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Catalytic Asymmetric Umpolung Allylation of Imines

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Ⓢ *Supporting Information*

ABSTRACT: Here we report an iridium-catalyzed asymmetric umpolung allylation of imines as a general approach to prepare 1,4-disubstituted homoallylic amines, a fundamental class of compounds that are hitherto not straightforward to obtain. This transformation proceeds by a cascade involving an intermolecular regioselective allylation of 2-azaallyl anions and a following 2-aza-Cope rearrangement, utilizes easily available reagents and catalysts, tolerates a substantial scope of substrates, and readily leads to various enantioenriched, 1,4-disubstituted homoallylic primary amines.

Because chiral amine units are present in a large number of pharmaceuticals, agrochemicals, and ligands to transition metals, synthetic methods for building these motifs have been pursued actively.[1] Attack of carbon-based nucleophiles to imines (as electrophiles) constitutes one of the most frequently utilized strategies to access chiral amines.[2] For example, numerous elegant catalytic asymmetric methods[2] have been developed to prepare enantioenriched homoallylic amines (**1**+**2** to **4** via **3**, Scheme 1a). Within this regime, a 1,2-disubstituted product **4** is usually formed when a linear allylmetal reagent such as **2**[3] is employed as the nucleophile, as explained by transition states **3**.[4] However, catalytic, enantioselective approaches to make 1,4-disubstituted homoallylic amines (cf. **10** in Scheme 1c) with general substrate scope are still rare to date.[5]

The umpolung[6] functionalization of imines, in which imines serve as nucleophiles via the intermediacy of 2-azaallyl anions,[7] represents a new paradigm for amine synthesis (**5** to **7** via **6**/**6′**, Scheme 1b). This strategy may not only obviate the generation and use of sensitive organometallic reagents and/or activated imine species (cf. **1** and **2** in Scheme 1a) but also readily lead to primary amines, arguably the most synthetically versatile class of amines under mild conditions. Moreover, through unconventional ways of bond connections, the umpolung reactions may give products that are traditionally challenging to prepare. In spite of these advantages, application of the umpolung reaction mode of imines in synthesis,[7−11] especially in the context of asymmetric catalysis, remains scarce.

Many factors may have hampered the development of such umpolung processes in Scheme 1b. For example, the products of these reactions (e.g., **7**) contain the same (imine) functional group as the starting materials (e.g., **5**) and therefore may undergo deprotonation (to give 2-azaallyl anions) under the reaction conditions too, an event that will deteriorate the stereointegrity of the initially formed products.[12] Moreover, although imines (as electrophiles) have only one reactive carbon center, 2-azaallyl anions (as nucleophiles) contain two, as reflected by the two resonance structures **6** and **6′**. From the perspective of product diversity, selective functionalization at the Cα (to form **7**) over the Cα' position (to form **7′**) is preferred. However, achieving such regioselectivity could be nontrivial. Breakthroughs in the enantioselective arylation[10] and Michael addition[11] of 2-azaallyl anions have been reported, and each was accomplished through sophisticated design of chiral catalysts or ligands. The asymmetric umpolung allylation of imines, which will lead to valuable homoallylic amines, is still an unmet challenge. Here we report a general, iridium-based approach to accomplish the catalytic, asymmetric umpolung allylation of imines (**5**+**8** to **10** via **9**, Scheme 1c). The overall process consists of a Cα'-selective allylation of imine **5** that gives terminal alkene **9** first, and a following facile, stereospecific 2-aza-Cope rearrangement[13] of **9** that delivers the Cα-functionalized product **10** ultimately. The whole transformation, which often occurs in tandem, utilizes readily available starting materials and displays significant substrate scope. This reaction provides a solution to

Scheme 1. (a) Classical Methods of Making Homoallylic Amines; (b) Umpolung Functionalization of Imines (Rare); (c) An Umpolung Allylation/2-aza-Cope Rearrangement Sequence to Chiral Homoallylic Amines (This work)

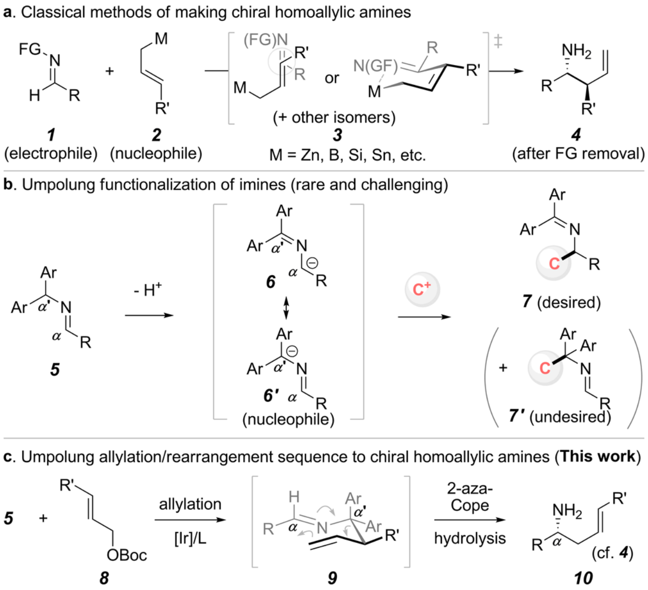

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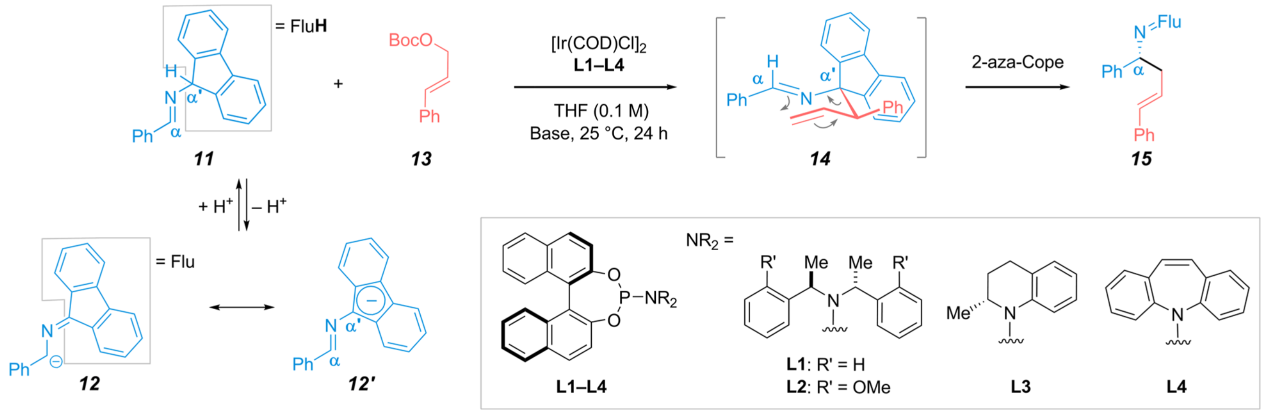
Table 1. Condition Optimization for Asymmetric Umpolung Allylation Reaction of Imine 11[a]



entry	base	ligand	yield	ee	entry	base	ligand	yield	ee
1	LiHMDS	**L1**	88%	50%	6	DABCO	**L1**	3%[b]	N.D.
2	KOtBu	**L1**	84%	17%	7	Et_3N	**L1**	<2%[b]	N.D.
3	LiOtBu	**L1**	48%	3%	8	DBU	**L2**	99%	96%
4	TMG	**L1**	69%	96%	9	DBU	**L3**	43%	−85%
5	DBU	**L1**	99%	95%	10	DBU	**L4**	38%	24%

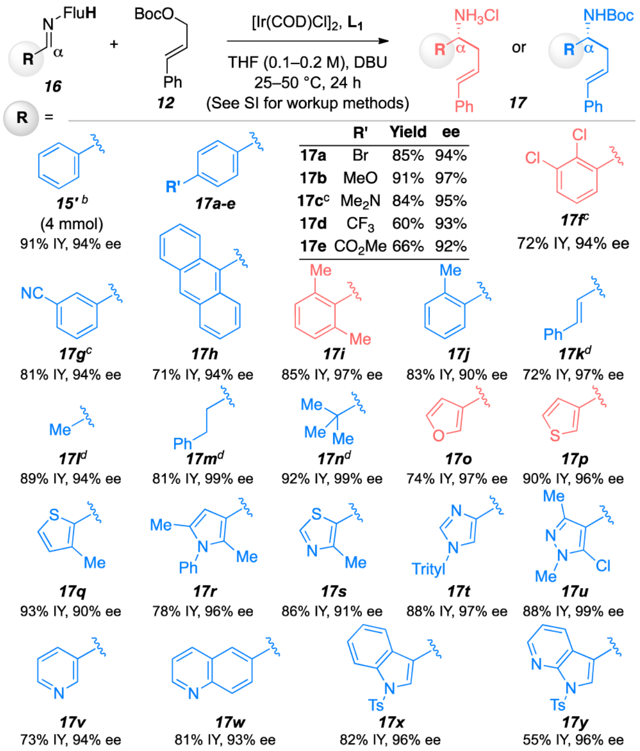
[a]Conditions: **11** (0.11 mmol), **13** (0.1 mmol), $[Ir(COD)Cl_2$ (3 mol %), **L** (6 mol %). [b]Starting materials recovered. Yields were determined by ^1H NMR spectroscopy with 1,3,5-trimethylbenzene as internal standard; ee's were determined by HPLC analysis.

the synthesis of enantioenriched, 1,4-disubstituted homoallylic amines.

We commenced our study of the umpolung reaction of imines by investigating the iridium-mediated allylation of *N*-fluorenyl imine **11** with *tert*-butyl cinnamyl carbonate (**13**, Table 1). Imine **11**[8i,j,10,14] was selected as our substrate for multiple reasons. First, it could be prepared readily and efficiently by the condensation between 9*H*-fluoren-9-amine and benzaldehyde, without the need for chromatography. Besides, because of the aromatic stablibilization of the resulting fluorenyl anion (cf. **12′**), the Cα'-H bond of **11** is fairly acidic and can be deprotonated under mildly basic conditions[15] (**11** to **12**/**12′**). We used iridium-based catalysts in this study for their outstanding performances in conducting selective allylation of various types of nucleophiles, as demonstrated by other groups[13a,16] and by our group[17] as well. In practice, we subjected **11** and **13** to the standard iridium-catalyzed allylation reaction conditions using **L1**[18] as the chiral ligand and LiHMDS as base (entry 1, Table 1). Under these conditions, we found that, somewhat to our surprise, product **15** (as the *E* isomer) was directly formed in a clean fashion. The direct formation of the linear (1,4-disubstituted) product **15** under the catalysis of an iridium complex that usually mediates branch-selective allylation was rationalized by (i) the initial branch-selective allylation of 2-azaallyl anion **12**/**12′** occurred at the (more encumbered) Cα' position selectively[8i,j,10] to deliver **14** first; and (ii) intermediate **14** underwent a 2-aza-Cope rearrangement[19] spontaneously at 25 °C to yield **15**. Each of these two outcomes might have benefited from the unique properties of the fluorenyl group in **11**, which could both control the regioselectivity of the allylation step (through stabilizing the negative charge at Cα' position) and facilitate the 2-aza-Cope rearrangement [through conjugation with the C═N bonds in the transition state (TS) and product]. The enantiomeric excess (ee) of **15** obtained under entry 1 conditions was moderate. We surmised that the strong amide base (LiHMDS) used is capable of deprotonating product **15** and responsible for its compromised ee. Guided by this thinking, we screened a few weaker bases. Although the use of metal alkoxides gave inferior results (entry 2 and 3), the use of organic base 1,1,3,3-tetramethylguanidine (TMG, entry 4) or 1,8-diazabicycloundec-7-ene (DBU, entry 5) afforded **15** with excellent enantiocontrol, with the latter furnishing **15** also in high yield. However, further tuning down the basicity of the reaction medium by the use of trialkylamine bases resulted in almost no product formation (entry 6 and 7). In the presence of DBU, we also examined the behaviors of other commonly used ligands in this reaction (**L2**–**L4**,[20] entry 8–10), and found that **L2** provided **15** with excellent results as well. Nonetheless, we used **L1** in most of the following reactions for its simplicity.

With optimal reaction conditions established, we continued to explore the scope of this transformation (Table 2 and 3). It is noteworthy that the products of these reactions were readily hydrolyzed to give primary amines, and isolated as the corresponding HCl salt or *N*-Boc amines. As shown in Table 2, a broad array of *N*-fluorenyl imines **16** participated in this reaction efficiently. For example, we found this reaction could be performed on a 4 mmol scale, using 1.5 mol % $[Ir(COD)Cl]_2$, with minimal effects on the yield and selectivity (**15′**). Moreover, imines containing electron-neutral (**17a**), electron-rich (**17b**–**c**) or electron-deficient (**17d**–**g**) aromatic rings all proved to be competent reaction partners. Notably, product **17f** could be derived to a potential pesticide in one step (Figure S2 in SI). Further, imines with sterically demanding groups (**17h**–**j**) underwent this transformation smoothly, and gave the Cα-functionalized products in high selectivities. Besides, imines originated from cinnamyl aldehyde (**17k**) or aliphatic aldehydes (**17l**–**n**) are also tolerated when **L2** was used as the ligand. Importantly, imines with various heteroaryl groups, including furan (**17o**), thiophene (**17p**–**q**), pyrrole (**17r**), thiazole (**17s**), imidazole (**17t**), pyrazole (**17u**), pyridine (**17v**), quinoline (**17w**), indole (**17x**), and azaindole (**17y**) can all be accommodated, underscoring the generality of this transformation. Lastly, this reaction displayed good regioselectivity for most substrates in this Table, although in the cases of **17c**, **17f**, and **17g**, formation of the corresponding branched isomers

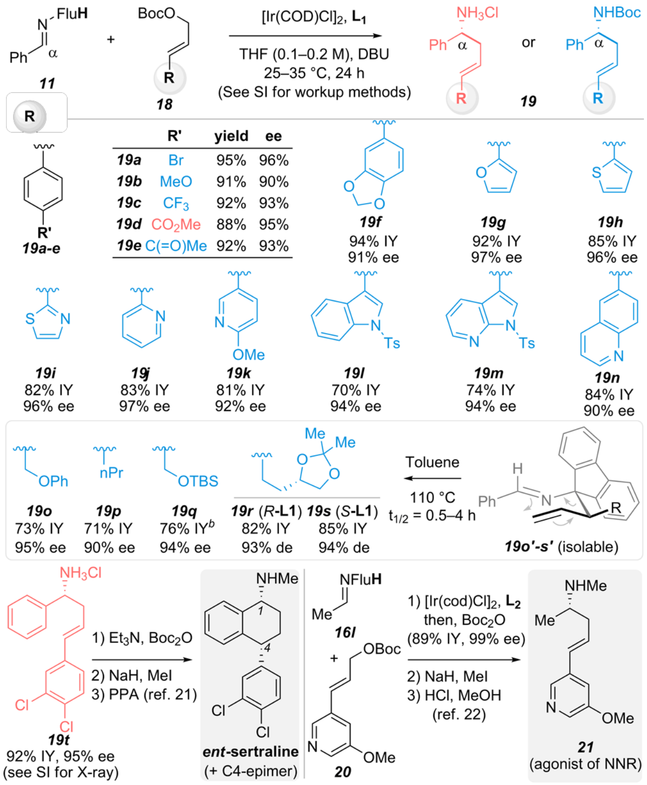
Table 2. Substrate Scope for Imine Reaction Partner[a]



	R′	Yield	ee
17a	Br	85%	94%
17b	MeO	91%	97%
17c[c]	Me_2N	84%	95%
17d	CF_3	60%	93%
17e	CO_2Me	66%	92%

[a]Conditions: **16** (0.33 mmol), **12** (0.3 mmol), $[Ir(COD)Cl]_2$ (3 mol %), **L1** (6 mol %). Isolated yields (IY) of the *N*-Boc amines or HCl salts were reported; ee's of imine products were determined by HPLC analysis. [b]4 mmol scale using $[Ir(COD)Cl]_2$ (1.5 mol %), **L1** (3 mol %), THF (0.2 M), 28 °C. [c]Branched isomer was also formed; the reported yield refers to that of the major isomer. [d]The reactions were run using **L2** as ligand. See SI for experimental details.

Table 3. Substrate Scope for Allylic Carbonates[a]



	R′	yield	ee
19a	Br	95%	96%
19b	MeO	91%	90%
19c	CF_3	92%	93%
19d	CO_2Me	88%	95%
19e	C(=O)Me	92%	93%

[a]Conditions: **11** (0.33 mmol), **18** (0.3 mmol), $[Ir(COD)C1]_2$ (3 mol %), **L1** (6 mol %). Isolated yields (IY) were reported; ee's and de's were determined by HPLC analysis. [b]The TBS group was removed during workup. NNR: neuronal nicotinic receptor. See SI for experimental details.

(~10%) [by the initial Cα (as opposed to Cα′) attack] was also observed (see SI).

This transformation demonstrated a broad scope with respect to the allylic carbonate reaction partner (**18**) as well. As summarized in Table 3, cinnamyl carbonates containing electron-donating (**19b**) or withdrawing groups (**19c−e**) could engage in this reaction, and those with functional groups such as halogen atoms (**19a**), esters (**19d**), ketones (**19e**), silyl ethers (**19q**), and acetonides (**19r−s**) were also tolerated. In addition, allylic carbonates bearing a heterocycle, such as dioxolane (**19f**), furan (**19g**), thiophene (**19h**), thiazole (**19i**), pyridine (**19j−k**), indole (**19l**), azaindole (**19m**), and quinoline (**19n**) partook in this reaction, delivering the corresponding amine products in good yields and selectivities. Intriguingly, when aliphatic allylic carbonates were used, the reaction stalled after the first allylation step, and the branched products **19o′-s′** were accumulated without further rearranging to the final linear products under the reaction conditions (i.e., at 25 °C for 24 h). The isolation of **19o′-s′** supports our proposed reaction pathway (Table 1). The fact that **19o′-s′** undergo rearrangement at slower rates than compound like **14** (Table 1) is congruent with the notion that, compared with aryl groups, alkyl groups are less able to stabilize the corresponding TS structures. Nonetheless, desired products **19o-s** could be obtained cleanly upon heating of **19o′-s′** (see SI).

To demonstrate further the synthetic utility of this method, we have made **19t** (see SI for X-ray structure), a precursor to an intermediate used in the synthesis of *ent*-sertraline[21] (Table 3). Likewise, our method is well suited for the preparation of **21**, an agonist of neuronal nicotinic receptor (NNR).[22] Some additional applications of this reaction can be seen in Figure S2 of SI.

In conclusion, through developing an iridium-catalyzed asymmetric umpolung allylation of imines, we have established a general protocol to prepare 1,4-disubstitued homoallylic amines, a class of compounds that are not straightforward to obtain using traditional methods. This transformation proceeded by a regioselective allylation reaction of 2-azaallyl anions and a facile (and often spontaneous) 2-aza-Cope rearrangement. This reaction permitted the use of a remarkable range of substrates, including those with electrophilic functional groups, bulky substituents, or nitrogen-containing heterocycles, yielding various 1,4-disubstituted homoallylic amines in high yields and enantioselectivities. Besides its immediate synthetic utility, we expect this method will inspire new development in the area of asymmetric umpolung functionalization of imines.

■ ASSOCIATED CONTENT

❺ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05288.

Experimental procedures and compound characterization (PDF)

Data for $C_{16}H_{16}Cl_3N$ (CIF)

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Author Contributions

‡These authors contributed equally. All authors have performed the experiments and given approval to the final version of the paper.

Notes

The authors declare no competing financial interest.

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