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Catalytic diastereo- and enantioselective additions of versatile allyl groups to N–H ketimines

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There are many biologically active organic molecules that contain one or more nitrogen-containing moieties, and broadly applicable and efficient catalytic transformations that deliver them diastereoselectively and/or enantioselectively are much sought after. Various methods for enantioselective synthesis of α-secondary amines are available (for example, from additions to protected/activated aldimines), but those involving ketimines are much less common. There are no reported additions of carbon-based nucleophiles to unprotected/unactivated (or N–H) ketimines. Here, we report a catalytic, diastereo- and enantioselective three-component strategy for merging an N–H ketimine, a monosubstituted allene and $B_2(pin)_2$, affording products in up to 95% yield, >98% diastereoselectivity and >99:1 enantiomeric ratio. The utility of the approach is highlighted by synthesis of the tricyclic core of a class of compounds that have been shown to possess anti-Alzheimer activity. Stereochemical models developed with the aid of density functional theory calculations, which account for the observed trends and levels of enantioselectivity, are presented.

Catalytic enantioselective additions of carbanions to ketimines deliver products with a nitrogen-substituted quaternary stereogenic centre (α-tertiary amine), but the development of these transformations[1–4] is hardly straightforward. Ketimines are less reactive than aldimines, and the reduced size difference between the substituents compared to aldimines makes enantiotopic face differentiation difficult. Catalytic enantioselective additions of allyl moities[5] to ketimines, while much in demand, remain scarce. One study shows that reactions of allyl–B(pin) (pin = pinacolato) with acyclic *N*-benzyl ketimines may be promoted by a chiral bis-phosphine–Cu complex (Fig. 1a)[6], and another deals with reactions of functionalized allylsilanes and tosyl-protected ketimines catalysed by phosphoramidite–Pd complexes (Fig. 1a)[7]. Other disclosures cover highly activated ketimines, including cyclic sulfonylimines and their reaction with potassium allyltrifluoroborates (with Rh-based catalysts)[8,9] and isatin-derived *N*-Boc-ketimines and their reaction with allylsilanes (with Pd-based complexes and stoichiometric silver fluoride)[10]. Other approaches involve either enantiomerically pure ketimines[11,12] or enantiomerically pure allyl reagents[13–15]. Our goal was to develop a method that would not require ketimine activation/protection and subsequent unmasking (Fig. 1b). The absence of a protecting group would bypass the intermediacy of *E* and *Z* mixtures of ketimine isomers, which can lead to lowering of enantioselectivity. Although preparation of N–H ketimines by condensation of ketones with ammonia followed by reaction with allylboron reagents is known[16], as far as we are aware, diastereo- and/or enantioselective variants have not been introduced.

Based on the earlier investigations regarding enantioselective additions to aldehydes or ketones[17–19], which were recently extended to *N*-anisidyl aldimines[20,21], we envisioned the sequence in Fig. 1b. N–H ketimines would be accessed by addition of an organolithium or a Grignard reagent to a nitrile, many of which are commercially available[22,23]. The ensuing catalytic process would combine an N–H ketimine, a monosubstituted allene and $B_2(pin)_2$ to generate homoallylic amines containing a pair of stereogenic centres and an alkenyl–B(pin) group. A number of biologically active organic molecules would thus become more readily accessible in enantiomerically enriched form. An example would be of the core structure of a class of polycyclic compounds shown to possess the ability to reduce beta-amyloid production (Fig. 1b)[24,25]. Complications typically associated with site-selective removal of protecting/activating units would thus be obviated, particularly when relatively strong reducing (for example, for an *N*-benzyl or an *N*-tosyl group, Fig. 1a) or oxidizing conditions[25] are needed and a benzylic C–N bond is present.

Results

Establishing feasibility. We began with the reaction of allene **2a** with N–H ketimine **1a**, obtained from the reaction of benzonitrile with methyllithium (MeLi, 88% yield; Table 1).

Diastereoselectivity was complete in every case (>98:2 d.r.), but efficiency was catalyst-dependent. There was 60–75% conversion to *rac*-**3a** with Cu complexes derived from triphenylphosphine, tricyclohexylphosphine or racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*rac*-binap) (entries 1–3). Evaluation of *N*-heterocyclic carbene (NHC) complexes (entries 4–6) showed that the combination of cyclohexyl-substituted imidazolium salt **4c** and CuCl is the most effective: *rac*-**3a** was obtained in 90% yield and >98:2 d.r. (Table 1, entry 6).

Identifying a chiral catalyst. Several types of Cu complexes were examined (Table 2). Enantioselectivity was minimal with binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, entry 1, 44:56 e.r.). The desired product was isolated in appreciable yield and e.r. with segphos (**5a**, 51% yield, 18:82 e.r., entry 2) or josiphos (**5b**, 51% yield, 19.5:80.5 e.r., entry 3), but less so with the more conformationally flexible **5c** (27%, 69:31, respectively, entry 4).

With imidazolinium salt **6** or sulfonate-bearing **7a**, enantioselectivity remained low (entries 5 and 6). However, when the mesityl (Mes) group of **7a** was replaced by a 3,5-diaryl-substituted phenyl moiety (**7b**, entry 7), enantioselectivity increased dramatically: **3a** was obtained in 95:5 e.r. (X-ray structure of the corresponding alcohol in Fig. 3a). The effectiveness of the **7b**-derived catalyst was surprising for several reasons. Enantioselectivity was considerably higher compared to the closely related *N*-mesityl-substituted variant

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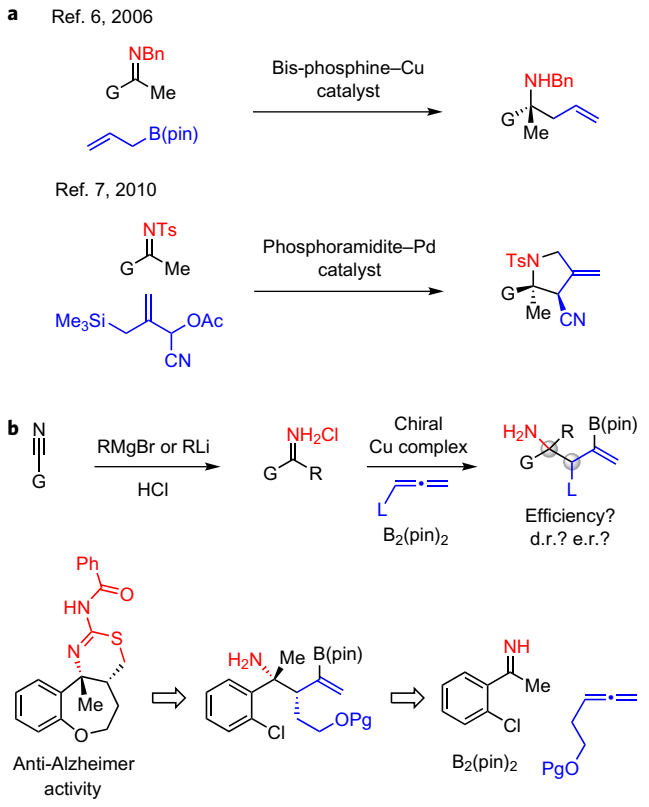
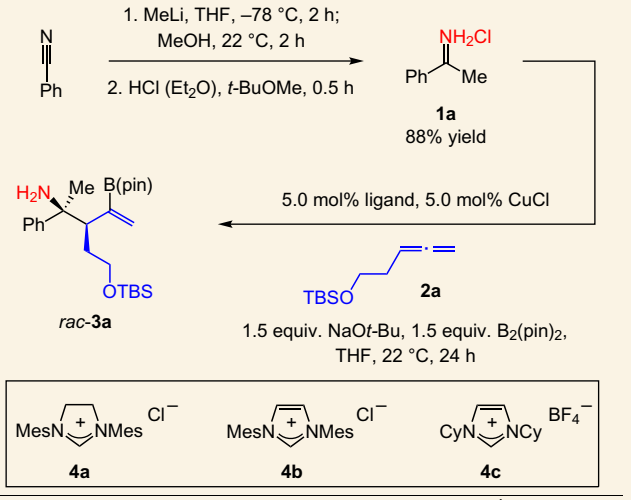


Figure 1 | State of the art in allyl additions to ketimines and goals of the study. There are significant existing limitations, and a number of compelling issues remain unaddressed. **a**, There are only a small number of methods for catalytic enantioselective addition of an allyl group to a ketimine. The substrate is typically equipped with an activating/protecting group, which might prove difficult to remove in the presence of similar functional groups within a product structure (for example, another *N*-benzylamine). **b**, A direct approach to synthesis of α-tertiary amines may entail preparation of the requisite unprotected N–H ketimine through alkylation of readily available nitriles followed by catalytic site-, diastereo- and enantioselective multicomponent addition of 2-boryl-substituted allyl groups. One application relates to synthesis of the core tricyclic structure of a set of heterocyclic molecules that exhibit strong anti-Alzheimer activity. Bn, benzyl; Ts, tosyl; Ac, acyl; pin, pinacolato; G, R, L, functional groups; Pg, protecting group.

(7a; see below; see the 'Stereochemical models' section for further analysis). Additionally, while sulfonate-containing NHC–Cu catalysts have been used for enantioselective allylic substitutions[26,27] and conjugate additions[28–30], none emerged as optimal for a 1,2-addition.

Applicability. The method has considerable scope (Table 3). At times, a higher catalyst loading was necessary for high conversion (for example, 3a, entry 1, Table 3 versus entry 7, Table 2) and the ketimine:allene ratio was changed to 1:1.5 for better yield (from 1.2:1). Regardless of whether the N–H ketimine had an *ortho* aryl substituent that is electron-donating (3b), electron-withdrawing (3c) or relatively sizeable (3f,g), products were isolated in 59–95% yield, >98:2 d.r. and 98.5:1.5 to 99.5:0.5 e.r. Reactions with *meta*-substituted N–H ketimines were similarly efficient and selective (entries 8–10, Table 3). In reactions of ketimines with different *para*-substituted aryl units (3k–3m) e.r. values ranged from 92.5:7.5 to 95:5. Products 3n,o (Table 3, entries 11 and 12), from reactions with the less electrophilic alkyl-substituted N–H ketimines, were isolated in 38 and 48% yield and 91:9 and 95:5 e.r., respectively. Fluoroaryl-substituted amines 3d,e (entries 4 and 5), 3h (entry 8) and 3l (entry 12) were obtained in 64–91% yield and 94:6–98:2 e.r.

Table 1 | Probing the efficiency and diastereoselectivity with different (achiral) catalyst types.



Entry	Ligand	Conv. (%)*	Yield (%)†	d.r.*
1	PPh_3	60	49	>98:2
2	PCy_3	71	52	>98:2
3	*rac*-binap	75	72	>98:2
4	4a	80	66	>98:2
5	4b	55	53	>98:2
6	4c	>98	90	>98:2

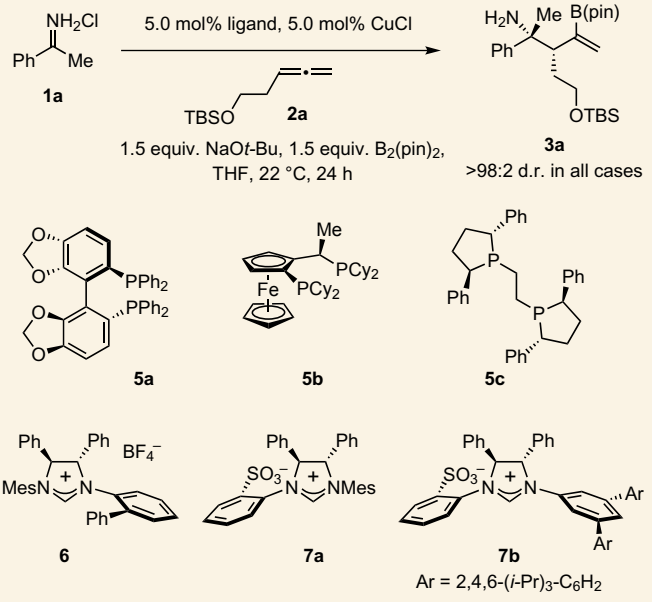
Reactions were carried out under an N_2 atmosphere and a 1.2:1 ratio of ketimine:allene was used. *Conversion (based on allene consumption) and diastereomeric ratio (d.r.) values were measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. Variance of values is estimated to be <±2%. †Yield of isolated and purified product (<±5%). See Supplementary Section 2 for details. TBS, *tert*-butyldimethylsilyl; pin, pinacolato; Mes, 2,4,6-$Me_3C_6H_2$; Cy, cyclohexyl; *rac*, racemic; binap, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

(>98:2 d.r.). The high yield and e.r. in these transformations, regardless of the position of the fluorine atom, show that the fluorine–metal interaction[31–33] does not exert an adverse influence. Diastereoselectivity was exceptional throughout (>98:2 d.r.).

Additions to heterocyclic N–H ketimines afforded products in high e.r. (cf. 3p–3r, Fig. 2a), although efficiency was slightly lower. Syntheses of amines 3s–3u show that different monosubstituted allenes may be used, but the size of the allene substituent impacts efficiency (41–78% yield, >98:2 d.r., up to >99:1 e.r.).

The method extends beyond methyl-substituted substrates. Ketimines bearing an *n*-alkyl or unsaturated alkyl group (for example, 3v–x, Fig. 2a) and the *iso*-propyl-containing ketimine precursor to 3y were converted to the desired amines efficiently and with exceptional diastereoselectivity. Nevertheless, e.r. varied depending on the substituent. Although 3v was formed in 94:6 e.r., there was gradual diminution in enantioselectivity as the side chain became longer (for example, 88:12 e.r. for *n*-butyl-substituted 3w, 85.5:14.5 e.r. for pentenyl-substituted 3x). More enantioselective was the reaction that afforded *iso*-poropyl-containing 3y (96:4 e.r.); the X-ray structure secured for the *N*-acetyl derivative of 3y (Fig. 2a) indicates that there is no reversal in stereochemical induction (Fig. 2a gives corroborative X-ray data). A possible rationale for these selectivity trends will be provided below (see the 'Stereochemical models' section). Various compounds of interest, such as those derived from intramolecular hydroamination that afford heterocyclic derivatives[34,35], may be accessed through functionalization of compounds such as 3x. Nonetheless, there are limitations. Reactions of ketimines that contain an α- or β-alkoxy or a benzyl group are inefficient, probably due to facile decomposition (enamine formation and β-elimination, respectively). The same applies to additions to trifluoromethyl-substituted ketimines (decomposition to unidentified products). There was no reaction with phenyl-*tert*-butyl N–H ketimine.

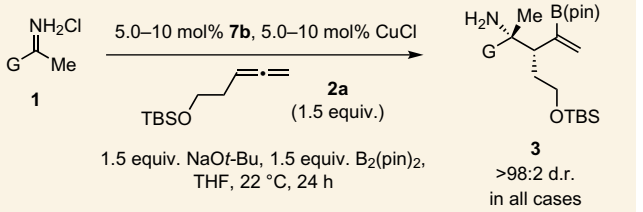
Table 2 | Studies to identify an effective chiral catalyst.



Entry	Ligand	Conv. (%)*	Yield (%)†	e.r.‡
1	*R*-binap	70	65	44:56
2	**5a**	55	51	18:82
3	**5b**	65	51	19.5:80.5
4	**5c**	29	27	69:31
5	**6**	80	51	40:60
6	**7a**	>98	65	55:45
7	**7b**	54	51	95:5

Reactions were carried out under an N_2 atmosphere, and a 1.2:1 ratio of ketimine:allene was used. *Conversion (consumption of allene) and d.r. values were measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. Variance of values is estimated to be <±2%. †Yield of isolated and purified products (<±5%). ‡Enantiomeric ratio (e.r.) values were determined by HPLC analysis (<±1%). See Supplementary Section 2 for details. TBS, *tert*-butyldimethyl silyl; pin, pinacolato; Mes, 2,4,6-$Me_3C_6H_2$; Cy, cyclohexyl; binap, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

Table 3 | Catalytic diastereo- and enantioselective additions to ketimines.



Entry	G	Mol%	Yield (%)*	e.r.†
1	C_6H_5 (**a**)	7.5	76	95:5
2	*o*-$MeOC_6H_4$ (**b**)	10	95	98.5:1.5
3	*o*-ClC_6H_4 (**c**)	7.5	91	99.5:0.5
4	*o*-FC_6H_4 (**d**)	7.5	72	97.5:2.5
5	*o,o*-$F_2C_6H_3$ (**e**)	7.5	91	98:2
6	1-Naphthyl (**f**)	10	66	98.5:1.5
7	*o*-MeC_6H_4 (**g**)	7.5	59	99.5:0.5
8	*m*-FC_6H_4 (**h**)	5.0	64	94:6
9	*m*-$MeOC_6H_4$ (**i**)	10	57	98.5:1.5
10	2-Naphthyl (**j**)	7.5	81	93:7
11	*p*-ClC_6H_4 (**k**)	7.5	56	92.5:7.5
12	*p*-FC_6H_4 (**l**)	5.0	71	95:5
13	*p*-$MeOC_6H_4$ (**m**)	7.5	39	92.5:7.5
14	$CyCH_2$ (**n**)	10	38	91:9
15	Cy (**o**)	10	48	95:5

Reactions were carried out under an N_2 atmosphere; >98% disappearance of ketimine in all cases. *Yield of isolated and purified products (<±5%). †Enantiomeric ratios determined by HPLC analysis (<±1%). TBS, *tert*-butyldimethylsilyl; pin, pinacolato; Cy, cyclohexyl. Experiments were performed at least in triplicate. See Supplementary Sections 2–3 for details and for results with achiral imidazolinium salt **4c**.

Utility. Catalytic enantioselective addition to ketimine **8** followed by oxidation of the C–B bond gave β-amino ketone **9a**, the product of a Mannich-type addition, in 70% overall yield and without any loss in d.r. (Fig. 2b). The efficiency with which **9a** was obtained is higher than those shown in Table 3 and Fig. 2a, indicating that there might be some decomposition during purification and that yields may be improved if the alkenyl–B(pin) moiety is modified. The absolute stereochemistry of the product was confirmed with an X-ray structure of primary alcohol **9b**. It merits note that catalytic enantioselective enolate additions to *N*-activated ketimines (for example, *N*-phosphinoylketimines[36,37] or those derived from α-ketoesters[38] or diethyl ketomalonate[39]) are limited in scope (see Supplementary Section 1 for additional references).

We then investigated the possibility of application to enantioselective synthesis of the core structure of the aforementioned anti-Alzheimer compounds (Fig. 2c). NHC–Cu-catalysed protodeboration[17] of enantiomerically enriched alkenyl–B(pin) amine **3c** furnished **10** in 72% yield. Synthesis of α-olefin **10** by a related route and with a sterically less demanding Cu–H complex (vs. Cu–B(pin) addition/protodeboration) would present a chemoselectivity issue (competitive reaction with ketimine[40]); moreover, we find that the presence of a B(pin) group is critical to high enantioselectivity (Fig. 3). Thiourea generation and removal of the silyl group afforded alcohol **11** in 71% overall yield. The cyclic ether was formed by treatment of **11** with 10 mol % CuI and 20 mol % 8-hydroxyquinoline (110 °C, 24 h)[41], affording oxepane **12** in 78% yield. Oxidative cleavage of the vinyl group, reduction of the resulting aldehyde, and subjection of the resulting primary alcohol to triflic anhydride (–20 °C, 2 h)[27] delivered **13** in 75% yield after recrystallization (this compound is unstable towards a variety of chromatography procedures). The aryl ring in **13** may be functionalized site selectively according to formerly reported procedures[42–44] (see Supplementary Section 1 for additional references).

Stereochemical models. The results of density functional theory (DFT) calculations are in agreement with the high diastereoselectivities (see Supplementary Section 4 for details). We then evaluated the role of the chiral NHC ligand that contains a pendant sulfonate moiety on enantioselectivity (Fig. 3a). The computational errors for modelling a charged species notwithstanding, we propose a similar steric and electronic environment, as suggested formerly vis-à-vis enantioselective allylic substitutions effected by the same catalyst class[27]. The sulfonate group is probably situated in the rear (**I** and **II**). This would allow for the large 3,5-bis-(2,4,6-(*i*-Pr)$_3$-phenyl)phenyl moiety to obstruct the right side of the complex and causes the sizeable B(pin) moiety to be situated in the less occupied left/front quadrant in **I** (Fig. 3a). In **II**, which would lead to the minor enantiomer, there is steric repulsion between the B(pin) moiety and the chiral ligand's *N*-aryl group and thus the energy barrier would be higher (7.4 kcal mol^{-1} less favoured than **I**). As discussed in the next paragraph (see also Supplementary Section 4), this is probably not the pathway through which the minor enantiomer is generated. Consistent with the above analysis (Fig. 3a), the high energy of **II** and the steric pressure involving the B(pin) moiety are reflected in a considerably widened C^{NHC}–Cu–C^1–C^2 dihedral angle (177.2° versus the optimal value of ~130°; see Supplementary Section 4). Calculations on the system containing the more diminutive NHC–Cu complex derived from **7a** point to energetically similar processes (energy difference of 0.6 kcal mol^{-1} between **III** and **IV**; Fig. 3a), which is in agreement with the lower e.r. obtained when the NHC–Cu complex derived from **7a** is involved (55:45 versus 95:5 e.r., Table 2).

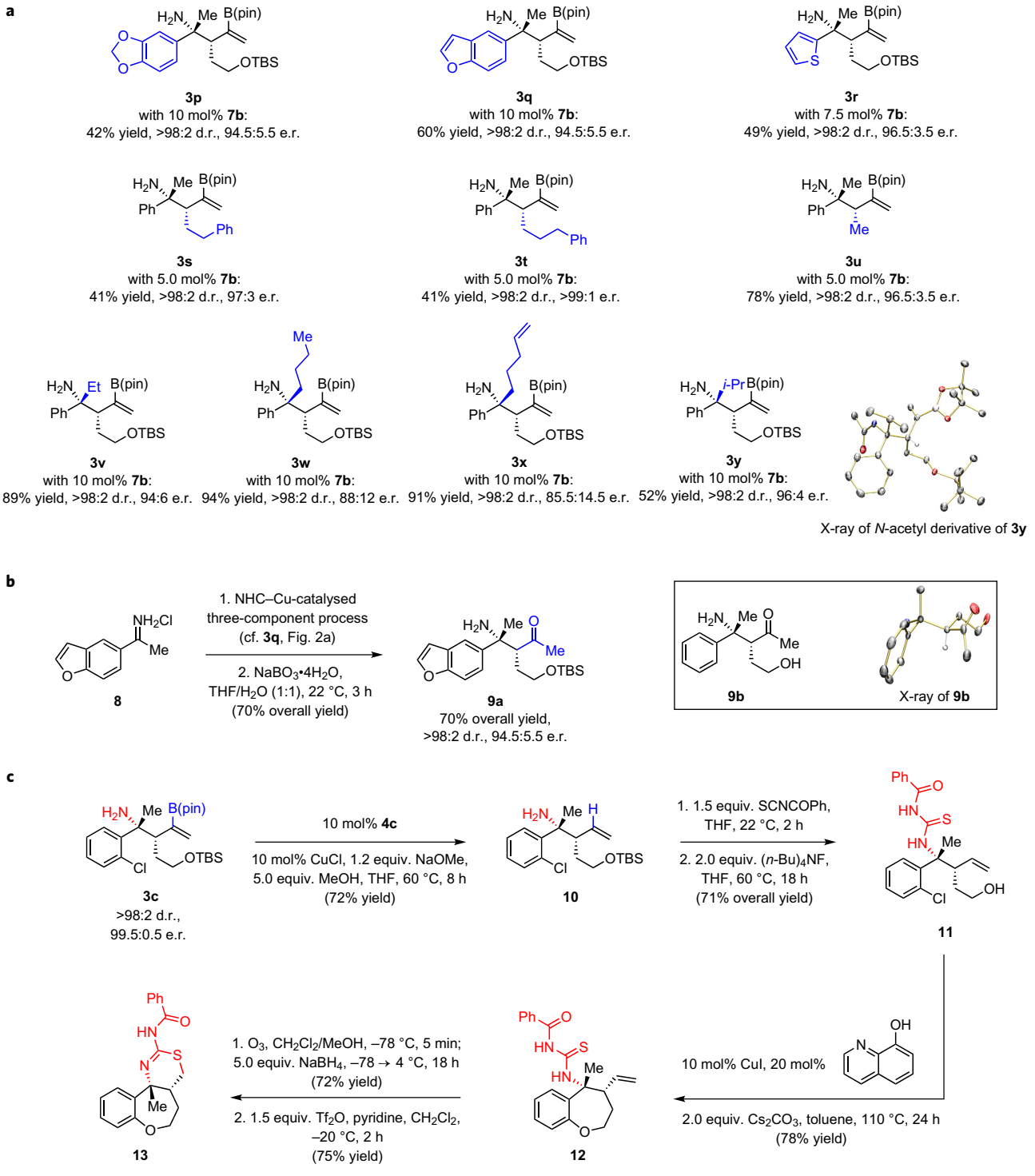


Figure 2 | Further exploration of scope and illustration of utility. A variety of desirable products can be synthesized. **a**, The method is applicable to different heterocyclic substrates and allenes. Products derived from ketimines containing *n*-alkyl or *iso*-alkyl substituents (versus methyl) can be obtained efficiently, in >98:2 d.r. and 85.5:14.5 to 96:4 e.r. depending on the substituent identity. Results with achiral imidazolinium salt **4c** are shown in Supplementary Table 1. **b**, Oxidation of the alkenylboronate moiety within the products derived from the NHC–Cu-catalysed multicomponent reactions proceed efficiently to deliver the corresponding β-amino ketones (for example, **9a**), which represent the products of diastereo- and enantioselective Mannich-type additions. **c**, The method may be applied to the synthesis of the polycyclic core of compounds recently implicated in the fight against Alzheimer's disease. Conversion of the C–B(pin) to a C–H bond promoted by a readily accessible NHC–Cu complex afforded **10**. Formation of the derived thiourea and another NHC–Cu-catalysed reaction generated the oxepane ring of **12**. A two-step procedure involving oxidative cleavage/reduction and activation of the resulting primary alcohol delivered the desired aminothiazine ring and strained tricyclic **13**. Reactions were performed under N_2. There was >98% disappearance of ketimine in all cases (might include decomposition products). Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). Diastereomeric ratios were determined by analysis of the 400 MHz ^{1}H NMR spectra of unpurified product mixtures (±2%). Enantiomeric ratios were determined by high-performance liquid chromatography (HPLC) analysis (±1%). See Supplementary Sections 2–3 for experimental details and spectroscopic analyses.

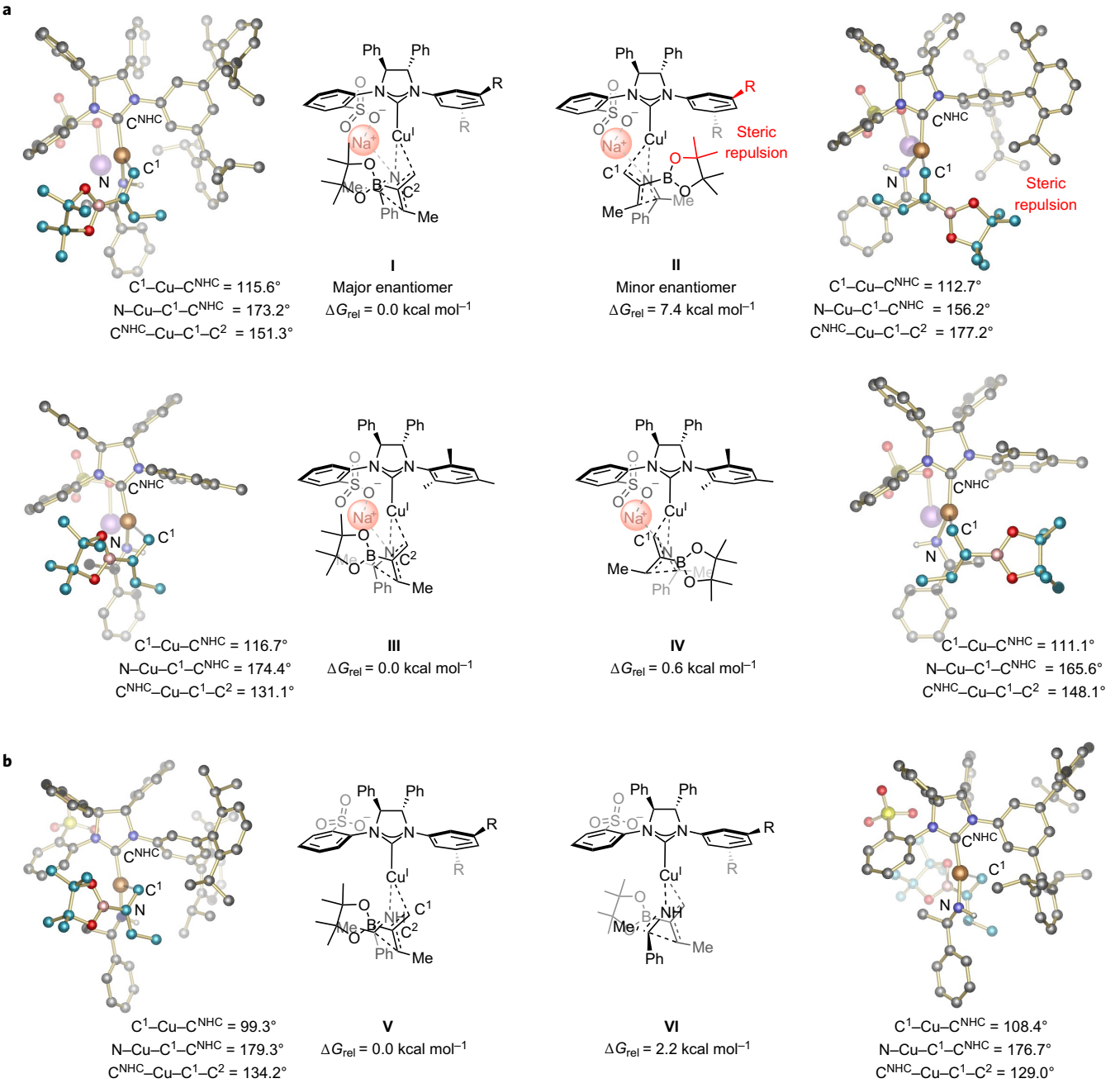


Figure 3 | Stereochemical models. DFT calculations shed light on the origins of enantioselectivity. **a**, Transition states with a N→Na interaction account for high e.r.; **I** represents the preferred mode. **b**, The model suggests that disruption of the N→Na coordination by the long, flexible alkyl ketimine chain (**3w**,**3x**, Fig. 2a) in **V** might render mode **VI** competitive, leading to lower e.r. Free energy values relative to the major pathway refer to the $MN12SX/Def2TZVPP_{THF(PCM)}$ level after geometry optimization performed with $M06L/Def2SVP_{(THF(PCM))}$. For details, see Supplementary Sections 4 and 5. NHC, *N*-heterocyclic carbene; THF, tetrahydrofuran.

The stereochemical model offers a rationale for why reactions with imines containing longer linear alkyl groups (for example, *n*-butyl or 4-pentenyl) are less enantioselective (Fig. 2a); these lower e.r. values might partly arise from an increase in attractive London dispersion forces between the 3,5-bis-(2,4,6-(*i*-Pr)$_3$-phenyl) phenyl group and the substrate's alkyl chain[45–47]. It is, however, more plausible that higher conformational mobility of the alkyl chains disrupts N→Na chelation (less optimal C^{NHC}–Cu–C^1–C^2 dihedral angle in **I** (151.3°) versus in **V** (134.2°)). The smaller energy difference between anionic structures **V** and **VI** (2.2 kcal mol^{-1}, Fig. 3b) supports the notion that enantioselectivity would probably be lower without a sodium bridge and that reaction via **VI** is probably the most competitive pathway leading to generation of the minor enantiomer versus the involvement of the most favoured **I**. The C^{NHC}–Cu–C^1–C^2 and N–Cu–C^1–C^{NHC} dihedral angles of **V** and **VI** are close to the optimal value of ca. 130° (see Supplementary Section 4), implying that some strain induced by N→Na association in **I** is released in **V**. With the less flexible isopropyl substituent in **3y**, the aforementioned chelation may remain intact, allowing for higher enantioselectivity (96:4 e.r.).

Conclusions

The catalytic method introduced here puts forward an expeditious strategy for the synthesis of α-tertiary amines in high diastereo-

and enantiomeric purity, thus providing a solution to an important and persisting problem in catalytic enantioselective synthesis. There are no more than a small number of catalytic enantioselective protocols that allow access to such coveted nitrogen-containing compounds, yet none involves an unprotected/unactivated imine. These investigations provide the first step towards the development of a series of catalytic enantioselective reactions involving N–H ketimines and other types of readily available and versatile carbon-based nucleophiles, and towards protocols that render a range of chiral drug candidates with one or more α-tertiary amine moieties much more accessible. Finally, this study further expands the utility of sulfonate-containing chiral NHC ligands, previously used in catalytic enantioselective conjugate additions[48], allylic substitutions[27] as well as copper-boryl additions to alkenes[49–54] and allenes[55] and copper–hydride additions to alkenes[56], to include allyl additions to ketimines.

Data availability. X-ray crystallographic data for compounds *rac*-**3a**, *N*-acetyl derivative of **3y**, and **9b** are freely available from the Cambridge Crystallographic Data Centre (CCDC 1547738, 1547736 and 1547737, respectively).

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Author contributions

H.J. and F.R. developed the catalytic method and its various applications. S.T. designed and performed the DFT calculations. A.H.H. directed the investigations and composed the manuscript, with revisions provided by the other authors.

Additional information

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Competing financial interests

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