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Cp*Co(III)-Catalyzed γ-Selective C–H Allylation/Hydroamination Cascade for the Synthesis of Dihydroisoquinolines

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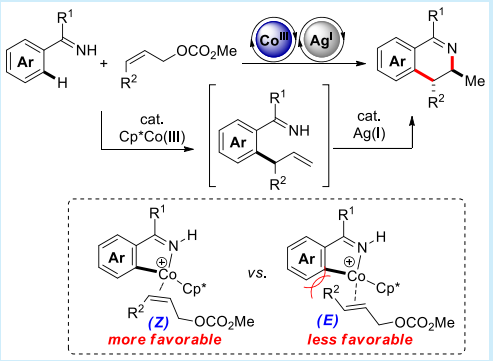
Supporting Information

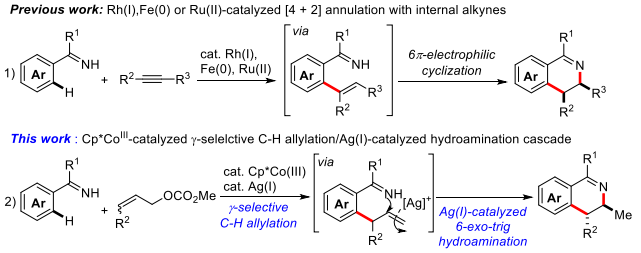
ABSTRACT: A Cp*Co(III)-catalyzed γ-selective C–H allylation/hydroamination cascade toward the synthesis of 3,4-dihydroisoquinolines (DHIQs) has been successfully developed, starting from NH ketimines and allyl carbonates. Notably, highly efficient and γ-selective C–H allylations were accomplished using γ-substituted allyl reagents, thus overcoming the issues of poor α/γ selectivity and low reactivity of previous transition metal-catalyzed C–H allylations. The stereochemistry of allyl carbonates was a crucial factor, and synthesis of the DHIQs was achieved using (*Z*)-allyl carbonates.



The introduction of useful functional groups via transition metal-catalyzed direct C–H activation offers remarkable atom and reaction step economics during synthesis.[1] The development of synthetic methods for direct C–H allylations is of particular interest because the allyl moiety is an exceptionally versatile building block that offers a wealth of opportunities for further functionalization.[2] Recently, significant advances have been made in C–H allylations using transition metals such as Rh(III),[3] Ru(II),[4] Co(III),[5] and Mn(I).[6] However, transition metal-catalyzed C–H allylations still suffer from the issues, namely, poor α/γ selectivity, olefin migration, and low reactivity, particularly in cases with allyl reagents in which the alkyl or aryl substituents are present at α or γ positions.[3,4] In addition, cascade reactions involving direct C–H allylation geared toward the synthesis of valuable heterocycles have been less studied.[7]

To address the challenges faced in C–H allylation and demonstrate its applicability in the synthesis of useful heterocycles, we envisioned a cascade reaction in which Cp*Co(III)-catalyzed γ-selective C–H allylation of NH ketimines was followed by intramolecular hydroamination in order to access dihydroisoquinolines (DHIQs). DHIQs are valuable structural motifs found in both natural products and biologically active molecules.[8] Subsequently, many synthetic methods have been developed, including the Bischler–Napieralski reaction.[9] A typical synthetic approach using a C–H bond activation strategy to construct DHIQs is the [4 + 2] annulation of NH imines and internal alkynes, which is catalyzed by Rh(I), Fe(0), or Ru(II) (Scheme 1a).[10] Although alkynes have been successfully utilized as 2-carbon synthons, all of these reported methods provided only *cis*-3,4-DHIQs. Considering the nucleophilic nature of the imine directing group and the availability of the allyl moiety in Heck-type

Scheme 1. Synthesis of Dihydroisoquinolines via Catalytic C–H Bond Activations of NH Imines



cyclization, a facile route was envisioned as a way to access 3,4-DHIQs via cascading Cp*Co(III)/Ag(I)-catalyzed C–H allylation and intramolecular hydroamination, starting from NH ketimines and γ-alkyl substituted allyl carbonates (Scheme 1b). We believe that this reaction cascade provides more opportunities for the synthesis of various *N*-heterocycles in two main aspects:

(1) Catalytic intramolecular additions of amines to alkenes have been reported,[11] but the hydroamination of imines has been underdeveloped.
(2) The stereochemistry of γ-substituted allyl reagents was found to be a crucial factor for improved selectivity and reactivity of C–H allylations.

To test the feasibility of this cascade, benzophenone imine (**1a**) and allyl methyl carbonate (**2a**) were subjected to a variety of reaction conditions in TFE (see Table S1 in the Supporting Information). Since initial tests revealed that the

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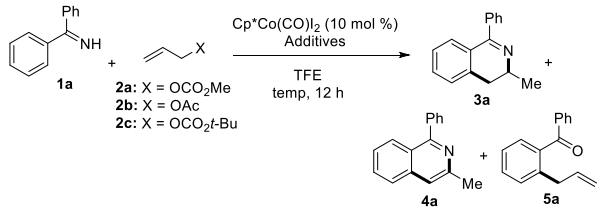
most extensive reactivity was seen with the Cp*Co(III) catalyst, various additives were further examined with 10 mol % of Cp*Co(III) (Table 1). The cascade reaction proceeded to

Table 1. Reaction Optimization[a]



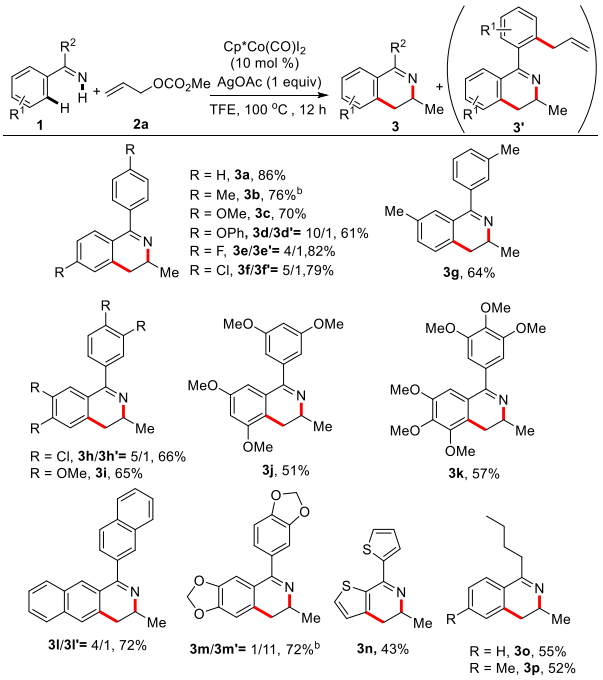
entry	additive(mol %)	2	temperature (°C)	Yield (%)[b] 3a	4a	5a
1	$AgSbF_6$ (20)	**2a**	120	3	–	–
2	AgOTf (20)	**2a**	120	2	–	–
3	AgOAC (20)	**2a**	120	31	3	4
4	NaOAc (20)	**2a**	120	17	1	3
5	AgOAc (100)	**2a**	120	61	6	2
6	CsOAc (100)	**2a**	120	23	8	1
7	CsOPiv (100)	**2a**	120	–	–	31
8[c]	AgOAc (100)	**2a**	100	75	14	1
9[c]	AgOAc (100)	**2b**	100	48	6	1
10[c]	AgOAc (100)	**2c**	100	60	6	2
11[c,d]	AgOAc (100)	**2a**	100	86	6	–

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), Cp*Co(CO)I_2 (10 mol %), and additives in TFE (1.0 mL) for 12 h under Ar. [b]Isolated yields. [c]Reaction was performed with 1.8 equiv of **2**. [d]2.0 mL of TFE was used.

afford the desired product **3a** in 31% yield in the presence of AgOAc (20 mol %) at 120 °C (Table 1, entry 3). Small amounts of the allylated product **5a** and the isoquinoline **4a**, which can be synthesized via *β*-hydride elimination of the cobalt-alkyl species followed by olefin migration,[3a,d,10c] were also isolated. Increasing the amount of silver acetate (100 mol %) improved the yield of **3a** to 61% (Table 1, entry 5), whereas other cesium salts were shown to be less effective. Increasing the loading of **2a** and lowering the temperature marginally improved the yield of **3a** to 75% and increased the yield of **4a** (Table 1, entry 8). Other allyl reagents, allyl acetate (**2b**) or allyl *tert*-butyl carbonate (**2c**), were also investigated; unfortunately, there were no improvements in the reactivity (Table 1, entries 9 and 10). The product **3a** was isolated in 86% yield by diluting the reaction medium, which diminished the yield of **4a** (Table 1, entry 11).

With the optimal reaction conditions in hand, the scope of the C−H allylation/hydroamination cascade was examined with various ketimines **1** and allyl methyl carbonate (**2a**) (Scheme 2). It was shown that electron-donating substituents (−Me, −OMe) in the *para*-position of the aryl ketimines **1b** and **1c** were well-tolerated. Interestingly, when the ketimines **1** bearing phenoxy (−OPh) or halogen groups (−F, −Cl) at the *para*-position were subjected to the optimized reaction conditions, the desired compounds **3d**−**3f**, as well as the DHIQs with additional *ortho*-allylation products **3d′**−**3f′**, were formed with a total yield ranging from 61% to 82%. The substrate containing methyl group at the *meta*-position of benzene ring gave **3g**, in which C−H allylation occurred selectively at the less-crowded 6-position. For the 3,4-dichlorinated NH ketimine **1h**, both the desired DHIQ **3h** and compound **3h′** were obtained in good yields. NH

Scheme 2. Scope of NH Ketimines[a]

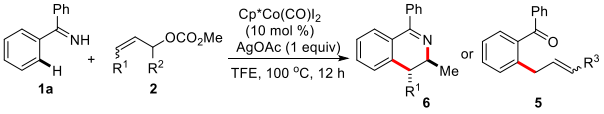


[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.36 mmol), Cp*Co(CO)I_2 (10 mol %), and AgOAc (1 equiv) in TFE (2.0 mL) at 100 °C under Ar, 12 h, isolated yields. [b]**2a** (2.0 equiv) was used.

ketimines bearing dimethoxy substituents at the 3,4-position or the 3,5-position and 3,4,5-trimethoxy substituents reacted smoothly with **2a** to selectively provide analogues **3i**−**3k**. In addition, reactions performed with substrates **1l**, which had a naphthyl group, was proven to be feasible. Notably, ketimines containing heterocycles such as 1,3-benzodioxole **1m** and thiophene **1n**, which are also pharmaceutically relevant compounds such as DHIQ,[12] were actively engaged in this type of reaction. Aryl alkyl ketimines also participated in this transformation and provided DHIQs **3o** and **3p**, although the yields were comparatively lower than those obtained for symmetrical aryl ketimines.

Encouraged by these results, we wondered whether *γ*-substituted allylic carbonates could be subjected to this cascade reaction. We hypothesized that more efficient *γ*-allylation occurred when the *γ*-alkyl-substituted allylic carbonates possess an (*Z*) stereochemistry, because the open coordination site of the (*Z*)-alkene predominated migratory insertion into the cobaltacycle.[13] When (*Z*)-**2d** was reacted with **1a** under standard conditions, the reactivity showed remarkable improvements, when compared with its (*E*)-**2d** counterpart, and the desired product, **6a**, was obtained in 84% yield (Scheme 3ii). To the best of our knowledge, the impact exerted by the stereochemistry of *γ*-substituents of the allyl

Scheme 3. Scope of Allylic Carbonates



(i) with **(*E*)-2d** (R^1 = Pr, R^2 = H) : **6a**, 16% (dr = 4:1)
(ii) with **(*Z*)-2d** (R^1 = Pr, R^2 = H) : **6a**, 84% (dr = 4:1)
(iii) with **(*Z*)-2e** (R^1 = Ph, R^2 = H) : **5b** (R^3 = Ph), 32%
(iV) with **2f** (R^1 = H, R^2 = Et) : **5c** (R^3 = Et), 46%

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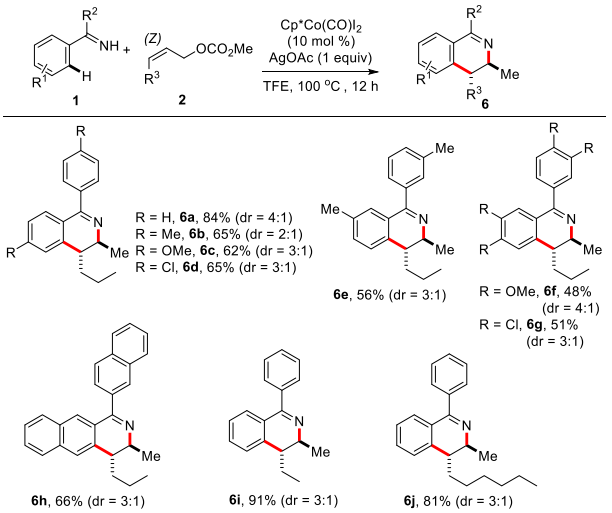
reagent on the reactivity observed during C−H allylation is yet to be reported. Unfortunately, the reactions of **1a** with the γ-aryl allylic carbonate (*Z*)-**2e** and the α-alkyl allylic carbonate **2f** afforded linear products **5b** and **5c**; cyclized products were not detected (Schemes 3iii and 3iv). Presumably, a terminal alkene is favored during the hydroamination process.

Subsequently, reactions involving the analogues of **1** with γ-alkyl allylic carbonates **2** that had a (*Z*)-stereochemistry were investigated (Scheme 4). When reacted with (*Z*)-hex-2-en-1-yl

Scheme 4. Scope of NH Ketimines and Allylic Carbonates[a]

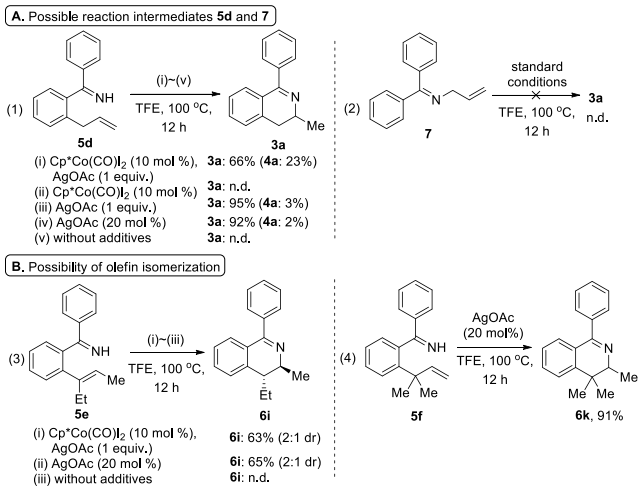


[a]Reaction conditions: **1** (0.20 mmol), **2** (0.36 mmol), Cp*Co(CO)I_2 (10 mol %), and AgOAc (1 equiv) in TFE (2.0 mL) at 100 °C under Ar, 12 h, isolated yields.

methyl carbonate (**2g**), ketimines bearing electronically varied substituents at the aromatic *para*-position, such as Me, OMe, and Cl, underwent the cascade reactions quite smoothly and provided the corresponding products **6b**−**6d** in yields ranging from 62% to 65% with a moderate diastereomeric ratio (dr). Interestingly, *trans*-3,4-DHIQs were obtained as the major products, as confirmed by nuclear Overhauser effect experiments (see the Supporting Information). Aromatic ketimine analogues of **1** that had *m*-Me, *m*,*p*-OMe, and *m*,*p*-Cl substituents on the phenyl ring and the naphthyl units were well-tolerated, thereby affording **6e**−**6h** in good yields. When the R^3 substituent of **2** was ethyl or hexyl, the reactivity was not significantly affected, and DHIQ **6i** and **6j** were isolated in 91% and 81% yield, respectively.

For insight into the reaction mechanism, a series of experiments was conducted (Scheme 5). We wondered whether the reaction intermediate of this cascade was **5d** or **7**, each possibly arising from *ortho* C−H allylation and N−H allylation (see Scheme 5A). We found that only **5d** provided the product **3a** under the standard conditions, indicating that **5d** was probably the reaction intermediate (reaction (1) in Scheme 5A). The cyclization of **5d** did not occur with only cobalt catalyst or without additives. On the other hand, **3a** was obtained in 92% yield, using catalytic amounts of Ag(I), suggesting the occurrence of a silver-catalyzed hydroamination over the course of the reaction. To investigate whether olefin isomerization occurred after C−H allylation, a more thermodynamically stable intermediate **5e** was synthesized. In the presence of AgOAc (20 mol %), an intramolecular

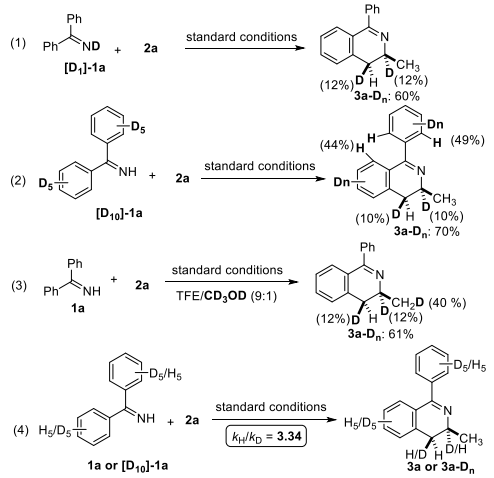
Scheme 5. Mechanistic Studies



hydroamination occurred in a *6-endo-trig* fashion to give the corresponding product **6i** in 65% yield (reaction (3) in Scheme 5B). This meant that olefin isomerization may be involved prior to hydroamination. In the absence of an additive, no product was observed, and thus 6π-electrocyclization of **5e** can be ruled out. To understand the major cyclization pathway, an imine **5f**, which is not capable of isomerization, was synthesized (see reaction (4) in Scheme 5B). Treatment of **5f** with a AgOAc (20 mol %) resulted in product **6k** in 91% yield, suggesting that *6-exo-trig* cyclization without olefin isomerization is the major cyclization pathway.

To better understand the hydrogen transfer process, deuterium labeling experiments were performed (Scheme 6).

Scheme 6. Deuterium Labeling Experiments



When a [D_1]-**1a** was subjected to the standard reaction conditions, 12% of the deuterium was incorporated at both the C-3 and C-4 positions (reaction (1) in Scheme 6). Similarly, the reaction with [D_{10}]-**1a** led to the incorporation of 10% of the deuterium at the C-3 and C-4 positions (reaction (2) in Scheme 6). These results suggested that an H/D exchange occurred between the imine and the *ortho*-position of benzene.[10a] Deuterium at the C-4 position of DHIQs would be incorporated from the NH group of allylated imine via a [1,5]-sigmatropic hydrogen shift.[10c,14] Contrary to the H/D scrambling results for the deuterated-**1a** substrates, when

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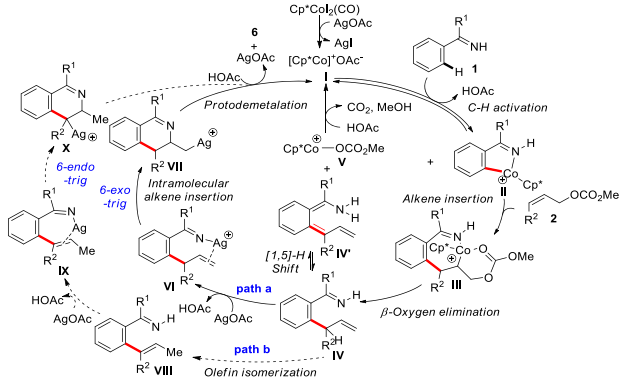
nondeuterated **1a** was reacted in the TFE/MeOD (9/1) solvent mixture, 40% of the deuterium was incorporated into the 3-methyl group as well as at the C-3 and C-4 positions (reaction (3) in Scheme 6). This result suggesting that *6-exo-trig* cyclization occurred, and the protic solvent may transfer deuterium during the protodemetalation process. From two parallel reactions of **1a** and [D_{10}]-**1a**, a KIE value of 3.3 was obtained, suggesting that C−H cleavage may be involved in the rate-determining step (reaction (4) in Scheme 6).

On the basis of the preliminary experiments and previous reports,[3−6,10] the reaction mechanism in Scheme 7 is proposed.

Scheme 7. Proposed Reaction Mechanism



Cobalt and silver salts are thought to lead to the generation of the active catalyst, **I**, which undergoes direct *ortho*-metalation with **1a** in a reversible manner to provide cobaltacycle **II**. The metallacycle **II** then coordinates at the open site of the alkene **2**. Alkene insertion leads to alkyl cobalt intermediate **III**, which subsequently undergoes rapid *β*-oxygen elimination to afford the allyl product **IV** and the cationic cobalt **V**. Next, the active cobalt species **I** is regenerated from **V** and AcOH. For the major pathway identified as "path a", Ag coordinates to the N atom of **IV** and undergoes intramolecular alkene insertion, which results in **VII**. Finally, protodemetalation of the **VII** in a protic solvent gives product **6** and regenerates the silver catalyst. Alternatively, olefin isomerization of **IV** generates the more thermodynamically stable product **VIII**, possibly via the formation of the *π*-allyl species. Coordination of **VIII** to Ag may facilitate *6-endo-trig* cyclization to afford **X**. Protodemetalation of **X** delivers the corresponding product **6** and regenerates the silver (path b).

In summary, we successfully developed a facile route to access 3,4-DHIQs via Cp*Co(III)-catalyzed *γ*-selective C−H allylation and cascading Ag(I)-catalyzed intramolecular hydroamination, starting from NH ketimines and allyl carbonates. The stereochemistry of allyl carbonates proved to be crucial for efficient *γ*-selective allylation with *γ*-substituted allyl reagents, and the (*Z*)-stereoisomer was preferred in this case. Silver-catalyzed intramolecular hydroaminations of imines proceeded smoothly, providing a new synthetic approach for a variety of DHIQs in a one-pot procedure. Given the pervasive interests in direct C−H allylations and further possible applications, this method is attractive for the development of catalytic reactions geared toward the synthesis of valuable heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03977.

Experimental procedures, characterization data (GC, HPLC, HRMS, and NMR), and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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