NHC-Ni(II)-catalyzed cyclopropene-isocyanide [5 + 1] benzannulation

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Isocyanides are common compounds in fine and bulk chemical syntheses. However, the direct addition of isocyanide to simple unactivated cyclopropene via transition metal catalysis is challenging. Most of the current approaches focus on 1,1-insertion of isocyanide to M-R or nucleophilic insertion. That is often complicated by the competitive homo-oligomerization reactivity occurring at room temperature, such as isocyanide 1,1-insertion by Ni(II). Here we show a (N-heterocyclic carbene)Ni(II) catalyst that enables cyclopropene-isocyanide [5 + 1] benzannulation. As shown in the broad substrate scope and a [trans-(N-heterocyclic carbene)Ni(isocyanide)Br2] crystal structure, the desired cross-reactivity is cooperatively controlled by the high reactivity of the cyclopropene, the sterically bulky N-heterocyclic carbene, and the strong coordination ability of the isocyanide. This direct addition strategy offers aromatic amine derivatives and complements the Dötz benzannulation and Semmelhack/Wulff 1,4-hydroquinone synthesis. Several sterically bulky, fused, and multi-substituted anilines and unsymmetric functionalized spiro-ring structures are prepared from those easily accessible starting materials expediently.
Aldenes and isocyanides are easily accessible primary starting materials that have often been used in both fine and bulk chemical syntheses through insertion, respectively (Fig. 1a-h). Their homo-dimerization and polymerization reactivity often occur readily in the presence of transition-metal salts at r.t. (Fig. 1b, c, e). Such a high homo-insertion reactivity implies that a selective cross-reaction is difficult to control. The current methods are mostly done indirectly by an in situ generated imidoyl-M species (i.e., a two-steps process), either through a 1,1-insertion of isocyanide to the M-R (Type 1: σ-bond insertion, Fig. 1g) or by a nucleophilic attack on the electrophilic isocyanide for a subsequent alkene insertion (Type 2: nucleophilic insertion, Fig. 1g). There are only handful of examples that can join them together directly. Pioneering examples are those using trienes and cyclobutenes with a stoichiometric amount of Zirconocene and Titanocene complexes, the corresponding catalytic version is still under development. Cyclopropene seems to be an obvious choice for further study, yet isocyanide just served as a ligand in metalloid insertion to cyclopropenes (Fig. 1h), and as an additive in Ni(II)/MAO catalyzed ethene polymerization at r.t. Recently, cationic (NHC)Ni(II) has been developed as an efficient and selective catalyst for insertion and cyclopropene rearrangement. This prompted us to investigate the (NHC)Ni(II) potential in directing a cross-reaction between a cyclopropene and an isocyanide.

In this work, instead of developing more practical imidoyl-M generation methods, we explore an alternate strategy that focuses on a formal addition of those two substrates in the absence of an additional component at the end. Here we show a catalytic intermolecular isocyanide-cyclopropene [5 + 1] benzannulation by NHC/NiBr2-DME/NaBARF (1:1:2). This work is the rare C-C forming reaction between electronic neutral cyclopropene and isocyanide (Fig. 1i). It generally provides ring-expanding rather than the ring-opening products reported in the early 70’s that rely on activated cyclopropene. In sharp contrast to those highly competitive homo reactivities of 1 or 2 as shown in Fig. 1c, 26,32,38, a (hetero)fused aromatic amine product 3 is obtained. That serves as an aza-synthetic alternative to the Dötz benzannulation formed by metal carbene and alkyne, the Semmelhack/Wulff 1,4-hydroquinones synthesis mediated by Cr/Mo/W(CO)6 (Fig. 1d), as well as the catalytic [2 + 2 + 2]/[4 + 2] cycloadditions of π-systems. This finding also complements the vinyl cyclopropanes [5 + 1] reactions reported recently as well as those imidoyl insertions reactivities. Unlike several other intramolecular ring-expanding strategies based on 1 for the syntheses of phenols and saturated N-cycles (e.g., cyclosimerizations of 1 bearing 3,3-dicarboxy) and [4 + 3] cycloadditions of 1 bearing N-heteroaromatics, respectively, our intermolecular strategy offers fused anilines and endocyclic dienes.

Overall, it signifies an exciting catalytic synthesis of aromatic products with a broad substrate scope from two structurally diverse and readily accessible substrates.

**Results and discussion**

**Catalyst development and optimization.** Inspired partly by the Ni-catalyzed alkene cyanation, and the high structural

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**Fig. 1 Challenges in catalytic intermolecular [5 + 1] benzannulation development by using cyclopropene and isocyanide as a substrate pair.**

- **a** Transition-metal mediated two-steps alkene-isocyanide insertion strategy.
- **b** Pd(II)-catalyzed cyclopropene polymerization, and the dimerization product structure.
- **c** Transition-metal catalyzed cyclopropene rearrangement to indene derivatives and subsequent dimerization.
- **d** Semmelhack/Wulff 1,4-hydroquinones synthesis.
- **e** Ni-catalyzed isocyanide polymerization.
- **f** Isocyanide insertion to Ni(II)R bonds for carbonyl derivatives preparation.
- **g** Nucleophilic insertion on Ni(II) isocyanide complex.
- **h** Isocyanide as a ligand in Pd-catalyzed metalloid insertion to cyclopropenes.
- **i** (NHC)Ni(II) catalyzed [5 + 1] benzannulation by cyclopropene and isocyanide.
similarities between the Ni(II)isocyanide and the L.A. activated Ni(II)CN (L.A. = Al, B)56,57, we surmised that a cyclopropene may undergo an isocyanide addition by a cationic (NHC)Ni(II) under appropriate condition. We commenced our investigation by using 1a and 2a as a substrate pair and the L1[NiBr2,DME/NaBARF (in 1:2 ratio, See Fig. 2 for L structure) as the catalyst in toluene for 12 hrs at 80 °C (Table 1, entry 1). Unlike the cross-hydroalkenylation rearrangement reactivity of 1a and alkene that we anticipated earlier26, an aromatic amine 3aa was obtained unexpectedly in ~15% yield rather than other possible acyclic products. The structure of 3aa was confirmed by crystallography, and it highly resembles a 1,4-dihydroquinone derived from an LM(CO)5 mediated cyclopropene-CO coupling process.

One might envision the [5 + 1] benzannulation of 1 and 2 involved a 6-π electron styrenyl ketenimine rearrangement process56 (c.f. Figs. 1d, 3a, typical operation temp: ~120–160 °C bearing electronic activators)58-61 instead of an isocyanide addition to an alkene. This is because a relevant styrenyl ketene intermediate can be obtained from 1 by an M(0) oxidative addition62-65 and/or acidic metal salts directed rearrangement to the vinylcarbenoid (then Type 3 isocyanide insertion to M(carbene)). So we decided to determine the active components and the catalyst oxidation state that are required for the desired reactivity before optimization. Interestingly, subjecting the independently synthesized styrenyl ketenimines to the (NHC)Ni(0)/(II) at 80 °C conditions did not offer the [5 + 1] benzannulation (Fig. 3b), and most of the ketenimine was hydrolyzed to amide after 12 hrs. Also, aromatic isocyanides (2a, 2b, and 2g, see structure later) did not participate in that reaction in either toluene at 80 °C or refluxing THF for 12 hrs. Indeed, the [5 + 1] benzannulation attempts were unproductive with various (NHC)Ni(0) species, like L1[Ni(methyl methacrylate)]66, L1[Ni(cod)]2, isolated L1Ni(2a)3, and in situ Ni(II) reduction86 (Table 1, entry 3). Moreover, common cyclopropene rearrangement products derived from vinylvincarbenoid14, 5b,69, 6b,70-73. The major side products obtained from 1a is a mixture of dimer 4a and oligomerization, which contrasts to the M(vinylvincarbenoid) mechanism predicted and is similar to the Pd(II) directed dimerization reactivity of 1 at r.t. (Fig. 1b). In other words, all the above results do not fit the rationale based on a typical 6-π electron styrenyl ketene rearrangement pathway. Thus, the similar performances of the Ni(II)halides were not caused by an unexpected reduction of Ni(II) to Ni(0) (entry 2). And it is not surprising to see a reasonably good reactivity by a L1Ni(II) at 40 °C, which is supposed to be a less favorable temperature for an oxidative cyclopropene-opening (entry 4 vs Fig. 3). Control experiments identified that the NHC, the Ni(II) salts, and the NaBARF are all crucial components for the desired reactivity (entry 5-9). In particular, the NaBARF was proved essential for a high catalyst performance (entry 2 vs 5) like the typical Ni(II) catalyzed alkene insertions74. Meanwhile, the NHC steric optimization showed an increase in yield and selectivity of 3 (entry 2, 10–15, Fig. 2, L1 vs L2-3, L6 vs L7). A good balance of desired reactivity and yield was achieved by L7-NiBr2 and NaBARF in a 1:2 ratio (entry 16–17), and this catalyst seems promising to cover smaller isocyanides (entry 1 vs 2, 15 vs 18, and 16 vs 19). Such progress was attributed mainly to an optimal steric repulsion among the NHC-Ni(II) and 2, whereby the strong coordination ability of 2 on cationic (NHC)Ni(II) was fine-tuned, and the desired reactivity of 1 was maintained (L1-7). Thus, a cationic Ni(II) catalyst free of NHC could not provide 3ab from 1a and bulky 2b (entry 9). Ran the reaction in the presence of TEMPO did not result in a significant drop in yield (entry 20, 1:1 to Ni(II)) while using (IPr)Ni(II)Cl dimer as a catalyst in chlorobenzene only gave ~5% desired product (no matter with NaBARF or not, see SI), both results suggesting that Ni(I) was not the active catalyst. By using our optimized catalyst under forcing conditions (i.e., without 2), the undesired conversion of 1a was dominated by oligomerization, and dimer 4a was still observed (entry 21). The [5 + 1] reaction can be done on a larger scale under a slightly modified condition (5 mmol), 1.28 g of 3ab was obtained successfully (81% yield of 3ab, 3 : 4 > 95/5, see SI).

Scope of the (NHC)Ni(II) catalyzed[5 + 1] benzannulation.

With the above basic information in mind, we decided to study the substrate scope and gain mechanistic insight accordingly. First, the scope of 1 was tested by 2b as a substrate pair and L7/NiBr2/NaBARF as a catalyst in toluene at 80 °C for 12 h. To our delight, the scope of R1 and R2 on 1 are broad (Fig. 4), it offers an exemplary method for making a fused aromatic aniline 3 with various side chains at the p- and m-positions (3ab-3ib). It covers linear/branch alkylic, functional groups vulnerable to oxidative addition, and radical and nucleophile 2b are compatible (e.g., cyclopropyl and benzyl ether). When a cyclopropene bearing a trisubstituted olefin, the ring-opening event occurs regioselectively, in which only a m- over o-substituted naphthamine regioisomers (3eb and 3fb) was obtained from 1e-f (Trisubstituted olefin with R1 = H, R2 = nBu, Aryl = p-C6H4CF3 could be used as a pair with 2b at ~120 degree and 20 mol% catalyst loading (see SI, 58% yield, r.r. > 95:5)). Besides, ring-strain relief was found as a key factor that governs the reaction76,77. Terminal alkene near the cyclopropene did not interfere with the desired reactivity and no new cyclopropane was formed there (3fb), suggesting that the postulated Ni(vinylvincarbenoid) commonly found in Ni(II) reaction with cyclopropane is not an active intermediate in this reaction again.

Such a [5 + 1] reactivity is not limited to 1 bearing an unsubstituted Ph only. Other electronic activated phenyls (1g-k), naphthyl (1l), and heteroaryls (1m-q) are all possible substrates in this catalysis (Fig. 5a-c). Electronically activated naphthamines at 5-, 6-, 7-positions, and (hetero)aryl-fused anilines78 with different relative positions to the NHR were prepared, respectively. This method represents a general route to build several medicinally79-88 and photochemically89-91 important cores bearing different activators and features92. Notably, 1r bearing a spiro ring was utilized successfully93. That opened up a route to prepare amine-functionalized 2,3-dihydro-1H-phenalenines, a common motif in OLEDs. After a closer look at the results, aromatic substituents on 1 which can donate a higher electron density to the cyclopropane 3-position are more effective substrates. This finding inspired us to consider a cyclopropane...
Table 1 Screening NHC for Ni(II) catalyzed [5 + 1] benzannulation of 1 and 2.

| Entry | NHC  | 2    | Conversion 1a/1b | Yield of 3 | 3:4a  |
|-------|------|------|-----------------|------------|-------|
| 1     | L1   | 2a   | 60%             | 15%        | >95:5 |
| 2     | L1   | 2b   | >95%; 82%; 85%  | 48%; 49%; 43% | >95:5; >95:5; 9:19 |
| 3     | L1   | 2b   | 10%             | -          | -     |
| 4     | L1   | 2b   | 40%             | 30%        | 95:5  |
| 5     | L1   | 2b   | 20%             | 5%         | -     |
| 6     | L1   | 2b   | <5%             | <5%        | -     |
| 7     | L1   | 2b   | <5%             | <5%        | -     |
| 9     | L1   | 2b   | >95%            | -          | -     |
| 10    | L1   | 2b   | >95%            | 41%        | >95:5 |
| 11    | L1   | 2b   | >95%            | 49%        | >95:5 |
| 12    | L1   | 2b   | >95%            | 53%        | >95:5 |
| 13    | L1   | 2b   | >95%            | 49%        | >95:5 |
| 14    | L1   | 2b   | >95%            | 57%        | >95:5 |
| 15    | L1   | 2b   | >95%            | 58%        | >95:5 |
| 16    | L1   | 2b   | >95%            | 89%        | >95:5 |
| 17    | L1   | 2b   | >95%            | 38%        | >95:5 |
| 18    | L1   | 2b   | 90%             | 35%        | >95:5 |
| 19    | L1   | 2b   | >95%            | 68%        | >95:5 |
| 20    | L1   | 2b   | 90%             | 61%        | >95:5 |

a) Substrate (cyclopropene 1a: isocyanide 2 = 1: 2) was added to a mixture of 5 mol% [NHC/NiBr2/DME/NaBARF] (0.025 mmol, in 1:1:2 ratio) catalyst in toluene and stirred for 12 h at 80°C. 4a is a mixture of 1a dimers and was assigned based on GCMS.
b) Yield of product 3 and selectivity were determined by 1H NMR.
c) NiBr2/NiCl2/NiI2 were used, respectively.
d) By the following L1Ni(0) sources generated in situ from NHC L1 + Ni(cod)2, L1 + Ni(methyl methacrylate)2, L1 + NiBr2/EtMgBr, and isolated L1Ni(2a)3.
e) At 40°C.
f) No NaBARF.
g) Only IPr; L:Ni:NaBARF = 1:1:1.
h) 10 mol% catalyst.
i) Only NaBARF: No catalyst, respectively. All in the absence of Ni at 80°C for 5 h, <10% 2b conversion.
j) 10 mol% catalyst.
k) L:Ni:NaBARF = 1:1:1.
l) With 10 mol% TEMPO.
m) 1 was converted to gel in 10 min.
ring-strain relief mechanism by the donor-acceptor push-pull reactivity of 1,2-disubstituted cyclopropanes reported in the literature \(^{30}\), in which the isocyanide serves as acceptor and the aryl at 3-position serves as a donor (see discussion later).

The above results in Fig. 4 and Fig. 5a–c implies that the benzannulation scope is not limited to cyclopropene substituted with an aryl. Other electron-donors on the cyclopropene C\(\text{sp}^3\) (3-position) that may form the proposed 1,2-disubstituted cyclopropane for the donor-acceptor push-pull reactivity should be a possible substrate of this reaction. Cyclopropenes with simple alkenyls and unsymmetric diaryls at the 3-position were tested next (Fig. 5d, e, \(1s-1z\)), assuming the isocyanide addition selectivity still follows the olefin ring-strain, the vinylcarbenoid formation remains slow, and the isocyanide addition is still accessible even when both the upper and lower sides of 3-position are sterically shielded heavily. Indeed, those substrates followed most of the above assumptions, revealed a route that can prepare alkyl-substituted anilines from non-aromatic cyclopropanes, and 3 substituted with different \(p\)-aryl substituents. In particular, cyclic and acyclic alkenyl groups with different substitution patterns are all compatible, 2,4-/3,4-dialkyl substituted anilines from isocyanide directly. Again, no cyclopropanation was detected here, in which a cyclohexenyl group was used to make an aniline fused with cycloalkyl structure (3s b) and indicated the isocyanide addition selectivity was not simply favored by a cyclic olefin. Up to 95% yield and reasonable \(\pi\)-system selectivity was observed in diaryl examples, despite the steric challenges is high and the electronic differences being moderate. However, the desired product was obtained with a small amount of indene derivative 5 (3:5 \(>95/5\)). This change in side product preference follows the typical cyclopropene reactivity trend reported in vinylcarbenoid formation literature.

Isocyanide scope exploration showed that an optimal steric interaction between the substrate and the NHC is one of the keys for achieving the desired reactivity and selectivity (Fig. 6). The L\(7\) can manage isocyanides with distinct and challenging structural

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**Fig. 3** Styrenyl ketene/ketenimine as an intermediate for 6-\(\pi\) electron cyclization. a Dötz Benzannulation and Semmelhack/Wulff synthesis. b 6-\(\pi\) electron cyclization attempts via styrenyl ketenimine.

**Fig. 4** Scope of cyclopropene substituents at \(R^1\) and \(R^2\). Standard condition was followed: IPent\(^{An}\) L\(7\) (0.05 mmol), NiBr\(_2\)DME, NaBARF = 1:1:2, cyclopropene \(1\): isocyanide \(2\) = 1:2 (0.5 and 1.0 mmol), at 80 \(^{\circ}\)C in 2 mL toluene for 12 h. Products were characterized by NMR after isolation. Ratio was determined by \(^1\)H NMR. Superscript \(^a\) indicates 2 mmol of \(2\) was used.
Fig. 5 Scope of cyclopropene substituents at 3-position. Standard condition was followed. Ratio was determined by 1H NMR. 

**a** Aryls; **b** Heteroaryls; **c** Spiro; **d** Alkenyl; **e** Diaryl. Superscript: 

- **a** Ratio of 6'-O-OMe regioisomers. 
- **b** at 60 °C. 
- **c** 2 mmol of 2. 
- **d** 0.5 mmol of 2 was added after 0.5 h.

All cases examined, including the sterically less bulky and more electron-rich N-alkyl-N-aryl secondary amines. Thus, both the NH on the N,N-disubstituted amine 3 and the Br are unlikely nucleophilic enough to form an amidinyl and an imidoyl species as the reaction intermediate (c.f. the Type 2 isocyanide insertion).

Other than the hints offered by the scope exploration and the relevant literature, several additional experiments were carried out to gain mechanistic insight into the reaction (Fig. 7). First, the 5 formation might be caused by the decomposed catalyst at an elevated temperature, since a parallel set of control experiments showed that the 5w was formed mainly by a NiBr2DME/NaBARF catalyst free of NHC L7 (Fig. 7a). This result indicated a strong NHC coordination to a Ni(II) center is important, it could suppress the 3,3-diaryl substituted cyclopropene rearrangement to the corresponding Ni(vinylcarbenoid). Second, we isolated the corresponding Ni(vinylcarbenoid). Second, we isolated the corresponding Ni(II) 3-position.
A cyclopropyl carbonitrile alkylation directed rearrangement;
e Syn-addition of a cationic (NHC)Ni(II) species to cyclopropene.

isocyanide complex (Fig. 7b). It was prepared in an excess amount of 2b, but the spectroscopic information obtained from the crystal structure revealed a trans-configuration between the NHC and the isocyanide in a 1:1 ratio, and the axial positions are shielded sterically by the isocyanide and the NHC substituents. This complex implied that the NHC can suppress the simultaneous coordination of two isocyanides. Thus, the oligomerization of isocyanide was not observed and

Fig. 6 Scope of aryl, alkenyl, and alkyl-substituted isocyanides. Standard condition was followed. Superscript a 2 mmol of 2. b Partial hydrolysis of the enamine was observed. Yield was determined after complete hydrolysis by stirring in MeOH/H2O.

Fig. 7 Mechanistic studies and reaction models. a Effect of NHC and the three-substituent on indene derivative formation; b [trans-IPr-NiBr2(CNDIPP)] crystal structure, IR studies, and NaBArF effect; c NHC effect on 2b oligomerization; d A cyclopropyl carbonitrile alkylation directed rearrangement; e Syn-addition of a cationic (NHC)Ni(II) species to cyclopropene.
Fig. 8 Working hypothesis of the cyclopropene and isocyanide [5 + 1] reactions by a (NHC)Ni(II) catalyst. a Benzannulation. b 1,3-Diene substituted spiro-rings. Postulated structures are in brackets, and the anion is omitted for clarity.
regioselective bromination on unsymmetrically substituted diaryl amine was achieved by simply using NBS as Br source (Fig. 9, ratio was determined by GCMS)\textsuperscript{102,103}. These functionalized sites may serve as additional handles for preparing other related structures with similar sets of cores.

We have developed an intermolecular cyclopropane-isocyanide [5 + 1] benzannulation by a cationic NHC-Ni(II) catalyst with a BArF anion, in which those two substrates were unreactive to each other before and were dominated by their own reactivities. These combinations showed the strength of this catalyst design in broadening the use of those structurally diversified starting materials with remarkably good functional group compatibilities and regulating competitive reactivities of those two substrates at an elevated temperature. This method serves as anaza-synthetic alternative for products structurally similar to those in Dötz benzannulation and Semmelhack/Wulff synthesis based on Cr/Mo/W(CO)\textsubscript{n} as well as those in styrenyl ketene \( \pi \)-complexes.

The study also provides a method to make unsymmetric and functionalized spiro-ringo structures catalytically. This work has revealed several opportunities to utilize isocyanide and cyclopropane for other potential applications.

**Methods**

*General procedure for the [5 + 1] Benzannulation.* To a catalyst mixture (0.05 mmol \( \eta^7\)NiBr\(_2\))DME, 0.10 mmol NaBARF) stirred in toluene (1 mL) for 3 min at 80 \( ^\circ \)C, an indicated amount of a premixed toluene solution of 1 and 2 (1 mL) was added in one-pot and stirred for an additional 12 h. After cooled down to r.t., it was diluted with 6 mL nhex/EtO (1:1) and filtered through a short plug of silica gel. The solvent was then removed on rotavap.

**Solvent**

| Yield | Selectivity |
|-------|-------------|
| CH\(_3\)CN | 81% | 99:1 |
| DMF | 85% | 1:99 |

![Fig. 9 Post-modification of the product. Solvent-controlled regioselective bromination on unsymmetrically substituted diaryl amine.](https://example.com/fig9)

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