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Introduction

Over the past decade, the field of visible-light photoredox catalysis has rapidly advanced as a sustainable methodology for exerting orthogonal activation modes to manipulate small organic molecules, in which photoinduced single-electron transfer triggers the in situ generation of active chemical species from organic substrates, thereby enabling a variety of unique chemical events to facilitate C–C and C–heteroatom bond formation. Recently, reaction promotion by combining photoexcitation and concomitant stereocontrol with the aid of catalytic chiral sources such as chiral Lewis acids or organocatalysts has become a topic of great interest and prompted the development of enantioselective photocatalysis. Herein, we report a cooperative catalytic system comprising a chiral Cu(I) complex and an Ir(III) photocatalyst fueled by visible-light irradiation that allows for seamless integration of the catalytic formation of α-amino alkyl radicals and subsequent enantioselective addition to α,β-unsaturated amides. A 7-aza-6-MeO-indoline attachment on the amide substrates plays a pivotal role in suppressing the undesired pathways, resulting in excellent enantioselectivity and enabling expedited access to valuable γ-aminobutyramides. The indoline amide was readily diversified with full recovery of the azaindoline attachment, highlighting the synthetic utility of this cooperative catalytic system.

Introduction of a 7-aza-6-MeO-indoline auxiliary in Lewis-acid/photoredox cooperative catalysis: highly enantioselective aminomethylation of α,β-unsaturated amides†

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An efficient cooperative chiral Lewis acid/photoredox catalytic system for engaging highly reactive radicals in highly enantioselective conjugate addition to α,β-unsaturated carboxyls is highly desirable. Direct photoexcitation of unbound substrates typically induces undesired background pathways for racemic products and remains a formidable challenge to be addressed in the area of enantioselective photocatalysis. Herein, we report a cooperative catalytic system comprising a chiral Cu(I) complex and an Ir(III) photocatalyst fueled by visible-light irradiation that allows for seamless integration of the catalytic formation of α-amino alkyl radicals and subsequent enantioselective addition to α,β-unsaturated amides.

A 7-aza-6-MeO-indoline attachment on the amide substrates plays a pivotal role in suppressing the undesired pathways, resulting in excellent enantioselectivity and enabling expedited access to valuable γ-aminobutyramides. The indoline amide was readily diversified with full recovery of the azaindoline attachment, highlighting the synthetic utility of this cooperative catalytic system.
Our recent efforts focusing on asymmetric catalysis led us to identify that 7-azaindoline amides are privileged substrates that drive a number of highly stereocontrolled C-C bond-forming reactions in the context of Cu(i) catalysis. However, the 7-azaindoline auxiliary had not been implemented in the field of photocatalysis and the use of inexpensive copper complexes is rarely explored in asymmetric photocatalysis. We reasoned that this auxiliary could also serve as a potential stereo-controlling unit in radical reactions and provide a powerful alternative to several challenging photocatalytic transformations. Herein, we established a photocatalytic additive-free protocol exerted by Cu(i)/Ir(m) dual catalysis to engage α,β-unsaturated 7-azaindoline amides and α-silylamines in a highly enantioselective radical conjugate addition. The intriguing substituent effect of the 7-azaindoline unit was first revealed by systematic studies and comparisons of the crystal structures of Cu(i)/amide complexes. The broad substrate generality is supported by divergent transformation of the 7-azaindoline moiety of the enantioenriched products and highlights the synthetic utility of the present catalytic protocol.

Results and discussion

We initiated our investigation with the prototypical 7-azaindoline amide 1a and α-silylamine 2a as an electrophile and radical source, respectively, where 1 mol% of [Ir(ppy)$_2$(dtb-bpy)]PF$_6$ was used as a photocatalyst under blue-light irradiation ($\lambda_{\text{max}}$ 448/455 nm). The initial attempt using a Cu(i)/amide complex as a typical chiral Lewis acid in acetonitrile at room temperature resulted in poor conversion to give the desired product 3aa (Table 1, entry 1). This is likely due to the decomposition of the Cu(i) complex as indicated by the deeply colored reaction mixture, preventing photoexcitation of the Ir(m) photocatalyst. In contrast, Cu(i) phosphine complexes emerged as a compatible chiral Lewis acid under blue-light irradiation, affording 3aa in moderate yield (entries 2–6). Among the chiral phosphines tested, a commercially available bimetal-type (R)-DM-Segphos (L2) afforded the highest enantioselectivity (89% ee), which was sensitive to the reaction temperature (entries 2–4). A protic solvent like ethanol was beneficial for increasing the yield to 73% (vide infra, see mechanistic discussion), but a reduction in solubility hampered the smooth progress of the reaction at −20 °C (entries 7 and 8). Aiming to attain homogeneity, we next evaluated a mixed solvent system, leading to the identification of EtOH : DME (1 : 3) as the optimal reaction media to give 3aa in 83% yield with 89% ee (entries 9–12). Lowering the reaction temperature to −30 °C did not further enhance the enantioselectivity, and the reaction became more sluggish (entry 13). No reaction occurred in the absence of a photocatalyst or light source, confirming that the photocatalytic activation of 2a is essential to the cooperative catalysis (entries 14 and 15). Conditions lacking a Cu(i) catalyst gave no product 3aa, indicating that the reaction system does not undergo a non-stereoselective background reaction (entry 16).

The necessity of the 7-azaindoline auxiliary was confirmed in a series of reactions using distinct α,β-unsaturated amides as acceptors of the in situ-generated radical (Table 2). Minute changing in the unsaturation of the heterocycle to 7-azaindole 4 resulted in no reaction. Isomeric 4-azaindoline 5 or indoline derivative 6 exhibited no reactivity, indicating that the coordination capability of the nitrogen atom at the 7-position is essential. Of note, a potentially chelating acyclic N-(2-pyridyl)amide 7 failed to promote the reaction, highlighting the exclusive nature of 7-azaindoline to engage the α,β-unsaturated carbonyl units in an asymmetric radical reaction. As expected, a Weinreb amide 8 and dimethyl amide 9 were incompatible substrates. Based on the apparent pivotal role of 7-azaindoline

| Entry | Ligand | Solvent | Temp (°C) | Yield (%) | ee (%) |
|-------|--------|---------|-----------|-----------|--------|
| 1     | L1     | MeCN    | 23        | 10        | ND     |
| 2     | L2     | MeCN    | 23        | 72        | 30     |
| 3     | L2     | MeCN    | 5         | 61        | 70     |
| 4     | L2     | MeCN    | −20       | 62        | 89     |
| 5     | L3     | MeCN    | 5         | 49        | 52     |
| 6     | L4     | MeCN    | 5         | 43        | −44    |
| 7     | L2     | EtOH    | 5         | 73        | 74     |
| 8     | L2     | EtOH    | −20       | Trace     | ND     |
| 9     | L2     | EtOH : MeCN (1 : 1) | −20 | 68 | 66 |
| 10    | L2     | EtOH : DME (1 : 1) | −20 | 77 | 76 |
| 11    | L2     | EtOH : DME (3 : 1) | −20 | 49 | 85 |
| 12    | L2     | EtOH : DME (1 : 3) | −20 | 83(80) | 89 |
| 13    | L2     | EtOH : DME (1 : 3) | −30 | 67 | 89 |
| 14    | L2     | EtOH : DME (1 : 3) | −20 | Trace | ND |
| 15    | L2     | EtOH : DME (1 : 3) | −20 | Trace | ND |
| 16    | L2     | EtOH : DME (1 : 3) | −20 | Trace | ND |

Table 1: Screening of the reaction conditions

Table 2: Necessity of the 7-azaindoline auxiliary

a Amide: 0.1 mmol, 2a: 0.25 mmol, blue light ($\lambda_{\text{max}}$ 448/455 nm).

b Determined by $^1$H NMR analysis of the crude reaction mixture with 1,1,2,2-tetrachloroethane as an internal standard.

c Determined by chiral stationary phase HPLC analysis.

Without a photocatalyst.

Reaction in the dark.

Without a Cu(i) catalyst.
to control stereoselection via strong bidentate coordination to the Cu(i) complex, we conducted a systematic study of substituent effects (Table 3). Installation of non-coordinating methyl or phenyl groups at the 6-position, the most biasing position to interfere with the coordination to Cu(i), significantly decreased the enantioselectivity (3ba, 3ca). In sharp contrast, upon introducing a potentially coordinative substituent, e.g., methoxy or chloro substituents, at the same position enhanced the yield and improved enantioselectivity up to 98% ee (3da, 3ea).

This finding was further supported by the negative effect of the 6-cyano substituent (3fa). This observation can be ascribed to the preferential end-on coordination mode of the cyano functionality, which hindered the coordination ability of the neighboring pyridyl nitrogen. Electronic effects on the pyridyl nitrogen were excluded on the basis of the minimal effect of methoxy or chloro substituents at the 4-position on the enantioselectivity (3ga, 3ha). Similarly, sterics at the 3-position had little effect on the reaction outcome (3ia), implying that delicate steric factors with coordination capabilities near the Cu(i) center are crucial toward achieving excellent enantioselectivity.

Reinvestigation of the reaction conditions with the proligand 3ib yielded further support for the influence of the 6-MeO substituent. A different bialyl ligand, (R)-DM-BINAP L3, armed with identical aromatic biasing groups (3,5-xylyl) on the phosphorus atom (Scheme 1b). To gain more insight into this notable substituent effect, single crystals of L3/Cu(i)/7-azaindoline amide complexes were grown to determine the structural differences induced by the absence or presence of the 6-MeO substituent (Fig. 1). Consistent with the previous observations, the 7-azaindoline amide moiety adopted the Z-conformation for bidentate coordination to Cu(i), even in the presence of the 6-MeO substituent, as revealed by X-ray crystallographic analysis of the L3/Cu(i)/amide 1m complex (Fig. 1a).

In-depth studies of the crystal structures of L3/Cu(i)/1m (with the 6-MeO substituent) and L3/Cu(i)/1j (without the 6-MeO substituent) elucidated the structural differences that may account for the positive effect of the 6-MeO substituent. In the absence of the 6-MeO substituent, the front view of the L3/Cu(i)/1j complex exhibited the ideal tetrahedral coordination around Cu(i), in which the amide 1i located perpendicular to the P–Cu–P fragment (Fig. 1c). Biasing 3,5-xylyl groups of L3 exist in the first and third quadrants, and the incoming radical predominantly approaches from the second quadrant to give the product with the observed absolute configuration (see the X-ray crystal structure of 3dd in Table 4). On the other hand, amide 1m with the 6-MeO substituent in the L3/Cu(i)/1m complex slightly rotated counterclockwise (Fig. 1b). Comparative analysis of the bond angles of the two complexes revealed a highly skewed tetrahedral coordination for the L3/Cu(i)/1m complex with deviated ∠P1–Cu–N (117.79°) and ∠P2–Cu–N (134.07°) angles. While the distance between Cu(i) and the 6-MeO substituent (2.88 Å) exceeded the sum of the van der Waals radii, the narrower ∠Cu–N–C(6) angle (117.83°) compared with that of the L3/Cu(i)/1j complex (119.74°) suggested that the weak

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**Table 3** Substituent effect of the 7-azaindoline auxiliary

| Substituent | Yield (%) | Enantiomeric excess (%) |
|------------|----------|-------------------------|
| Me         | 77       | 98                      |
| Cl         | 76       | 98                      |
| MeO        | 70       | 98                      |
| Et         | 78       | 98                      |
| Ph         | 73       | 98                      |

Notes: 1: 0.1 mmol, 2a: 0.25 mmol. Yields were determined by 1H NMR analysis of the crude reaction mixture with 1,1,2,2-tetrachloroethane as an internal standard.
attractive interaction between Cu(I) and the 6-MeO group results from the skewed coordination mode. Indeed, a competitive binding study using an equimolar mixture of the L3/Cu(I) complex, 1j, and 1m resulted in a nearly 1 : 1 mixture of L3/Cu(I)/1j and L3/Cu(I)/1m complexes, suggesting that the 6-MeO group is not merely imparting a steric bias to disfavor complexation (see Section 9 in the ESI for 1H-NMR analyses of these complexes†).

The deviation of the position of amide 1m from the horizontal line rendered the β-position of the amide more likely to be shielded by the 3,5-xylyl group at the third quadrant, leading to higher enantioselectivity. We believe this mechanism is also operative with 6-Cl-substituted 7-azaindoline amide 1e, in which the enantioselectivity was similarly increased despite the smaller magnitude of enhancement (Table 3, 3ea).

Having determined the optimal cooperative catalytic system and incorporating the newly generated the 7-aza-6-MeO-indoline attachment, we next investigated the substrate scope of the catalytic asymmetric aminomethylation (Table 4). The reaction of archetypal β-Me-substituted unsaturated amide could be performed on a gram scale with lower catalyst loading (Cu: 10 mol%, L2: 12 mol%, photocatalyst 0.3 mol%), albeit with a marginal loss in enantioselectivity. Linear, branched, and cyclic β-alkyl substituents were largely accommodated to deliver the corresponding products in high yield and with high enantioselectivity (3na–3ra). β-Aromatic amides were successfully accommodated as tractable substrates to deliver the corresponding γ-aminomethyalted products with high enantioselectivity, irrespective of the presence of electron-donating or -withdrawing substituents (3la, 3sa–3za). Potentially coordinative heteroaromatic units did not interfere with the catalysis (3ma, 3aaa), although the reaction was complicated by the presence of an α-Me substituent on the amide substrate, giving a mixture of diastereomers in moderate yield with moderate enantioselectivity (3aba). Sterically more (N-Bn, iPr) or less (N-H) demanding α-silylamines 2b–d as well as 2e bearing an o-F

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**Fig. 1** Crystal structures of Cu(I)/amide complexes. (a) Crystal structure of a (R)-DM-BINAP (L3)/Cu(I)/amide 1m (with 6-MeO substituent) complex. (b) Front view of the L3/Cu(I)/amide 1m complex (with 6-MeO substituent). (c) Front view of the L3/Cu(I)/amide 1j complex (without 6-MeO substituent). The quadrant representation is applied to structures in (b and c), where the shaded area of the first and third quadrants represents the shielded area by 3,5-xylyl groups on the phosphorus. SD: standard deviation. Thermal ellipsoids are drawn at the 50% probability level. Hydrogens are omitted for clarity. Color code: gray, carbon; blue, nitrogen; red, oxygen; purple, phosphorus; green, copper.

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**Table 4 Substrate generality**

| R1 | R2 | R3 | R4 | R5 | R6 | R7 |
|----|----|----|----|----|----|----|
| 0.1 mmol | 0.12 mmol |

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*The reaction was run for 96 h with reduced catalyst loading (Cu: 10 mol%, L2: 12 mol%, photocatalyst 0.3 mol%). Combined yield of diastereomers. Color code: white, hydrogen; gray, carbon; blue, nitrogen; red, oxygen.*
substituent were compatible, affording the desired γ-amino amides (3db-3de) in high yield with high enantioselectivity.

The proposed catalytic cycle is delineated in Fig. 2. 7-Aza-6-MeO-indoline amide 1d readily interacts with the L2/Cu(I) complex to form complex I, mitigating the direct excitation of 1d for [2 + 2]-photocycloaddition. Independently, α-silylamine 2a is oxidized by the photoexcited Ir(III)* complex generated by blue-light irradiation, catalytically producing α-amino radical II and TMS cations. At low temperature, the coordinated amide in complex I is sufficiently more electrophilic than non-ligated 1d, and undergoes coupling with radical II with excellent stereoccontrol, as described in Fig. 1.

The thus-formed α-amide radical III was quenched with the Ir(u) complex via single-electron transfer to give amide enolate IV while concomitantly regenerating the ground state Ir(u) complex to close the photocatalytic cycle. The co-solvent EtOH protonated the amide enolate to liberate γ-amino amide product 3da, as evidenced by the 85% deuterium incorporation (see Fig. S4 and S5 in the ESI for HRMS and 1H NMR analyses, respectively†) when using EtOH-d4 in place of EtOH. The 6-MeO-7-azaindoline attachment was readily removed after taming the reactivity of the cooperative asymmetric catalysis, allowing for diverse functional group transformations (Scheme 2). Simple acidic hydrolysis of product 3da gave Me ester 11 or acid 12 depending on the acid concentration and reaction media. This class of compounds provides potentially useful intermediates for γ-aminobutyric acid derivatives, a key structural motif shared in several marketed therapeutics for central nervous system disorders.75–76 The 7-azaindoline unit served to stabilize the tetrahedral intermediate formed upon reaction with an organolithium reagent, delivering methyl ketone 13 without over-alkylated product. For secondary amine product 3dd, simple treatment with KOtBu at 0 °C afforded lactam 14. In all cases, the 6-MeO-7-azaindoline attachment was recovered in over 95% yield.

Conclusions

In conclusion, we developed a new protocol for a highly enantioselective catalytic conjugate addition of α-amino radicals fueled by visible light irradiation. A chiral Cu(i) catalyst and an Ir-based photocatalyst exert their influence orthogonally to promote the smooth reaction, where the 7-azaindoline unit of the α,β-unsaturated amides plays a key role in both the reaction progress and stereoselection. Substituents at the 6-position of the 7-azaindoline attachment had a significant effect on the reaction, shedding light on the stereoccontrol of the privileged Cu(i)/7-azaindoline combination in asymmetric catalysis. The substrate generality and functional group transformation of the products will be highly applicable to practical organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by KAKENHI (17H03025 and 18H04276 in Precisely Designed Catalysts with Customized Scaffolding) from JSPS and MEXT. S. K. P. thanks the German Research Foundation (DFG: PA 3350/1-1; Project Number: 407493001) for the postdoctoral research fellowship. Dr Roman Pluta is gratefully acknowledged for his fruitful discussions during the project. We are grateful to Dr Kiyoko Iijima, Dr Ryuichi Sawa, Yumiko Kubota, and Yuko Takahashi at the Institute of Microbial Chemistry for technical assistance in NMR and MS analyses. We especially thank Dr Tomoyuki Kimura for the single crystal X-ray analyses for 1w (CCDC 1985034), 3dd (CCDC 1985035), and a (R)-DM-BINAP (L3)/Cu(I)/amide 1m (with 6-MeO substituent) complex (CCDC 1985036).

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