstituted benzaldehyde (**2r**), 2-naphthaldehyde (**2s**), and heteroaromatic aldehydes (**2t**-**2w**) were suitable substrates as well ((*E*)-**3ar**-(*E*)-**3aw**, 60%-98%, 80%-95% ee). Moreover, α,β-unsaturated aldehyde (**2x**) underwent 1,2-addtion predominantly, which was transformed to (*E*)-**3ax** in 75% yield with 84% ee. The absolute configuration of (*E*)-**3aa** was determined to be *S* by its transformation to a known compound (for the details, see SI). Analogously, the stereochemistry in other products was assigned tentatively.

The scope of aliphatic aldehydes was investigated with allylazaarenes **1b** as the pronucleophile and (*R*,*R*)-QUINOXP* as the ligand at 0 ^{o}C (Table 3). Usually, the aliphatic aldehydes are challenging electrophiles at basic conditions as α-deprotonation easily occurs to induce some side reactions, including self-aldol reaction. Fortunately, cycloalkyl aldehydes (**2a′**-**2c′**), α-branched aldehyde (**2d′**), β-branched aldehyde (**2e′**), γ-branched aldehyde (**2f′**), and linear aldehyde (**2g′**) served as acceptable substrates to give the desired products in moderate yields with excellent enantioselectivity ((*E*)-**3ba′**-(*E*)-**3bg′**, 41%-75%, 95%-98% ee). Subsequently, with (*R*,*R*)-QUINOXP* as the ligand, the investigation on the scope of allylazaarenes was carried out. Evidently, the electronic biases of the azaarenes lead to different acidity of the α-protons in allylazaarenes. Therefore, different amount of Barton's Base was used to enable efficient deprotonation and different reaction temperature was employed to achieve satisfactory yield and enantioselectivity.

The reaction of 4-allyl-2-chloropyrimidine (**1a**) and benzaldehyde (**2a**) generated *ent*-(*E*)-**3aa** in 90% yield with 88% ee. 2-Allylpyridines bearing two or three electron-withdrawing groups (**1b**-**1i**) were appropriate substrates to afford the corresponding products in high to excellent yields with excellent enantioselectivity ((*E*)-**3ba**-(*E*)-**3ia**, 85%-97%, 91%-99% ee). However, in the reaction with **1d**, the (*E*)/(*Z*) ratio was only 5/1. Moreover, 2-allylpyridines with a strong electron-withdrawing group, such as **1j**, **1k**, and **1l** underwent the vinylogous aldol-type reaction smoothly in excellent yields with high enantioselectivity ((*E*)-**3ja**-(*E*)-**3la**, 94%-95%, 81%-86% ee). Notably, 2-allyl-3-Cl-pyridine (**1m**) and 2-allyl-3-Cl-quinoline (**1n**) also took part in the reaction and provided pleasing results ((*E*)-**3ma**-(*E*)-**3na**, 82-99%, 95-97% ee). Other allyl heterocycles containing electron-withdrawing groups, such as pyrazine, quinoxaline, pyrimidine, quinazoline and benzo[*d*]imidazole (**1o**-**1y**), were also well tolerated with satisfying reaction results ((*E*)-**3oa**-(*E*)-**3ya**, 63%-97%, 88%-98% ee).

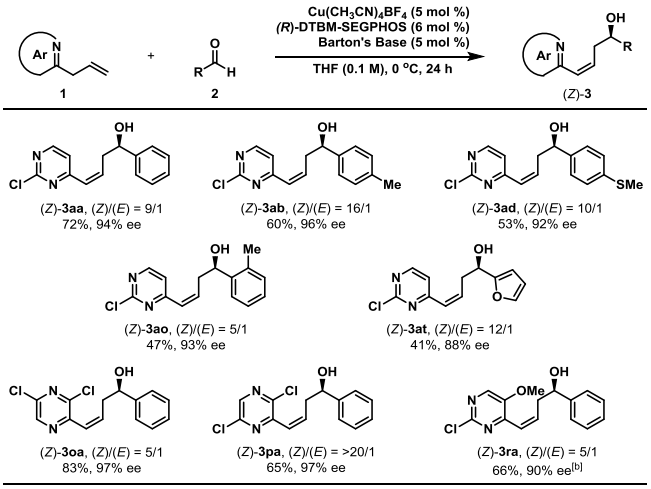
Table 3. Substrate Scopes of Both Aliphatic Aldehydes and Allylazaarenes.[a]



[a] **1**: 0.6 mmol, **2**: 0.2 mmol. The (*E*)/(*Z*) ratio was determined by ^{1}H NMR analysis of the crude mixture. Isolated yield. The enantioselectivity was determined by chiral-stationary-phase HPLC analysis. [b] -20 ^{o}C. [c] -40 ^{o}C. [d] -60 ^{o}C. [e] 3 mol % base. [f] 20 mol % base. [g] 40 mol % base. [h] 50 mol % base. [i] rt. 5 mol % Verkade's Base. [j] 3 mol % Verkade's Base. Verkade's Base = P(^{i}PrNCH$_2$CH$_2$)$_3$N.

Subsequently, challenging substrates with relatively high α-*p*K$_a$ were tried. The reaction of 2-allylpyrazine (**1z**) in the presence of 40 mol % Barton's Base occurred nicely to give the desired product ((*E*)-**3za**) in 81% yield with 75% ee. However, the reaction of 2-allylquinoline (**1a′**) proceeded scarcely in the presence of Barton's Base. By using much more basic Verkade's Base,[20] the desired product ((*E*)-**3a′a**) was obtained in 90% yield with 72% ee. Interestingly, 2-allylquinoxaline (**1b′**) underwent the vinylogous aldol-type reaction smoothly in the presence of 20 mol % Barton's Base ((*E*)-**3b′a**, 94%, 90% ee), indicating that the α-*p*K$_a$ of **1b′** was significantly lower than that of **1a′**. To our joy, more challenging 2-allyl-3-Me-pyridine (**1c′**) served as a competent substrate to produce (*E*)-**3c′a** in 82% yield with 92% ee. However, the reaction of 3-Me-4-allyl-pyridine led to the corresponding product in moderate enantioselectivity (48% ee), suggesting that 2-allyl was indispensable for the excellent asymmetric induction (for the details, see SI). Moreover, 3-allyl-4-Me-pyridine was completely inert under the present reaction conditions, indicating that the activation of 3-allyl group by the pyridine moiety was not enough (for the details, see SI). Obviously, the presence of a substituent *ortho* to the allyl group was beneficial for higher enantioselectivity (for the

details, see SI). With the absolute configuration of *ent*-(*E*)-**3aa** in hand (*R*), the stereochemistry of other products in Table 3 was deduced by analogy.

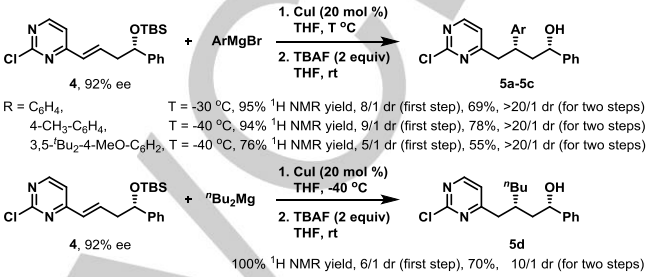


[a] **1**: 0.6 mmol, **2**: 0.2 mmol. The (*E*)/(*Z*) ratio was determined by ^{1}H NMR analysis of the crude mixture. Isolated yield. The enantioselectivity was determined by chiral-stationary-phase HPLC analysis. [b] For the isolated sample, (*Z*)/(*E*) = >20/1.

Table 4. Preliminary Investigation of the (*Z*)-Selective Addition.[a]

With (*R*)-DTBM-SEGPHOS as the ligand, a preliminary substrate scope of aromatic aldehydes in the (*Z*)-selective vinylogous aldol-type reaction was investigated, as shown in Table 4. Compared to benzaldehyde, 4-Me-C_6H_4CHO, 4-SMe-C_6H_4CHO, and 2-Me-C_6H_4CHO were less satisfactory substrates as the corresponding products ((*Z*)-**3ab**, (*Z*)-**3ad**, and (*Z*)-**3ao**) were generated in lower yields with similarly high enantioselectivity (47%-60%, 92%-96% ee). Moreover, the (*Z*)/(*E*) ratio in the reaction of **2o** was decreased to 5/1. A heteroaromatic aldehyde **2t** was also tried, which furnished (*Z*)-**3at** in 41% yield with 12/1 (*Z*)/(*E*) ratio and 88% ee. The moderate yields are attributed to the competitive α-addition. Moreover, three allylazaarenes (**1o**, **1p**, and **1r**) underwent the (*Z*)-selective vinylogous aldol-type reaction in moderate to high yields with moderate to high (*Z*)/(*E*)- and excellent enantioselectivities. The absolute configuration of (*Z*)-**3aa** was identified to be *R* by transforming it to a known compound (for the details, see SI). Analogously, the stereochemistry in other seven products was deduced.

To some extent, α,β-unsaturated azaarenes are quite similar to α,β-unsaturated carbonyl compounds, which are typical Michael acceptors in conjugate addition. **4** was easily prepared from (*E*)-**3aa** (92% ee) in 83% yield by TBS-protection. Then, the asymmetric addition of organometallic reagents to **4** was performed as described in Scheme 2. In the presence of 20 mol % CuI at -30 °C, the conjugate addition of PhMgBr to **4** proceeded smoothly to afford the correspond product in 95% yield with 8/1 dr. However, the diastereoisomers in this step were not separable in silica gel column. Therefore, TBAF-promoted deprotection was carried out, which gave **5a** in 69% isolated yield with >20/1 dr for two steps. Similarly, the additions of 4-CH_3-C_6H_4MgBr and 3,5-^{t}Bu$_2$-4-MeO-C_6H_2MgBr to **4** were studied. After deprotection, products **5b** and **5c** were obtained in moderate isolated yields with excellent dr. Subsequently, the addition of ^{n}Bu$_2$Mg to **4** was studied. The reaction occurred smoothly at -40 °C to deliver the corresponding product in quantitative yield with 6/1 dr. After deprotection, **5d** was obtained in 70% yield with 10/1 dr for two steps. The absolute configuration of **5c** was determined unambiguously by X-ray analysis of its derivative's single crystals (for the details, see SI). The absolute configurations of **5a**, **5b**, and **5d** were assigned by analogy.



Scheme 2. CuI-Catalyzed Asymmetric Conjugate Addition with Organometallic reagents.

In summary, by using easily available allylazaarenes as the pronucleophiles, a novel copper(I)-catalyzed asymmetric vinylogous aldol-type reaction of aldehydes was achieved, which furnished a series of chiral γ-hydroxyl-α,β-unsaturated azaarenes in moderate to excellent yields with high to excellent regio- and enantioselectivities. The geometry of the newly formed carbon-carbon double bond was well controlled by using different bisphosphine ligands. Various *N*-heterocycles, including pyrimidine, pyridine, pyrazine, quinoline, quinoxaline, quinazoline, and benzo[d]imidazole were well tolerated. The produced chiral alkenyl azaarene was found as a satisfactory Michael acceptor towards CuI-catalyzed conjugate addition with organomagnesium reagents. The mechanistic origins of the unusual ligand-based stereodivergence in this system are currently being investigated in further studies.

Acknowledgements

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Keywords: azaarene • vinylogous reaction • allylation • copper catalyst • asymmetric catalysis

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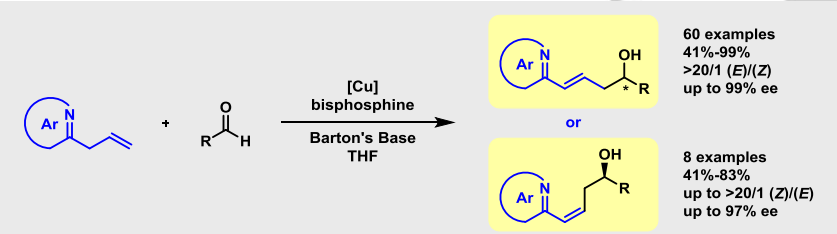

A copper(I)-catalyzed asymmetric vinylogous aldol-type reaction of allylazaarenes is disclosed, which provides an array of chiral γ-hydroxyl-α,β-unsaturated azaarenes in moderate to excellent regio-, (*E*)/(*Z*)-, and enantioselectivities.

*Si-Qing Wang, Zong-Ci Liu, Wen-Jun Yue, Liang Yin**

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