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Copper-catalyzed asymmetric allylation of chiral *N*-*tert*-butanesulfinyl imines: Dual stereocontrol with nearly perfect diastereoselectivity

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Copper-catalyzed asymmetric allylation of chiral *N*-*tert*-butanesulfinyl imines has been described. Dual stereocontrol, through the combination of chiral auxiliary and chiral copper complex, has played an important role in achieving the nearly perfect diastereoselectivities (all d.r. > 99:1), especially for ketimine substrates.

Chiral homoallylic amines not only serve as extremely significant synthetic intermediates in organic synthesis, particularly for alkaloid synthesis,[1] but also exist in a wide range of naturally-occurring compounds and chiral drugs, for instance, (–)-Albine,[2] ORG 34167,[3] (–)-Histrionicotoxin 259A,[4] NNZ 2591,[5] (–)-Quinolizidine 207I,[6] and 3-(2-propenyl)-Yohimban-17-one[7] (Fig. 1). Such importance has stimulated numerous research activities toward their enantioselective synthesis. Among various methods, *N*-*tert*-butylsulfinyl imines have found excellent applicability due to its feasibility of preparing both enantiomers in large scale and readily removing the chiral auxiliary under acidic conditions. In the last decade, Yus,[8] our group[9] and other research groups[10] established several efficient methods using Zn- or In-mediated asymmetric allylation of *N*-*tert*-butanesulfinyl imines to obtain enantioenriched homoallylic amines (Scheme 1a). In this case, the chiral imine substrates determined the stereochemistry outcome. An alternative powerful allylation was to react with achiral imines using chiral ligand-mediated asymmetric transformation (Scheme 1b). Up to now, Cu,[11] Zn,[12] In,[13] Rh,[14] and small organic molecules[15] were successfully applied in such enantioselective processes between various imines and allylic boron compounds.[16] However, homoallylic amines with extremely high optical purity (> 98% *ee*) are generally rather difficult to achieve. To this end, the dual stereocontrol process,[17] through the combination of chiral auxiliary and chiral copper complex, was developed and presented herein (Scheme 1c). Nearly perfect diastereoselectivities (all d.r. > 99:1) were successfully reached, especially for ketimine substrates.

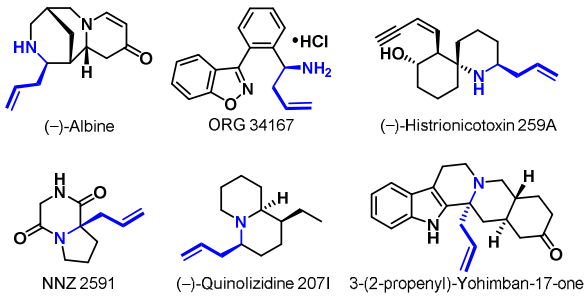
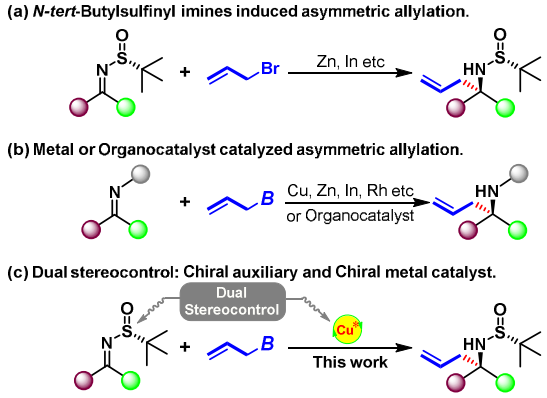


Fig. 1 Chiral-homoallylic-amine-containing natural products and drugs



Scheme 1 Dual stereocontrol in Cu-catalyzed asymmetric allylation

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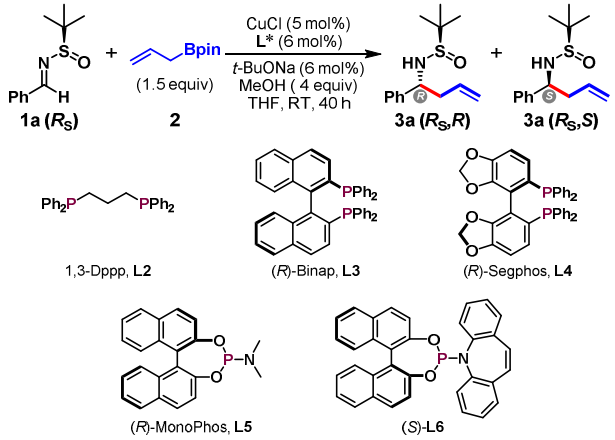
With this challenge in mind, a set of representative phosphorus ligands were evaluated for Cu-catalyzed asymmetric allylation of chiral *N*-*tert*-butanesulfinyl aldimine **1a**, and the results are summarized in Table 1. Initially, poor diastereoselectivity (d.r. = 1.9:1) was obtained when no ligand was applied in this reaction (Table 1, entry 1). Using the simple triphenylphosphine (**L1**) as ligand, the d.r. value was greatly increased to 19:1 (Table 1, entry 2). Three bisphosphine ligands, **L2**–**L4**, were subsequently investigated, however almost no desired product was observed, along with only partial decomposition of starting material (Table 1, entries 3–5). Thus we turned our attention back to monophosphine ligand. The d.r. value was further raised to 35:1 with (*R*)-MonoPhos (**L5**) as ligand (Table 1, entry 6). To our delight, bulky phosphoramidite ligand (*S*)-**L6**[18] could dramatically improve the reaction yield and diastereoselectivity up to 80% and >99:1 d.r. value, respectively (Table 1, entry 7). Utilizing racemic **L6** as ligand had little impact on the outstanding diastereoselectivity (99:1 d.r.) and only the yield decreased to 65% (Table 1, entry 8), which revealed that the chiral bulky phosphoramidite ligand **L6** only acted as a large coordination group. Increasing the allylboronic acid pinacol ester (**2**) loading to 2.0 equiv resulted in considerable improvement of yield (Table 1, entry 9). Using (*R*)-**L6** as ligand, the nearly perfect diastereoselectivity had no change and only the yield reduced slightly to 89% (Table 1, entry 10).

Table 1 Initial evaluation of various ligands[a]

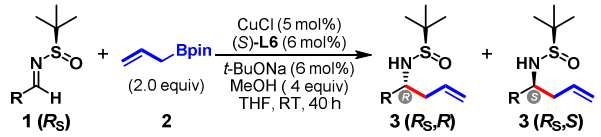


Entry	L	Conversion (%)[b]	Yield (%)[c]	d.r.[d]
1	–	48	45	1.9:1
2	**L1** (PPh_3)	61	49	19:1
3	**L2**	24	1.2	2.6:1
4	**L3**	25	trace	–
5	**L4**	23	trace	–
6	**L5**	83	68	35:1
7	(*S*)-**L6**	81	80	>99:1
8	*rac*-**L6**	71	65	99:1
9[e]	(*S*)-**L6**	100	93	>99:1
10[e]	(*R*)-**L6**	100	89	>99:1

[a]The reaction was carried out with **1a** (0.2 mmol), allylboronic acid pinacol ester (**2**, 0.3 mmol, 1.5 equiv), CuCl (5 mol%), chiral ligand (**L***, 6 mol%), NaO*t*Bu (6 mol%) and anhydrous MeOH (32 μL, 4.0 equiv) in THF (2.0 mL) at room temperature under Ar atmosphere. [b]Based on the isolated and recovered **1a**. [c]Yield of the isolated product. [d]d.r. = (R_S,*R*)-**3a**: (R_S,*S*)-**3a**, Determined by ^{1}H NMR analysis. [e]**2** (2.0 equiv) was used. Bpin = (pinacolato)boron.

With the optimal reaction conditions identified, various *N*-*tert*-butanesulfinyl aldimines were investigated, and the results are summarized in Table 2. All substituted phenyl aldimine substrates, regardless of the electron-donating or electron-withdrawing property of the substituent at the phenyl ring, afforded the corresponding chiral homoallylic amine products in excellent yields (90–99%) and nearly perfect diastereoselectivities (all d.r. > 99:1, Table 2, entries 1–10). As for the alkyl aldimine substrates, the allylation reaction also proceeded smoothly and the reaction yields and diastereoselectivities still maintained at an excellent level (Table 2, entries 11–13).

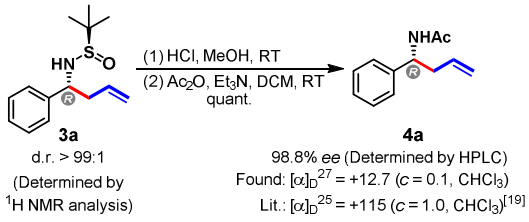
Table 2 Substrate scope of various aldimines.[a]



Entry	1	R	*t* (h)	3	Yield (%)[b]	d.r.[c]
1	**1a**	C_6H_5	40	**3a**	97	>99:1
2	**1b**	4-Me-C_6H_4	40	**3b**	99	>99:1
3	**1c**	4-Cl-C_6H_4	40	**3c**	93	>99:1
4	**1d**	4-CF_3-C_6H_4	40	**3d**	99	>99:1
5	**1e**	4-MeO-C_6H_4	40	**3e**	98	>99:1
6	**1f**	3-Me-C_6H_4	40	**3f**	99	>99:1
7	**1g**	3-Cl-C_6H_4	40	**3g**	92	>99:1
8	**1h**	2-Me-C_6H_4	40	**3h**	90	>99:1
9	**1i**	2-Cl-C_6H_4	40	**3i**	91	>99:1
10	**1j**	β-naphthyl	40	**3j**	94	>99:1
11	**1k**	ethyl	10	**3k**	99	>99:1[d]
12	**1m**	isopropyl	20	**3m**	90	>99:1
13	**1n**	phenethyl	40	**3n**	91	>99:1[d]

[a]The reaction was carried out with **1** (0.2 mmol), allylboronic acid pinacol ester (**2**, 0.4 mmol, 2.0 equiv), CuCl (5 mol%), (*S*)-**L6** (6 mol%), NaO*t*Bu (6 mol%) and anhydrous MeOH (32 μL, 4.0 equiv) in THF (2.0 mL) at room temperature under Ar atmosphere. [b]Yield of the isolated product. [c]d.r. = (R_S,*R*)-**3** : (R_S,*S*)-**3**, Determined by ^{1}H NMR analysis. [d]d.r. = (R_S,*S*)-**3**: (R_S,*R*)-**3**.

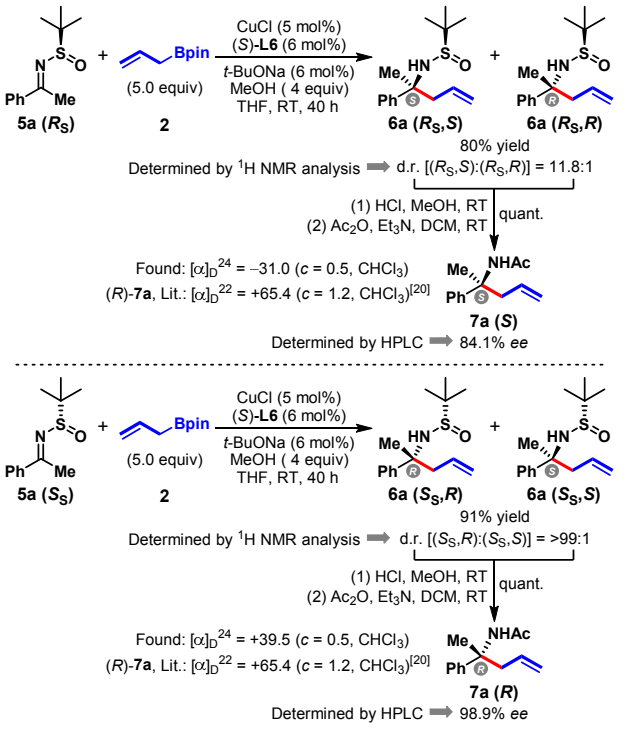
The absolute configuration and d.r. values of homoallylic amines **3** were determined on the basis of their ^{1}H NMR analysis and chemical correlation with the known compounds.[9] The nearly perfect d.r. value of **3a** was further confirmed by the HPLC analysis of its acetyl derivative **4a**,[19] which ensured the accuracy of ^{1}H NMR analysis (Scheme 2).



Scheme 2 Determining the absolute configuration and d.r. value of **3a**.

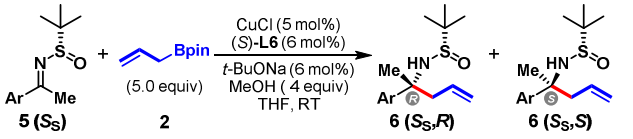
Given the highly diastereoselective nature of this allylation reaction, ketimine substrates were also examined. At the outset, (R_S)-**5a** was subjected to this reaction, only 11.8:1 d.r. value was observed, which probably suggested that the chiral ligand (*S*)-**L6** mismatched the enantioenriched substrate (R_S)-**5a** (Scheme 3). To verify this hypothesis, (S_S)-**5a** was used in this

reaction. As we expected, > 99:1 d.r. value was achieved, which clearly suggested that the chiral ligand (*S*)-**L6** matched the enantioenriched substrate (S_S)-**5a**. The dual stereocontrol, with the combination of chiral auxiliary and chiral copper complex, pushed the diastereoselectivity to a nearly perfect level. It should be noted that 5 equivalent of allylboronic acid pinacol ester (**2**) must be used to ensure the full conversion of **5a**. The absolute configuration and d.r. values of quaternary homoallylic amine **6a** were determined on the basis of their ^{1}H NMR analysis and chemical correlation with the known compounds, and further confirmed by HPLC analysis of its acetyl derivative **7a**.[20]



Scheme 3 Investigation of matching/mismatching ketimine substrate.

Table 3 Substrate scope of various ketimines.[a]

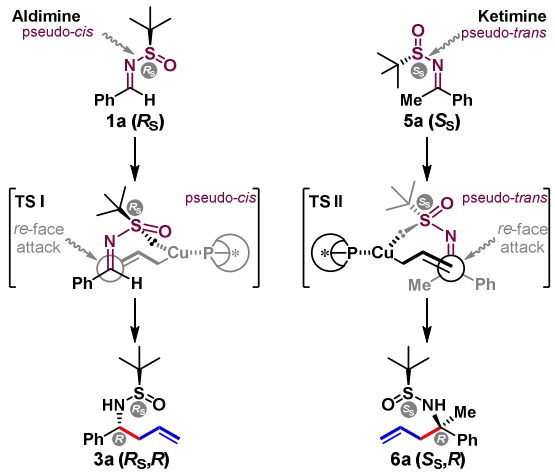


Entry	5	Ar	*t* (h)	6	Yield (%)[b]	d.r.[c]
1	**5a**	C_6H_5	40	**6a**	91	>99:1
2	**5b**	4-Me-C_6H_4	70	**6b**	93	>99:1
3	**5c**	3-Me-C_6H_4	70	**6c**	93	>99:1
4	**5d**	2-Br-C_6H_4	70	**6d**	91	>99:1
5	**5e**	4-F-C_6H_4	70	**6e**	92	>99:1
6	**5f**	4-Cl-C_6H_4	70	**6f**	92	>99:1
7	**5g**	4-Br-C_6H_4	70	**6g**	91	>99:1
8	**5h**	4-MeO-C_6H_4	70	**6h**	93	>99:1
9	**5i**	4-CF_3-C_6H_4	70	**6i**	90	>99:1
10	**5j**	3-Cl-C_6H_4	70	**6j**	91	>99:1

[a]The reaction was carried out with **4** (0.2 mmol), allylboronic acid pinacol ester (**2**, 1.0 mmol, 5.0 equiv), CuCl (5 mol%), (*S*)-**L6** (6 mol%), NaO*t*Bu (6 mol%) and anhydrous MeOH (32μL, 4.0 equiv) in THF (2.0 mL) at room temperature under Ar atmosphere. [b]Yield of the isolated product. [c]Determined by ^{1}H NMR analysis.

With the known matching pattern of the enantioenriched imine substrate and chiral ligand, various *N*-*tert*-butanesulfinyl ketimines were subsequently tested, and the results are summarized in Table 3. With a substituent, regardless of its electron-donating or electron-withdrawing property, at the phenyl ring, the reaction could readily provide the corresponding quaternary allylic amine (Table 3, entries 1–10). It is worth mentioning that excellent yield and d.r. value were both achieved for the sterically hindered 2-substituted phenyl substrate **5d** (Table 3, entry 4).

The different stereocontrol outcome between aldimine and ketimine might be mainly attributed to their conformation difference. In *N*-*tert*-butanesulfinyl aldimine **1c**, the C=N bond is pseudo-*cis* to the S=O bond, whereas a pseudo-*trans* conformation is observed in ketimine **5f**.[9a] The common Zimmerman-Traxler chair-like transition states should be firstly excluded from the attack pathway because of the steric congestion imposed by the bulky ligand (*S*)-**L6** bonding to copper. Due to the steric hindrance induced by tertiary butyl group and its inherent pseudo-*cis* conformation between C=N bond and S=O bond, allylcopper attacked the less hindered *re*-face of aldimine (R_S)-**1a** to offer (*R*)-homoallylic amine **3a** (Scheme 4, TS I). In contrast, the allylic addition took place at the *re*-face of ketimine (S_S)-**5a** to afford (*R*)-homoallylic amine **7a**, owing to its intrinsic pseudo-*trans* conformation between C=N bond and S=O bond (Scheme 4, TS II).



Scheme 4 Mechanistic proposals relating to the allylation stereocontrol.

Conclusions

In summary, copper-catalyzed asymmetric allylation of chiral *N*-*tert*-butanesulfinyl imines, including aldimines and ketimines, has been successfully established. This reaction proceeded smoothly at room temperature, affording optically active homoallylic amines with excellent yields (90–99%) and diastereoselectivities (all d.r. > 99:1). Notably, ketimine substrates, through the matched dual stereocontrol from chiral auxiliary and chiral copper complex, could also provide nearly perfect diastereoselectivity. Further studies on the applications of homoallylic amines are in progress in our laboratories.

Acknowledgments

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