Title: Organocatalytic Asymmetric α-C–H Functionalization of Alkyl Amines

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Abstract: Catalytic enantioselective α-C–H functionalization of achiral amines could provide an ideal synthetic approach toward chiral amines. The alkyl amines constitute the most diverse and synthetically important class of achiral amines. However, the inert nature of the α-C–H of alkyl amines renders the activation of alkyl amines as carbanionic nucleophiles for catalytic asymmetric reactions an important yet unmet challenge. We describe here that *N*-arylidene alkyl amines could be activated as carbanions for asymmetric conjugate addition and Mannich reaction. In their own right, these results represent a new and generally useful approach to the synthesis of chiral α,α-dialkyl amines. More importantly, they highlight the enormous potential of *N*-arylidene amines as readily available and widely applicable synthons for the asymmetric synthesis of chiral amines.

One-Sentence Summary: A metal-free catalytic strategy for asymmetric α-C–H functionalization of alkyl amines.

Main Text: Chiral amine motifs existed in numerous biologically active molecules such as drugs and natural products. Therefore, tremendous efforts have been directed to the development of catalytic asymmetric reactions for the preparation of chiral amines (*1*). Catalytic asymmetric amine α-C–H functionalization is a particularly appealing strategy because of the ready availability of a wide variety of achiral amines. Over the last few decades, tremendous strides have been made in the α-C–H functionalization of amines bearing a α-π-motif, such as carbonyl (*2–7*), aryl (*8–12*), alkenyl (*13*) and alkynyl (*14*) groups. Acyclic alkyl amines are the most abundant but challenging substrates for amine α-C–H functionalization. Indeed, only recently the development of highly enantioselective catalytic asymmetric α-C–H functionalization of these amines have begun to appear in the literatures (*15–20*). Specifically, Yu and co-workers reported *N*-thioacyl-directed α-C–H activation using Pd for asymmetric arylation of ethylamine (Fig 1A) (*21*); Martin and co-workers reported Ir-Ni catalyst-mediated arylation of *N*-benzoyl pentylamine with photo-homolysis of α-C–H (Fig 1B) (*22)*; Huo and co-workers reported Ir-Ni catalyst-mediated acylation and arylation of *N*-benzoyl amines with photo-homolysis of α-C–H (*23*, *24*) (Fig 1C); Shi and co-workers reported Ni-promoted α-alkylation and alkenylation of *N*-sulfonyl amines with styrenes and 1,2-diphenyl ethyne via dehydrogenation of *N*-sulfonyl amines to *N*-sulfonyl imines (Fig 1D) (*25, 26*); and Phipps and co-workers reported an HAT-driven chiral phosphoric acid-mediated arylation of *N*-acetyl amines with pyridine and quinoline derivatives (Fig. 1E) (*27*). In these studies, the alkyl amines were activated as metallocarbanions, radicals, and imine intermediates. Despite these advances, direct catalytic asymmetric conversion of achiral amines to chiral amines remains highly desirable yet elusive. Significant progress has been made in development of various superbase organocatalysts for deprotonation of basic C-H to form α-carbonyl carbanions (*28-30*). In this study, however, we are pleased to report the successful activation of acyclic alkyl amines as α-nitrogen carbanions for the asymmetric synthesis of chiral amines (Fig. 1F).

We postulated that an *N*-arylidene group could act as an activator of alkyl amine α-C–H toward deprotonation with chiral ammonium catalyst (Fig. 1F). Furthermore, the *N*-arylidene group is an easily removable *N*-protecting group. We therefore began to investigate the α-C–H functionalization of *N*-arylidene amines, mediated by chiral ammoniums, with the ultimate goal of establishing an asymmetric route toward chiral α,α-dialkyl amines. First, we examined the reactions of a variety of *N*-aryliene-2-phenylethylamines **1** with acrolein (**2a**). In the presence of chiral ammonium catalyst C-**1** and aqueous KOH (50 wt %) (*31, 32*), no reaction was detected with *N*-(4-nitrophenyl)methylene amine **1a** after 12 h at room temperature. Substitution of the nitro group with various electron-deficient substituents, such as cyano (**1b**), trifluoromethyl (**1c**), methoxycarbonyl (**1d**) groups, did not lead to active *N*-aryliene-2-phenylethylamines. Next, we tried *N*-(4-nitrophenyl)methylene amines bearing an extra electron-withdrawing substituent such as halogen (**1e**, **f**), trifluoromethyl (**1g**) and nitro (**1h**) groups. These *N*-arylidene amines (**1e**–**h**) were also inactive. Other commonly used *N*-protecting groups, such as *N*-diphenylmethylene (**1i**) and *N*-fluorylidene (**1j**) groups (*2*), were tried but also failed to activate the α-C–H toward deprotonation. However, we noticed that α-iminonitriles could be prepared in one-pot fashion from amines, aldehydes, and TMSCN (*33, 34*). We expect the presence of nitrile group could increase the acidity of the amine α-C-H through inductive electron withdrawing effect (see supplementary information for the computation of the pKa of amine **1A** and **1a**'s α-C-H). We therefore reasoned that α-iminonitirles might be suitable as an activator of alkyl amine α-C–H toward deprotonation, although to our knowledge this possibility had never been explored. With that in mind, we prepared **1A** in one pot from 2-phenylethylamine and 4-nitrobenzaldehyde in 72%

yield. To our delight, when **1A** was stirred with acrolein (**2a**) and C-**1** in toluene/aq. KOH for 12 hours, the desired adduct **4Aa** was generated as a major product in 93:7 er. However, the conversion was found to be only 10%, so we set out to optimize the reaction.

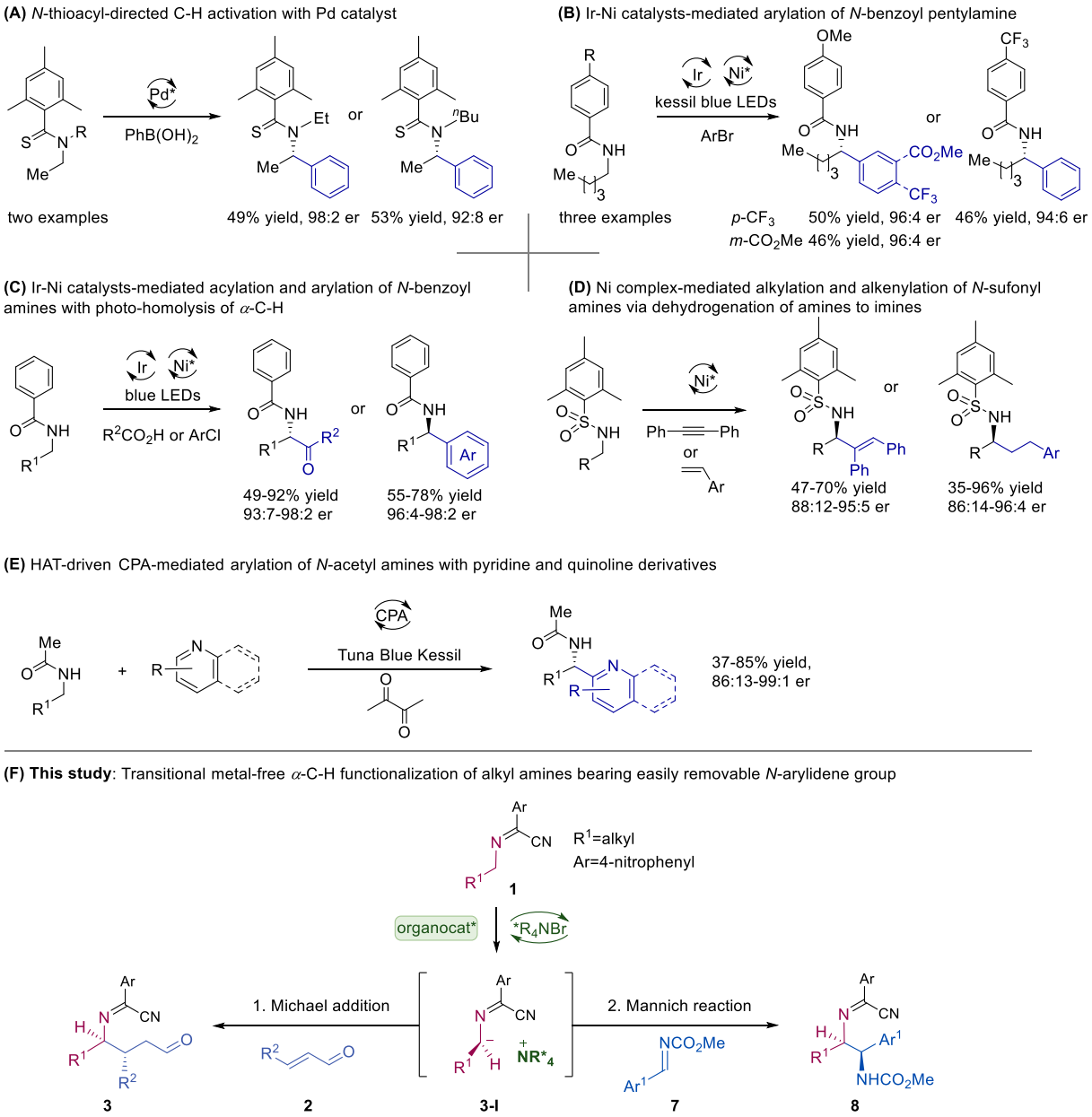


Fig. 1 Catalytic asymmetric α-C–H functionalization of acyclic alkyl amines without α-π motifs. (A) Pd complex-mediated arylation of *N*-thioacyl ethylamines. (**B**) Ir-Ni catalysts-promoted arylation of *N*-benzoyl propylamines. (**C**) Ir-Ni catalysts-promoted acylation and arylation of *N*-benzoyl amines. (**D**) Ni complex-mediated alkenylation and alkylation of *N*-sulfonyl amines. (**E**) HAT-driven CPA-catalyzed Minisci reaction of *N*-acetyl amines. (**F**) Transitional metal-free α-C–H functionalization of alkyl amines bearing easily removable *N*-arylidene group.

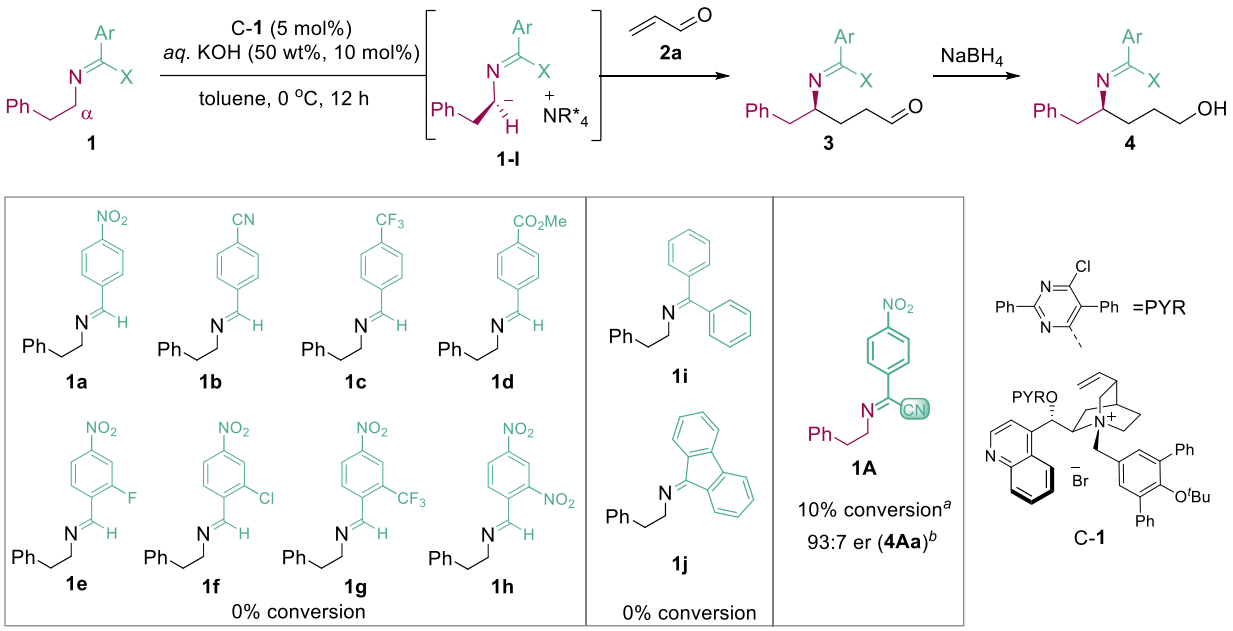
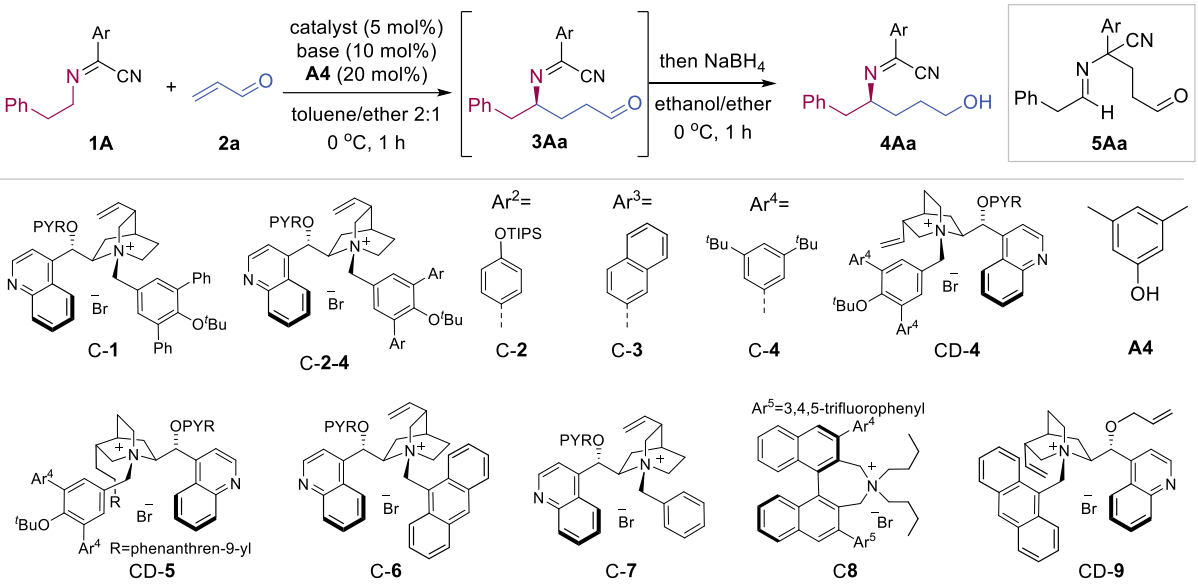


Fig. 2 Screening studies of the *N*-arylidene groups. The reaction was performed with amine **1** (0.05 mmol), acrolein (**2a**, 0.1 mmol), C-**1** (0.0025 mmol, 5 mol %), aq. KOH (50 wt %, 10 mmol %) in toluene (0.5 mL) at 0 °C. [a]conversion was determined by NMR analysis. [b]ee was determined by SFC with a chiral column.

We observed that the addition of phenol derivatives dramatically increased the reaction conversion (see Fig. S1 for detail) (*35*, *36*). With 20 mol % of 3,5-dimethylphenol, the reaction proceeded to 68% conversion in 12 h while the er of **4Aa** was improved from 93:7 to 95:5 er (Fig. 3, entry 2). With further optimization in base and solvent, the reaction conversion was raised to 77% without compromising regioselectivity and enantioselectivity (Fig. 3, entries 3, 4). We then focused on fine-tuning the terphenyl group in the chiral ammonium catalyst (Fig. 3, entries 5–7). Catalyst C-**4** was found to afford a complete reaction in 1 hour to afford (*S*)-**4Aa** in 95:5 er and 93:7 rr (Fig. 3, entry 7). Using CD-**4** (a pseudo-enantiomer of C-**4**) (*R*)-**4Aa** was obtained in 92:8 er and with a regioselective ratio of 94:6 (Fig. 3, entry 8). However, the conversion was only 45%. Further optimization revealed that CD-**5** afforded significantly higher activity and enantioselectivity (81% conversion, 95:5 er), while the regioselectivity also remained high (Fig. 3, entry 9).

To examine the role played by the *N*-terphenylmethyl group, we examined analogues of C-**4** bearing *N*-anthracenylmethyl and *N*-benzyl groups (*37*, *38*). Using these catalysts, the regioisomer **5Aa** was the only detectable product (Fig. 3, entries 10 and 11). The same regioisomer was also the only product in reactions using well-known chiral ammonium catalysts such as the Maruoka and Corey catalysts (*39*, *40*), as well as *tetra*-butylammonium bromide (TBAB), (Fig. 3, entries 12–14). These results indicated that the presence of the *N*-terphenylmethyl group is critical for C-**4** to furnish the desirable regioselectivity. In summary, C-**4** is responsible for both activity and enantioselectivity in amine α-C–H functionalization.



entry	catalyst	solvent	base	phenol	conversion[a]	rr (3Aa:5Aa)[a]	er (4Aa)[b]
1[c]	C-**1**	toluene	KOH	-	<10%	n.d.	93:7
2[c]	C-**1**	toluene	KOH	**A4**	68%	61:39	95:5
3[c]	C-**1**	toluene	LiOH	**A4**	70%	68:32	96:4
4	C-**1**	toluene: ether 2:1	LiOH	**A4**	77%	64:36	93:7
5	C-**2**	toluene: ether 2:1	LiOH	**A4**	97%	76:24	96:4
6	C-**3**	toluene: ether 2:1	LiOH	**A4**	70%	77:23	95:5
7	C-**4**	toluene: ether 2:1	LiOH	**A4**	99%	93:7	95:5
8	CD-**4**	toluene: ether 2:1	LiOH	**A4**	45%	94:6	8:92
9	CD-**5**	toluene: ether 2:1	LiOH	**A4**	81%	93:7	5:95
10	C-**6**	toluene: ether 2:1	LiOH	**A4**	71%	0:100	n.d.
11	C-**7**	toluene: ether 2:1	LiOH	**A4**	45%	0:100	n.d.
12	C**8**	toluene: ether 2:1	LiOH	**A4**	63%	0:100	n.d.
13	CD-**9**	toluene: ether 2:1	LiOH	**A4**	75%	0:100	n.d.
14	**TBAB**	toluene: ether 2:1	LiOH	**A4**	70%	0:100	n.d.

Fig. 3 Reaction conditions and catalyst optimization. The reactions were performed with achiral amine **1A** (0.05 mmol), acrolein (**2a**, 0.1 mmol), catalyst (0.0025 mmol, 5 mol %), base (10 mmol %) in solvent (0.5 mL) at 0°C. [a]conversions and ratio of **3Aa**/**5Aa** were determined by NMR analysis. [b]er was determined by SFC on a chiral column. [c]12 hours.

Under these optimized conditions, we examined the scope of amine α-functionalization reactions using enals as electrophile (Fig. 4). A wide range of *N*-(4-nitrophenyl)cyanomethylene

amines **1A-U** reacted smoothly with acrolein (**2a**) at 0 °C, generating chiral amines **4A**–**U** in 93:7–96:4 er and 72:28–>95:5 rr with 54–78% yields. Aryl and heteroaryl bearing electron-donating and electron-withdrawing substituents at various positions of the aromatic rings were well tolerated (**4Ba**–**4Ha**). Other common functional groups such as ethers (**4Ia**–**4Ka**), acetal (**4La**), alkene (**4Ma**), alkynes (**4Na**–**Oa**) and bromide (**4Pa**) were also included in the substrates. Furthermore, this reaction could be applied to the functionalization of various fluorinated amines to generate the corresponding fluorinated chiral amines **4Qa**–**Ua** in 92:8-96:4 er, >95:5 rr and 58–76% yields. Not surprisingly, unfunctionalized alkyl amine **1V** is a more challenging substrate. Nevertheless, we found that it was also converted into chiral amine **4Va** in 93:7 er and 76:24 rr, albeit with a comparatively low yield of 35%. Amine α-C–H functionalization also occurred satisfactorily with β-substituted enals **2**. These reactions produced chiral amines with two continuous stereocenters (**4Ab**, **4Hb**, **4Ib**, **4Ac**, **4Ad**) in 92:8–94:6 er, 90:10–>95:5 dr, 93:7–>95:5 rr and 45–69% yields. As shown, β-substituents of the enals such as methyl (**4Ab**, **4Hb**, **4Ib**), ethyl (**4Ac**) and (benzyloxy)methyl (**4Ad**) were tolerated. It was also noted that chiral amines **4** can be easily separated from regioisomers by silica gel chromatography. Overall, this amine α-C–H functionalization provides a general method for the enantioselective conversion of alkyl amines into chiral amines.

Chiral vicinal diamines constitute widely useful chiral building blocks in organic synthesis. Accordingly, tremendous efforts have been devoted to the development of asymmetric synthesis of chiral vicinal diamines (*41*–*44*). The amine α-C–H functionalization with imines as electrophile constitutes a particularly attractive strategy by utilizing two class of readily available achiral compounds as starting materials for the asymmetric synthesis of chiral vicinal diamines. However, attempts to explore this strategy have met with very limited success. To our knowledge, only two examples of catalytic asymmetric α-C–H activation of benzyl amines for Mannich reaction have been reported (*8*, *9*), and high enantioselectivity was achieved with 2- or 4-nitrobenzyl amines using a chiral copper catalyst (*9*). Therefore, the realization of the potential of this attractive strategy remained an important yet unmet challenge. We postulated that a highly diastereoselective and enantioselective Mannich reaction by way of α-C–H activation of alkyl amines, using chiral ammonium as the catalyst, could provide a way forward.

We therefore began to investigate α-C–H functionalization of amine **1A** and aldimine **7a** (Figure 5). In the presence of CD-**10**, which promoted efficient imine cross-coupling reactions (*30*), chiral diamine **8Aa** was generated in >95:5 rr, >95:5 dr and 92:8 er (Fig. 5, entry 1). However, the reaction conversion was only 69%. Our efforts to optimize the reaction revealed that adding 2,6-dimethyl-4-chlorophenol accelerated the reaction to completion in 16 hours. Moreover, chiral diamine **8Aa** was obtained with significantly improved enantioselectivity (95:5 er) without compromising regioselectivity and diastereoselectivity (Figure 5, entry 2, see table S4, S5 for details). We next carried out catalyst screening studies, from which CD-**11** afforded the optimal regioselectivity, diastereoselectivity, and enantioselectivity (Figure 5, entries 3–5). On the other hand, C-**4** produced the antipode of **8Aa** in >95:5 rr, >95:5 dr, albeit in 12:88 er. Notably, promoted by TBAB, the reaction reached only 50% conversion furnishing **8Aa** in 15:85 rr. These results indicate that the catalyst CD-**11** is responsible for both activity and stereoselectivity in the generation of **8Aa**.

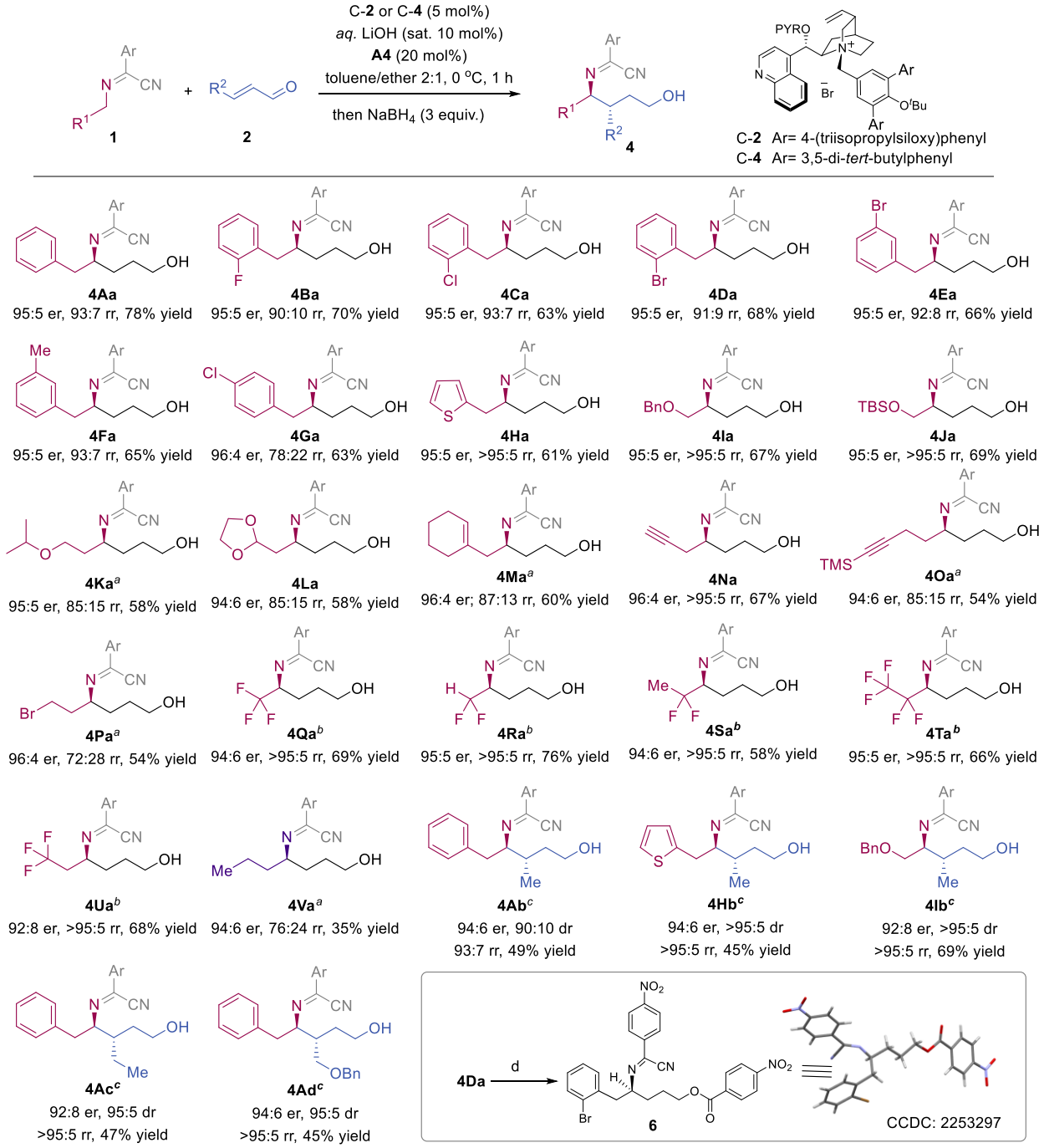
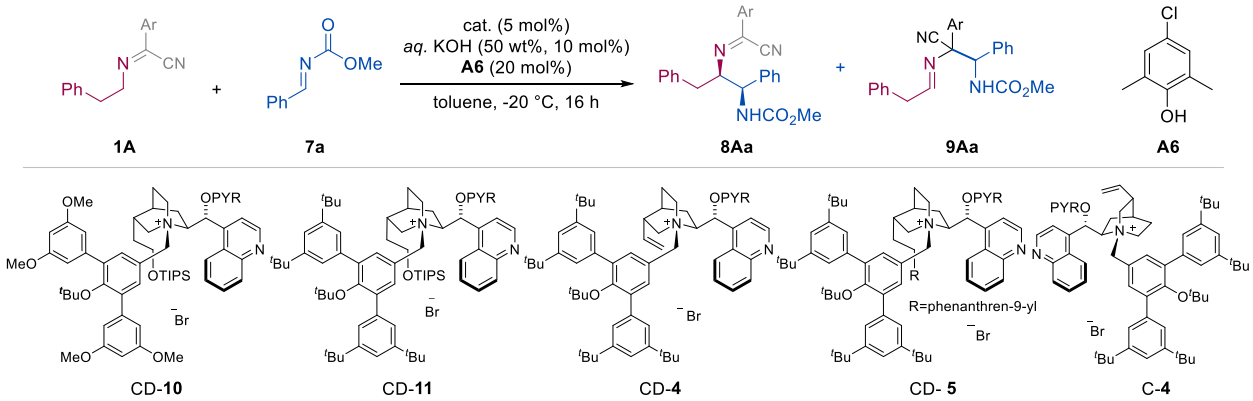


Fig. 4 Substrate scope of amine α-C–H functionalization with enals. The reactions were performed with achiral amine **1** (0.2 mmol), enal **2** (0.4 mmol), catalyst C-**4** (0.01 mmol, 5 mol %), **A4** (0.04 mmol, 20 mol %), saturated aqueous LiOH (10 mol %) in toluene/ether (1.3 mL/0.7 mL) at 0°C; rr (**3**/**5**) and dr were determined by NMR analysis; er was determined by SFC on a chiral column; yields of isolated chiral amines **4**; the absolute configurations of **4** were assigned by analogy. [a]C-**2** (0.01 mmol, 5 mol %), aqueous KOH (50 wt %, 10 mol %) were used. [b]**A4** was not used, toluene (4 mL) was used, -20 °C. [c]C-**2** (0.01 mmol, 5 mol %), **A4** (0.04 mmol, 20 mol %), aqueous KOH (50 wt %, 20 mol %) in toluene (2.0 mL) at 0 °C. [d]*p*-nitrobenzoyl chloride (1.0 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2 (0.1 M), 0 °C.



entry	catalyst	conversion	rr (8Aa/9Aa)	dr (8Aa)	er (8Aa)
1[a]	CD-**10**	69%	>95:5	>95:5	92:8
2	CD-**10**	>99%	>95:5	>95:5	95:5
3	CD-**11**	>99%	>95:5	>95:5	97:3
4	CD-**4**	95%	>95:5	>95:5	90:10
5	CD-**5**	36%	>95:5	>95:5	94:6
6	C-**4**	94%	>95:5	>95:5	12:88
7	TBAB	50%	15:85	--	--

Fig. 5 Catalyst optimization. The reaction was performed with amine **1A** (0.2 mmol), aldimine **7a** (0.4 mmol), **A6** (20 mol %), catalyst (0.01 mmol, 5 mol %), aqueous KOH (50 wt %, 10 mmol %) in toluene (2 mL) at -20°C; conversion, rr and dr were determined by NMR analysis; er was determined by SFC on a chiral column. [a]In the absence of **A6**.

We subsequently investigated the substrate scope under these optimized reaction conditions. In the presence of CD-**11**, a variety of *N*-arylidene alkyl amines **1** underwent smooth α-C–H functionalization with various aldimines **7**, producing chiral diamines **8** in >95:5 rr, >95:5 dr, 90:10–98:2 er and 71–92% yields. CD-**11** demonstrated excellent tolerance of organic functionalities, such as thiophene (**8Ha**), ethers (**8Ia**–**Ka**), acetal (**8La**), alkene (**8Ma**) and alkyne (**8Oa**), bromide (**8Pa**), trifluoromethyl (**8Ua**), alkane (**8Va**) and ester (**8Wa**). The substrate scope of aldimines **7** was also examined (Fig 5B). As shown, halogens (**8Ab**–**d**, **8Af**–**g**, **8Al**–**m**, **8Kb**), alkoxy (**8Ae**, **8Ai**, **8Ve**), alkyl (**7Ah**, **8Aj**, **8Am**, **8Wj**) and carbonyl (**8Ak**) were tolerated at various positions on the aromatic ring. Aldimines bearing naphthalene (**8An**) and thiophene (**8Ao**) were also tolerated. This tolerance of variations in both amines **1** and imines **7** allowed the reaction to provide direct access to a broad range of chiral diamines.

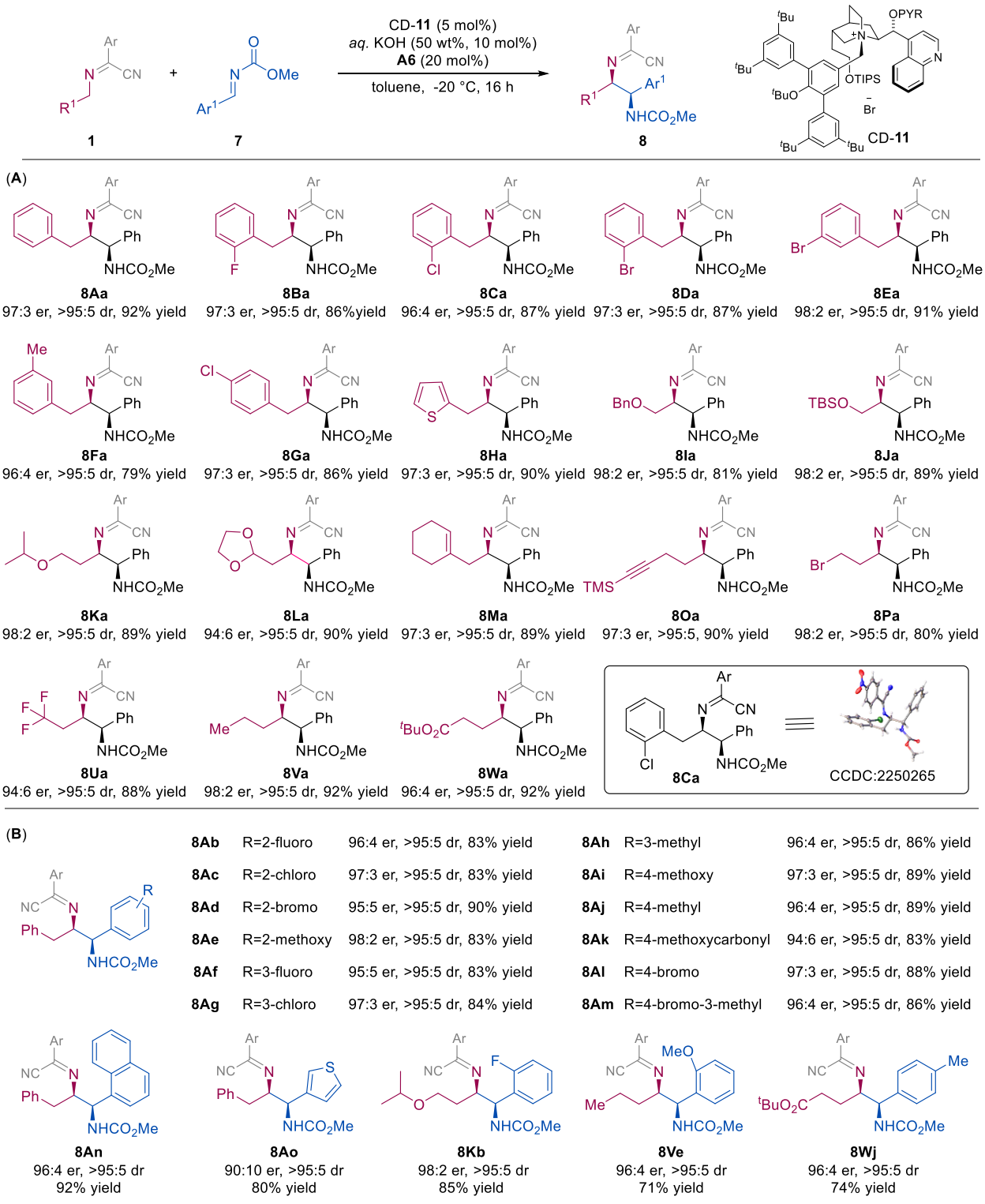


Fig. 6 Substrate scope of amine α-functionalization with aldimines. The reaction was performed with amine **1** (0.2 mmol), aldimine **7** (0.4 mmol), **A6** (20 mol %), catalyst CD-**11** (0.01 mmol, 5 mol %), aqueous KOH (50 wt %, 10 mmol %) in toluene (2 mL) at -20°C; rr and dr were determined by NMR analysis; er was determined by SFC on a chiral column; yields of isolated chiral diamines **8**.

As shown in Figure 7A, the reaction of *N*-arylidene amine **1A** with acrolein (**2a**) was carried out at a preparative scale without deterioration in selectivities. Notably, we found that the *N*-(4-

nitrophenyl)methylene group of **4Aa** is readily removed by methanolic hydrochloride at room temperature to produce chiral amine **11** as hydrogen chloride salt (Figure 7A). Treatment of the Mannich product **8Aa** with 3*M* HCl at room temperature removed the *N*-(4-nitrophenyl)methylene group, leaving the methylcarbamate group intact (Figure 7B). The chiral α,α-dialkyl amines **3Aa** were converted to other functionalized α,α-dialkyl amines (Figure 7C).

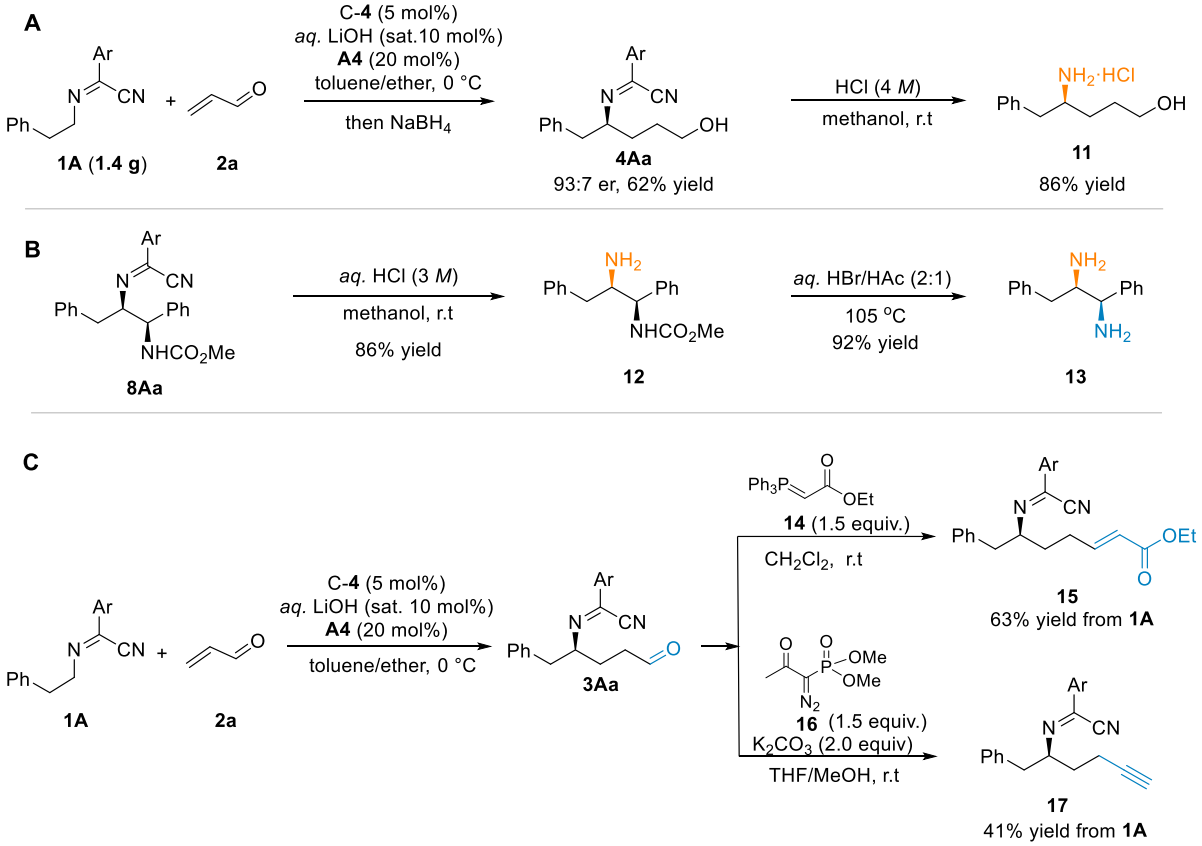


Fig. 6 Gram-scale reaction and product derivatizations.

In this study, we show that *N*-arylidene alkyl amines can be activated as α-nitrogen carbanions in asymmetric nucleophile-electrophile reactions. These results provide a new strategy for asymmetric transformation of achiral alkyl amines into chiral amines. We anticipate that this strategy could find wide applications in metal- and organo-catalytic transformations involving α-nitrogen carbanions.

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Acknowledgments: We thank the Instrumentation and Service Center for Molecular Sciences and the Instrumentation and Service Center for Physical Sciences at Westlake University for assistance in measurement/data interpretation. We thank Dr. Xingyu Lu and Dr. Xiaohuo Shi at Westlake University for assistance in the NMR measurement, Dr. Yinjuan Chen at Westlake University for assistance of the HRMS measurement, and Dr. Xiaohe Miao at Westlake University for assistance in the X-ray measurement.

Funding:

National Natural Science Foundation of China U22A20389

Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang 2020R01004

Foundation of Westlake University

Author contributions:

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Writing – review & editing: JL, LD, TD, XH

Competing interests: The authors declare no competing interests.

Data and materials availability: All data are available in the main text or the supplementary materials.

Supplementary Materials

Materials and Methods

Supplementary Text

Figure S1-2

Tables S1 to S5

References (*1-7*)