Chapter

Recent Advances in Cooperative N-Heterocyclic Carbene Catalysis

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Abstract

The N-heterocyclic carbenes (NHCs) open the new field of organocatalysis, leading to the dramatic progress on the cooperative NHC catalysis with transition-metal catalysts or photocatalysts.

Keywords: NHC, catalysis, organocatalyst, transition-metal, photocatalyst

1. Introduction

In the past few decades, N-heterocyclic carbenes (NHCs) open the new field of organocatalysis in synthetic organic chemistry [1]. Particularly, chiral NHCs have gained increasing attention as a powerful and versatile organocatalyst for the enantioselective synthesis of various molecules with structural diversity and complexity [2–7]. Although a wide variety of chiral NHC precursors were developed, chiral thiazolium-derived carbenes are the most widely used catalysts for asymmetric synthesis. Based on the characteristic structures, chiral thiazolium precursors can be classified as aminoindanol-based thiazoliums, morpholine-based thiazoliums, pyrrolidine-based thiazoliums, and acyclic thiazoliums [6]. Furthermore, new methods and strategies for NHC catalysis are emerging continuously, leading to remarkable progress on cooperative catalysis using NHC/Lewis acid, NHC/Brønsted acid, and NHC/hydrogen-bonding organocatalyst [8, 9]. In recent years, cooperative catalysis has been expanded by the combination of NHCs with transition-metal catalysts or photocatalysts [10]. This chapter highlights the recent dramatic progress in the cooperative NHC catalysis with transition-metal catalysts or photocatalysts.

2. Cooperative NHC catalysis with transition-metal catalysts

In recent years, the use of transition-metal catalysts in the NHC catalysis has become a widespread strategy for cooperative catalysis, although NHCs are known to act as a ligand for transition metals.

The palladium-catalyzed allylic substitutions are wildly used for achieving cooperative NHC catalysis. Initially, the successful combination of NHC catalysis with transition-metal catalysis was reported in the cascade reactions involving the addition of NHC-catalyzed product to π-allyl palladium intermediate [11–13]. In 2014, cooperative catalysis was achieved by the simultaneous activation of substrates using NHC catalyst and palladium catalyst [14]. This cooperative transformation proceeded via the addition of the Breslow intermediate, generated from the NHC catalyst, into the π-allyl palladium intermediate.
The palladium-catalyzed allylic substitutions are applied to the enantioselective NHC catalysis [15–20]. The cooperative catalysis was achieved by using chiral NHC catalyst and palladium catalyst (Figure 1) [15–17]. In the presence of palladium catalyst [Pd(PPh₃)$_4$ (5 mol%) and chiral NHC generated from NHC precursor (5aS,10bR)-A1 (15 mol%) and Cs₂CO₃ (1 equiv), the enantioselective [4 + 3] annulation reaction between vinyl benzoxazinanone 1 and cinnamaldehyde 2 were performed in THF at room temperature. The benzazepine derivative 3 was obtained in 86% yield with 99% ee [15]. The proposed catalytic cycle involves the NHC-catalyzed activation of enal 2 followed by the Pd(0)-catalyzed allylic alkylation. Initially, the palladium-catalyzed decarboxylation of vinyl benzoxazinanone 1 gives the π-allyl palladium(II) complex, which reacts with the azolium homoenolate generated from cinnamaldehyde 2 and NHC. The subsequent cyclization provides benzazepine 3 accompanied by the regeneration of the NHC catalyst. In this communication, the stereochemical outcome was explained by the proposed transition state, in which the formation of...

Figure 1.
Enantioselective catalysis using NHC and π-allyl palladium(II) complex.
hydrogen-bonding interaction promotes allylic substitution. Later, a comprehensive investigation of the mechanism was conducted to understand the features of this reaction [16]. A detailed study shows that NHC not only serves as an organocatalyst to activate enal 2 but also a ligand of palladium. Furthermore, the cooperative catalysis was applied to the enantioselective [4 + 1] annihilation between benzoazainonone 1 and sulfur ylide 4. When NHC precursor (5aS,10bR)-A2 and Pd(PPh3)4 were employed, the desired annihilation product 5 was obtained in 80% yield with 88% ee [16]. The combination of chiral NHC, generated from precursor (5aS,10bR)-A2, and a chiral palladium catalyst, generated from Pd2(dba)3 and ligand L1, promoted the highly enantioselective [5 + 2] annihilation reaction between phenyl vinylene carbonate 6 and cinnamaldehyde 2 [17]. In this reaction, the use of a bidentate phosphine ligand L1 is crucial to prevent the coordination of NHC to the active Pd catalyst.

NHCs can invert the reactivity of aldehyde from electrophilic to nucleophilic by the formation of Breslow intermediate as an acyl anion equivalent from NHC catalyst and aldehyde. The cooperative NHC/palladium reactions through the nucleophilic addition of Breslow intermediate to the π-allyl palladium(II) complex were investigated (Figure 2) [21–26]. The 2:1 coupling reaction of pyridine-2-carboxaldehyde 8 and allyl acetate 9 has been developed [21]. Under the optimized reaction conditions using Pd(PPh3)4 and NHC generated from precursor A3 and triethylamine, 2-methyl-1,4-di(pyridin-2-yl)butane-1,4-dione 10 was obtained in 83% yield as a 2:1 coupling product. The proposed catalytic cycle involves the formation of Breslow intermediate as an acyl anion equivalent from NHC catalyst and aldehyde 8 through the addition of NHC to the formyl group of 8 followed by the proton transfer. Next, the addition of Breslow intermediate to the π-allyl palladium(II) complex, generated from allyl acetate 9 and Pd(PPh3)4, leads to the formation of unsaturated ketone 11 via the liberation of NHC. In this transformation, the N atom of the pyridine ring acts as a coordination site toward the palladium of the π-allyl complex. Finally, ketone 11 is converted to product 10 through condensation with another Breslow intermediate. This cooperative catalysis was extended to C-glycosylation using aldehyde 8 and glucal 12 [22].

The propargylation reaction of pyridine-2-carboxaldehyde 8 was also developed [23]. The propargylic ketone product 15 was obtained in 74% when propargylic carbonate 14 was used under the cooperative NHC/palladium catalytic conditions. Furthermore, the reaction of widely available aldehydes with diarylmethyl carbonates was studied [24]. When aliphatic aldehyde 16 and diarylmethyl carbonates 17 were employed under the cooperative conditions using NHC precursor A4, α-arylated ketone 18 was obtained in 78% yield.

The cooperative NHC/palladium reaction for the umpolung 1,4-addition of aryl iodides or vinyl bromides to enals was developed [27, 28]. The combination of NHC, generated from precursor A5, and a palladium catalyst, generated from Pd2(dba)3 and ligand L3, promoted the 1,4-addition of iodobenzene 19 to cinnamaldehyde 2 to give methyl β,β-diphenyl propanoate 20 in 71% yield (Figure 3) [27]. This reaction is the palladium-catalyzed arylation of NHC-bound homoenolate equivalent generated from cinnamaldehyde 2 and NHC. The oxidative addition of palladium catalyst to iodobenzene 19 generates the activated PhPdL(Ln) as an electrophile, which reacts with nucleophilic homoenolate equivalent. The subsequent reductive elimination provides the NHC-bound intermediate, which reacts with MeOH to afford methyl β,β-diphenyl propanoate 20. Additionally, 1,4-addition of vinyl bromides to enals was also studied under similar reaction conditions [28].

The cooperative catalysis using NHC and copper catalyst was investigated (Figure 4) [29, 30]. The catalytic reaction using alkyne 21, tosyl azide 22, and isatin-derived imine 23 was investigated by using NHC precursor A6 and CuI [29]. The spiro-azetidine oxindole 24 was obtained in 83% yield with 85:15 er. Initially,
**Figure 2.** Cooperative catalysis based on umpolung of aldehydes.

**Figure 3.** Cooperative catalysis for umpolung 1,4-addition to cinnamaldehyde.
copper acetylide is generated from 21 and Cu(I) under the basic conditions. The proposed catalytic cycle involves the formation of ketenimine intermediate via triazole generated by [3+2] cycloadditions between copper acetylide and azide 22. Subsequently, ketenimine reacts with NHC to form azolium enamide, which undergoes the formal [2+2] cycloaddition with imine 23 to afford product 24. In the presence of NHC precursor A7 (10 mol%), Cu(OTf)$_2$ (5 mol%) and Et$_3$N (1 equiv), [4 + 3] annulation between ethynyl benzoxazinanone 25 and isatin-derived enal 26 led to the formation of spirooxindole 27 in 98% yield with 96% ee [30]. In this catalysis, the decarboxylation of copper acetylide leads to copper allenylidene, which reacts with the NHC-linked homoenolate generated from enal 26. Since NHC serves as a ligand of copper, chiral Cu(I)-NHC complex would participate in the control of stereochemistry, together with chiral NHC catalyst.

The cooperative catalysis using NHC and gold catalyst was reported (Figure 5) [31]. When NHC precursor A8 (20 mol%), PPh$_3$AuCl/AgPF$_6$ (10 mol%), and DABCO (25 mol%) were employed, the relay reaction of ynamide substrate 28 with enal 29 gave the bicyclic lactam 30 in 84% yield with 99% ee. In this catalysis, Au(I) promotes the cyclization of ynamide 28 to generate $\alpha,\beta$-unsaturated imine as a key intermediate. The subsequent reaction of $\alpha,\beta$-unsaturated imine with the NHC-linked enolate, generated from enal 29 and NHC, gives the bicyclic product 30.

The combination of NHC catalysis and ruthenium redox catalysis was investigated [32–34]. The oxidation of the Breslow intermediate leads to the formation of
α,β-unsaturated acyl azolium via radical cation (Figure 6) [34]. In the presence of chiral NHC generated from precursor (5aR,10bS)-A1, RuCl₃, and O₂, the oxidative reaction of cinnamaldehyde 2 with 2,4-pentanedi酮 31 were performed in 1,4-dioxane, affording lactone 32 in 98% yield with 93% ee. The proposed reaction mechanism involves the oxidation of Breslow intermediate, generated from NHC and enal 2, by SET from RuCl₃. The second oxidation of radical cation intermediate by RuCl₃ gives α,β-unsaturated acyl azolium, which undergoes [3 + 3] annulation with 2,4-pentanedi酮 31. In this catalysis, Ru(III) is regenerated through the oxidation of Ru(II) by molecular oxygen. Furthermore, cooperative catalysis using NHC and iridium catalyst was also developed [35, 36].

3. Cooperative NHC catalysis with photocatalysts

The combined use of NHC and photocatalyst has gained increasing attention as novel redox catalysis. The compatibility of NHC with ruthenium photocatalyst was demonstrated (Figure 7) [37]. Acylation of N-phenyltetrahydroisoquinoline 34 with butanal 33 was promoted by using chiral NHC, generated from precursor (5aS,10bR)-A9 and photocatalyst Ru(bpy)₃Cl₂ in the presence of m-dinitrobenzene
as an oxidant. This transformation proceeds via the generation of Breslow intermediate, which undergoes the addition to iminium intermediate generated by the photocatalytic oxidation of \(34\). Finally, the release of free NHC catalyst results in the formation of acylated product \(35\). The decarboxylative carbonylation reaction also proceeded via a similar mechanism [38].

The cooperative catalysis was applied to the oxidative transformation of aldehydes (Figure 8) [39–42]. The oxidative esterification of cinnamaldehyde \(2\) was achieved by the dual organocatalysis based on the cooperation between NHC and rhodamine 6G as an organophotocatalyst [39]. In this reaction, Breslow intermediate is photocatalytically oxidized to acyl azolium via the radical intermediate. The subsequent reaction of acyl azolium with MeOH gives ester \(36\). Furthermore, the alklylation and esterification reaction of \(\gamma\)-oxidized enal \(37\) was developed [40].

When racemic precursor \(A1\) and photocatalyst Ru(bpy)\(_3\)(PF\(_6\))\(_2\) were employed, the reaction of \(\gamma\)-oxidized enal \(37\) with iodoacetonitrile \(38\) and MeOH gave \(\gamma\)-alkylated ester \(39\) in 86% yield. In this Ru-photocatalysis, iodoacetonitrile \(38\) acts as not only a radical source but also an oxidant. The oxidative Smiles rearrangement was also reported [42]. Under the cooperative catalysis conditions using NHC and 9-mesityl-10-methyl-acridin-10-ium as an organophotocatalyst, the oxidative Smiles rearrangement of \(O\)-aryl salicylaldehyde \(40\) proceeded effectively to give the aryl salicylate \(41\) in 79% yield. Initially, the photocatalytic oxidation of Breslow intermediate, generated from salicylaldehyde \(40\) to acyl azolium leads to the generation of the acid intermediate via the subsequent reaction of acyl azolium with H\(_2\)O. The subsequent oxidation of acid intermediate by photocatalysis promotes Smiles rearrangement to give another radical via the spirocyclic intermediate. Finally, the photocatalytic reduction of this radical gives the aryl salicylate \(41\).

The cooperative catalysis for preparing ketones from carboxylic acid derivatives was studied (Figure 9) [43, 44]. The synthesis of ketone \(44\) was achieved by the combined NHC and Ir-photoredox catalysis of acyl imidazole \(42\) with benzyl Hantzsch ester \(43\) as a benzyl radical source [43]. In the presence of precursor \(A12\) (15 mol%), photocatalyst [Ir(dFCF\(_3\)ppy)\(_2\)(dtbpy)]PF\(_6\) (1 mol%), and Cs\(_2\)CO\(_3\), the reaction between imidazole \(42\) and Hantzsch ester \(43\) led to the formation of ketone \(44\) in 79% yield under the LED irradiation. In this catalysis, the iridium-photocatalyzed one-electron reduction of acyl azolium, generated from NHC and acyl imidazole \(42\), affords a radical intermediate. This radical undergoes the subsequent radical-radical coupling with a benzyl radical generated by the iridium-photocatalyzed one-electron oxidation of benzyl Hantzsch ester \(43\). The cooperative triple catalysis using NHC catalyst, Ru-photocatalyst, and sulfinate catalyst was
developed [44]. When precursor A13 (15 mol%), Ru(bpy)$_3$(PF$_6$)$_2$ (1.5 mol%), and 4-Cl-PhSO$_2$Na (25 mol%) were employed, the acylation of 4-methylstyrene 46 with benzoyl fluoride 45 was promoted under the CFL irradiation to give ketone 47 in 78% yield. This triple catalysis involves photocatalysis, NHC catalysis, and sulfinate catalysis. The NHC catalysis gives a ketyl radical via the photocatalytic reduction of acyl azolium, generated from benzoyl fluoride 45 and NHC. In the sulfinate catalysis, the photocatalytic oxidation of 4-Cl-PhSO$_2$Na affords sulfonyl radical, which adds to 4-methylstyrene 46 leading to the adduct radical. Finally, radical/radical cross-coupling between these two radicals leads to the acylated product 47.
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DOI: http://dx.doi.org/10.5772/intechopen.101328

In addition to the cooperative NHC catalysis with photocatalysts, the combined use of NHC catalysis and photoredox reaction in the absence of a photocatalyst has gained increasing attention as novel catalysis [45–47].

4. Conclusions

The N-heterocyclic carbenes (NHCs) are powerful and versatile organocatalysts that induce synthetically valuable chemical transformations. In addition to the cooperative catalysis using NHC/Lewis acid, NHC/Brønsted acid, and NHC/hydrogen-bonding organocatalyst, the cooperative NHC catalysis combined with transition-metal catalysts are emerging continuously. In the last few years, the combined use of NHC and photocatalyst has gained increasing attention as dual redox catalysis. The recent dramatic progress in NHC-induced cooperative catalysis disclosed a broader aspect of the utility of NHC-organocatalysis for synthetic organic chemistry. This chapter will inspire creative new contributions to organic chemists.

Acknowledgements

Our work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (C) Grant Number 16K08188.
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