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Chiral Ugi-Type Amines: Practical Synthesis, Ligand Development, and Asymmetric Catalysis

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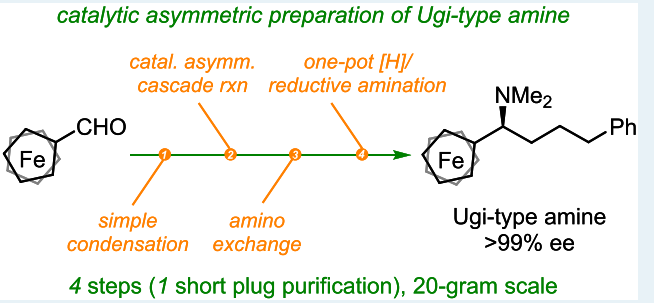
ABSTRACT: Ugi's amine has become one type of privileged chiral skeleton for chiral ligand design bearing central/planar chirality, and such ligands have exhibited tremendous success in various asymmetric catalysis. However, the current access to enantiopure Ugi's amine is quite tedious and relies heavily on optical resolution, which impedes its practical applications, to some extent. Herein, we present a facile asymmetric synthesis of enantioenriched Ugi-type amines bearing a long-carbon chain through Ir-catalyzed cascade allylation/2-aza-Cope rearrangement, followed by amino exchange and Pd/C-catalyzed one-pot hydrogenation/reductive amination. The protocol could be readily scaled up, and it has been conducted in 20-g-scale asymmetric synthesis of (*S*)-Ugi-type amine from commercially available reagents, in >99% ee and >70% overall yield in four steps with one short silica gel-plug purification. (S,R_p)-PPFA-type and (S,R_p)-Josiphos-type ligands, readily prepared from the achieved Ugi-type amine, exhibited higher or comparable asymmetric induction and catalytic efficacy in several Cu(I)-catalyzed asymmetric reactions, which indicated great potential of the applications of the readily accessible Ugi-type amines in ligand/catalyst design.



KEYWORDS: *asymmetric synthesis, ligand design, chiral amine, planar chirality, central chirality*

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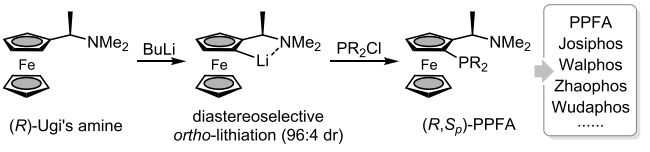
The development of efficient chiral ligands derived from privileged chiral structures incorporating central, axial, and/or planar chirality are significantly important in transition-metal-catalyzed asymmetric synthesis.[1] As an example, *N,N*-dimethyl-1-ferrocenylethylamine (Ugi's amine)[2] represents one type of the privileged chiral skeleton, which could readily induce additional planar chirality from its intrinsic central chirality.[3] Since the seminal pioneering contribution of Ugi and co-workers on the C2 functionalization of enantiopure Ugi's amine via diastereoselective *ortho*-lithiation[2] and further unique stereospecific S_N1-type substitution reaction of the dimethylamino moiety with configuration retention (Scheme 1),[4] a variety of chiral ligands, such as PPFA,[5] TRAP,[6] Josiphos,[7] Walphos,[8] Bophos,[9] Zhaophos,[10] Wudaphos,[11] etc., have been developed and exhibited tremendous success and efficacy in broad types of transition-metal-catalyzed asymmetric transformations.

Scheme 1. Ugi's Amine, Diastereoselective *ortho*-Lithiation, and Selected Ugi's Amine-Based Chiral Ligands



Despite the significance of Ugi's amine in ligand design, the modulation of such a skeleton is extremely challenging and the current available methods to access enantioenriched Ugi's amine are still rather limited. The classical method to chiral Ugi's amine relies heavily on the optical resolution of racemic Ugi's amine using a stoichiometric amount of resolving agents, as shown in Scheme 2a,[2] and only a few attempts have been documented on this type of framework by the catalytic asymmetric preparation of enantioenriched 1-ferrocenyl alcohols, followed by acetylation with acetic anhydride and amination with dimethylamine (Scheme 2b).[12,13] The catalytic asymmetric construction of Ugi-type amines remained a formidable task and is highly desirable from the viewpoint of synthetic practicability. Previously, We and others have reported transition-metal-catalyzed asymmetric cascade allylations/2-aza-Cope rearrangement of aldimines to deliver chiral homoallylic amines.[14,15] We envisioned that the strategy of chirality transfer might also work for ferrocenecarboxaldehyde-derived imine and therefore allow for a direct and catalytic

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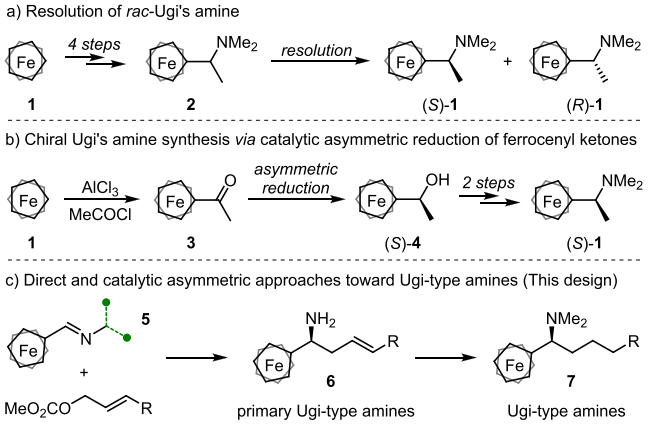
Scheme 2. Reported Approaches to Enantioenriched Ugi's Amine Derivatives and This Design

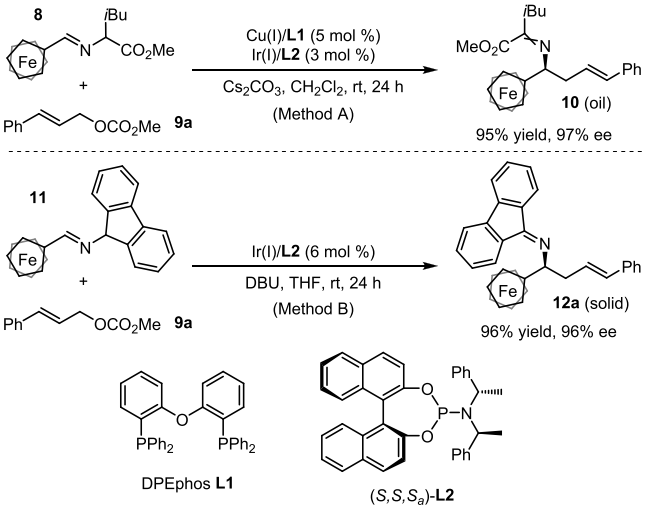


asymmetric approach toward primary Ugi-type amines (Scheme 2c). The long-chained Ugi-type amines are expected to induce better planar stereochemical control in diastereoselective *ortho*-lithiation, considering that the diastereoselectivity in the case of Ugi's amine arises from a strong repulsive interaction between the methyl group at the central stereocenter and the lower Cp ring.[2] However, one conspicuous challenge had to be met for the successful realization of this design: would the cascade protocol also provide the stereointegrity for both the initial allylation and the ensuing rearrangement, with respect to the aldimine emanated from the sterically bulky three-dimensional aldehyde? Herein, we illustrate that a scalable catalytic asymmetric synthesis of enantioenriched long-chained Ugi-type amines, the development of chiral ligands with this new skeleton and preliminary applications in enantioselective catalysis.

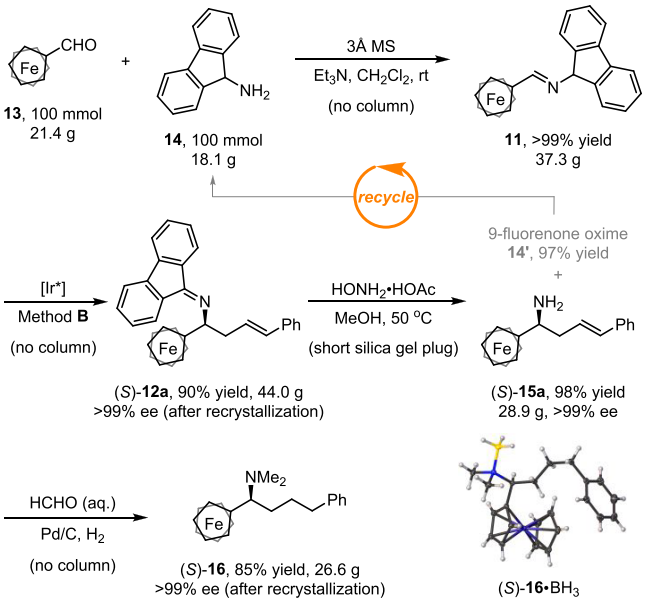
The aldimine substrates **8** and **11** were readily prepared in quantitative yield by simple condensation of ferrocenecarboxaldehyde with methyl *l*-leucinate hydrochloride and 9-aminofluorene hydrochloride, respectively (for details, see the Supporting Information). Since the bimetallic Cu/Ir[14a] and monometallic Ir catalysts[15a16] have been discovered particularly effective for chiral homoallylic amine synthesis, we initially surveyed these two catalytic systems for the designed cascade allylation/2-aza-Cope rearrangement of **8** and **11**, respectively (see Scheme 3). The desired rearranged products **10** and **12a** were respectively obtained in high yield with excellent enantioselectivity under each optimal reaction conditions, which demonstrates that the sterically bulky three-dimensional ferrocene moiety does not deteriorate the efficacy and stereointegrity of this cascade transformation. Although the cost-efficiency favors a bimetallic system, because of the much less expensive starting material methyl *l*-leucinate hydrochloride,[17] monometallic catalytic system turned out to be the better one given that the solid product **12a** is easier to be handled for the scale-up synthesis (vide infra) (For the experimental results with other allylic carbonates, see the Supporting Information for details.)

Encouraged by these experimental results, tens-gram-scale synthesis of enantioenriched long-chained Ugi-type amine **16** was conducted (see Scheme 4). Ferrocenecarboxaldehyde-derived *N*-fluorenyl imine **11** could be easily obtained in quantitatively yield through simple condensation of commercially available ferrocenecarboxaldehyde **13** and 9-aminofluorene hydrochloride **14** under basic conditions. Through

Scheme 3. Initial Study on the Synthesis of Chiral Long-Chained Ugi-Type Amine Derivative



Scheme 4. Practical Preparation of Enantioenriched Long-Chained Ugi-Type Amine (*S*)-15 and (*S*)-16



aforementioned Ir-catalyzed cascade allylation/2-aza-Cope rearrangement of *N*-fluorenyl imine **11** at 100 mmol scale, the rearranged product (*S*)-**12** could be purified via recrystallization and obtained in 90% yield with >99% ee. Subsequent amino exchange with $HONH_2$•HOAc released primary amine (*S*)-**15** in quantitative yield[14a] without erosion of enantioselectivity through a short plug of silica gel purification. Meanwhile, 9-fluorenone oxime, isolated in quantitively yield, could be directly hydrogenated back to 9-aminofluorene in 90% yield. The target long-chained Ugi-type amine (*S*)-**16** was readily obtained as a brown crystalline solid, *which is an unexpected bonus for further manipulation, compared to the oil Ugi's amine*, in 85% yield from (*S*)-**15** via Pd/C-catalyzed one-pot hydrogenation/reductive amination. Note that the entire four-step synthetic sequence was efficiently accomplished on a 20-g scale with only one short silica gel plug purification, and the key intermediate (*S*)-**12** could be readily achieved through simple crystallization. The absolute config-

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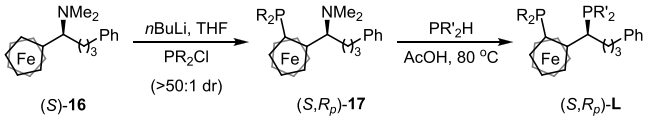
uration of (*S*)-**16** was determined by X-ray diffraction (XRD) analysis of (*S*)-**16**·BH_3 complex.[18]

Having established the readily scalable synthetic route to access enantioenriched long-chained Ugi-type amine (*S*)-**16**, we next prepared some chiral ligands with this novel chiral skeleton and examined their performance in transition-metal-catalyzed asymmetric transformations. As shown in Scheme 5,

Scheme 5. Synthesis of Chiral PPFA-Type and Josiphos-Type Ligands



(*S*,R_p)-**17a** (R = Cy): 89% yield
(*S*,R_p)-**17b** (R = Ph): 88% yield

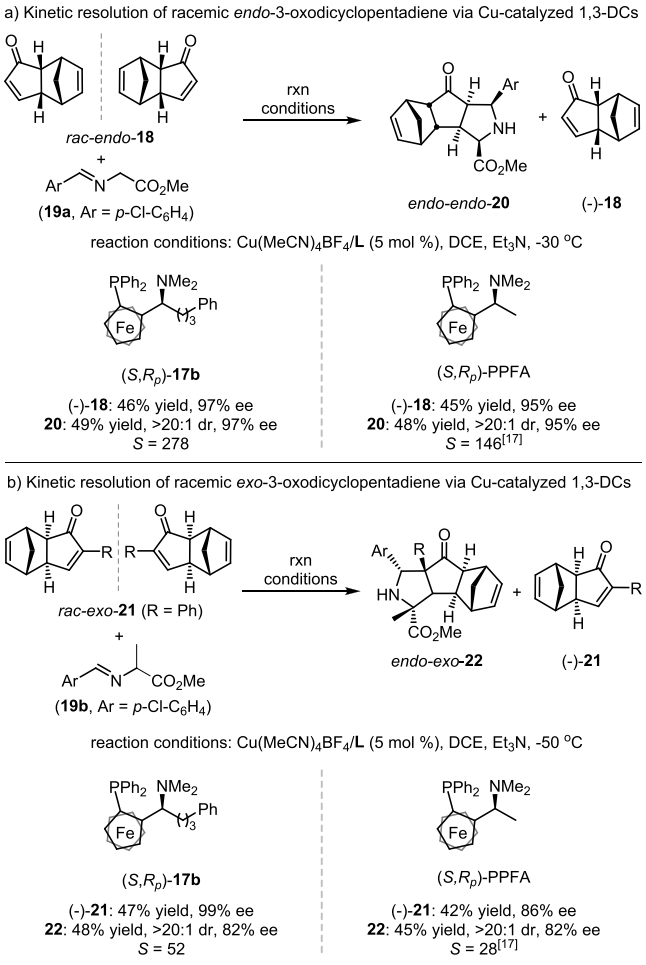
(*S*,R_p)-**L3** (R = Cy, R' = Ph): 87% yield
(*S*,R_p)-**L4** (R = Cy, R' = Cy): 81% yield
(*S*,R_p)-**L5** (R = Ph, R' = Cy): 84% yield
(*S*,R_p)-**L6** (R = Ph, R' = Ph): 93% yield

treatment of (*S*)-**16** with *n*-BuLi at room temperature via direct diastereoselective *ortho*-lithiation followed by trapping with PR_2Cl, led to easy access to PPFA-type ligands (*S*,R_p)-**17a** and (*S*,R_p)-**17b** in high yield with impressive diastereoselectivity (>50:1 diasteromeric ratio (dr), based on the crude ^{31}P NMR), which is ascribed to the long carbon chain on the stereogenic center.[2] Subsequent stereospecific S_N1-type reaction of the dimethylamino moiety with PR'_2H reagent, which occurred with full retention of configuration, furnished Josiphos-type chiral bisphosphine ligands (*S*,R_p)-**L3**−**L6** in satisfactory yields.

PPFA-type ligands (*S*,R_p)-**17** were used for the direct comparison of their catalytic performances with the original PPFA ligand in transition-metal-catalyzed asymmetric reaction. We conducted a comparative ligand evaluation in kinetic resolution of the racemic convex (±)-*endo*-3-oxodicyclopentadiene and (±)-*endo*-3-oxodicyclopentadiene via Cu(I)-catalyzed 1,3-dipolar cycloaddition, and (*S*,R_p)-PPFA was originally revealed as the superior chiral ligand in effecting such asymmetric transformations.[19] The newly developed (*S*,R_p)-**17b** was also found equally potent in this Cu(I)-catalyzed kinetic resolution protocol with racemic (±)-*endo*-3-oxodicyclopentadiene **18** as the dipolarophile, affording the recovered (−)-*endo*-**18** in 46% yield with 97% enantiomeric excess (ee), accompanied by the cycloadduct *endoendo*-**20** in 49% yield with exclusive diastereoselectivity and 97% ee (*S* = 278) (Scheme 6a). Although (*S*,R_p)-PPFA was also identified as the best ligand for the kinetic resolution of racemic (±)-*exo*-3-oxodicyclo-pentadienes, racemic (±)-2-phenyl-substituted *exo*-3-oxo-dicyclopentadiene **21** was revealed as a challenging molecule and was only resolved with *S* factor of 28 (45% yield and 82% ee for *endoexo*-**22**; 42% yield and 86% ee for *exo*-(−)-**21**) through this protocol in previous work. Pleasingly, employing (*S*,R_p)-**17b** as the chiral ligand under otherwise identical reaction conditions, (±)-*exo*-**21** could be efficiently resolved with the significantly enhanced *S* factor (52), delivering a 47% yield of recovered *exo*-(−)-**21** with 99% ee, accompanied by a 48% yield of cycloadduct *endoexo*-**22** with 82% ee (Scheme 6b), which is obviously better than that obtained with the corresponding (*S*,R_p)-PPFA.[19]

Cu-catalyzed asymmetric Michael addition of organometallic reagents to α,β-unsaturated compounds has been extensively investigated over the past decades.[20] (*R*,S_p)-Josiphos and (*R*)-Tol-BINAP have been demonstrated to be the highly

Scheme 6. Comparative Studies of (*S*,R_p)-PPFA and (*S*,R_p)-17b in Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides



enantioselective ligands for Cu(I)-catalyzed asymmetric Michael addition of Grignard reagents to α,β-unsaturated esters for the synthesis of enantioenriched β-substituted esters.[21] Given these facts, we begin by evaluating Josiphos-type ligands (*S*,R_p)-**L3**−**L6** in the model addition reaction of ethyl magnesium bromide **24a** to methyl (*E*)-5-pheynlpent-2-enoate **23a**. After a thorough optimization (see the Supporting Information for details), ligand (*S*,R_p)-**L3** was revealed as the best choice, in terms of reactivity and enantioselectivity with $Cu(CH_3CN)_4BF_4$ as the metal source and dichloromethane as the solvent, and the reaction proceed smoothly, affording the desired product **25a** in 93% yield with 92% ee (Table 1, entry 1). Under the optimized reaction conditions, we further investigated the generality of substrate scope of Grignard reagents and α,β-unsaturated esters. As shown in Table 1, a series of linear alkyl Grignard reagents were well-tolerated in this Cu(I)/(*S*,R_p)-**L3**-catalyzed asymmetric Michael addition to methyl (*E*)-5-pheynlpent-2-enoate **23a**, affording the corresponding adducts **25b**−**25e** in high yields with excellent enantioselectivity (Table 1, entries 2−5). With MeMgBr as the nucleophile, consistent with previous reports,[21] the corresponding adduct **25f** could be obtained in high enantioselectivity albeit with moderate yield (Table 1, entry 6). Grignard reagent **24g** containing the C═C bond was also a viable nucleophile, providing the corresponding product **25g** in 94% yield with 97% ee (Table 1, entry 7). Next, the scope

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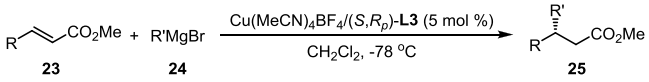
Table 1. Scope of Cu(I)-Catalyzed Asymmetric Michael Addition of Grignard Reagents to α,β-Unsaturated Esters[a]



entry	R	R′	25	yield[b] (%)	enantiomeric excess, ee[c] (%)
1	$PhCH_2CH_2$	Et	**25a**	93	92
2	$PhCH_2CH_2$	*n*Pr	**25b**	89	94
3	$PhCH_2CH_2$	*n*Bu	**25c**	88	97
4	$PhCH_2CH_2$	*n*Pentyl	**25d**	84	97
5	$PhCH_2CH_2$	*n*Heptyl	**25e**	93	97
6[d]	$PhCH_2CH_2$	Me	**25f**	45	91
7	$PhCH_2CH_2$	$CH_2{=}CH(CH_2)_2$	**25g**	94	97
8	Me	Et	**25h**	97	91
9	*n*-Pr	Et	**25i**	88	94
10[e]	*n*-Pr	Et	**25j**	81	91
11	*n*-hexyl	Et	**25k**	85	95
12[e]	*n*-hexyl	Et	**25l**	77	91
13	*i*-Pr	Et	**25m**	86	98
14[e]	Cy	Et	**25n**	87	95
15[f]	Ph	Et	**25o**	94	91
16	$PhCH_2$	Et	**25p**	96	92
17	2-furyl	Et	**25q**	74	97
18	2-thienyl	Et	**25r**	84	96

[a]All reactions were performed with 0.30 mmol **23** and 1.5 mmol **24** (1.0 M in ^{t}BuOMe) in 1.5 mL of CH_2Cl_2 within 8−12 h. [b]Yields refer to the isolated products after chromatographic purification. [c]The ee value was determined by chiral HPLC or GC analysis. [d]Reaction was performed at −40 °C. [e]Ethyl ester was used. [f]CuBr·SMe_2 was used.

generality, with respect to α,β-unsaturated esters, was further investigated, and an array of variety of α,β-unsaturated esters bearing linear or branched alkyl group, aryl or heteroaryl groups, all reacted smoothly with EtMgBr, affording the corresponding adducts in 74%−97% yields with 91%−98% ee (Table 1, entries 8−18). Those achieved comparative experimental results of Cu(I)/(S,R_p)-**L17b**-catalyzed 1,3-dipolar cycloaddition reactions and Cu(I)/(S,R_p)-**L3**-catalyzed Michael addition of Grignard reagents showcased great potential of the long-chained Ugi-type amines in asymmetric catalysis.

In summary, a practical catalytic asymmetric synthesis of Ugi-type amine has been successfully developed. Ir-catalyzed asymmetric cascade allylation/2-aza-Cope rearrangement of ferrocenecarboxaldehyde-derived *N*-fluorenyl imine, followed by amino exchange and Pd/C-catalyzed one-pot hydrogenation/reductive amination, led to chiral Ugi-type amine bearing long-carbon chain in excellent enantioselectivity (>99% ee). The current protocol represents the first method to access Ugi-type amine in catalytic asymmetric manner, featuring with readily available reagents, easy manipulation and scale-up to tens of grams, which pave the way for the practical utility of this privileged scaffold in asymmetric catalysis. PPFA-type and Josiphos-type chiral ligands bearing both central chirality and planar chirality were expediently prepared through C2 functionalization via a highly efficient diastereoselective *ortho*-lithiation and the ensuing stereospecific substitution. More importantly, the long-chained Ugi-type amine-based chiral ligands exhibited higher or comparable asymmetric induction and catalytic efficacy in several transition-metal-catalyzed asymmetric reactions, indicating great potential of the newly developed Ugi-type amines in ligand/catalyst design. Further investigation on mechanistic origin of the high enantioselectivity control and efficacy of Ugi-type amine-based ligands, as well as development of other kind of ligands/catalysts, are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04077.

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC spectra, (PDF)

Crystallographic data for (S)-**16**·BH_3 (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Xumu Zhang on the occasion of his 60th birthday.

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