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Cobalt-Catalyzed Regioselective Synthesis of Indenamine from *o*-Iodobenzaldimine and Alkyne: Intriguing Difference to the Nickel-Catalyzed Reaction

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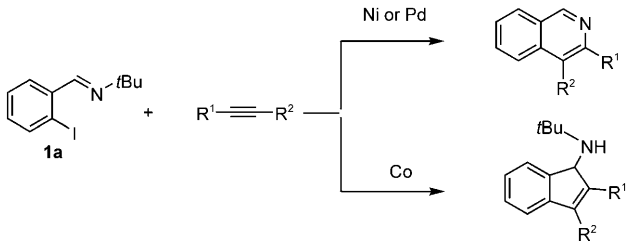
Indene derivatives[1,2] are known to show various pharmacological properties, such as enzyme inhibitors,[1a] reuptake blocking,[1b] biogenic transporters,[1c] and anti-arrhythmic activity.[1d] In addition, they have also found applications in material science as discotic liquid crystals,[1e] coating materials for steel,[1f] conducting polymers,[1g] ligands for metallocene complexes,[1h,i] and so forth. Indenamine derivatives were recently synthesized by reacting chloroindan[1c] with the desired amines and by nucleophilic addition into nitrile derivatives,[3a] whereas indenones were prepared by oxidation of the corresponding indene derivatives[3b] and by catalytic intramolecular isomerization–aldolization[3c] of allyl alcohol with aldehyde. In this paper, we report a new convenient method for the regioselective synthesis of indenamine from the corresponding *o*-halobenzaldehyde, amine, and alkyne in the presence of zinc powder catalyzed by cobalt complexes. Moreover, these compounds can be conveniently converted to the corresponding substituted indenone derivatives.

Recently, we and other groups had found methods for the synthesis of isoquinoline derivatives[4] from 2-iodobenzaldimines (**1**) and alkynes catalyzed by nickel[4a] and palladium complexes, respectively.[4b–f] Our interests in the cobalt-catalyzed reactions[5] and the recent observation of activation of arylhalides by cobalt complexes[5] have prompted us to investigate the use of cobalt complexes for the reaction of *N*-*tert*-butyl-2-iodobenzaldimine (**1a**) with alkyne. To our surprise, when we treated **1a** with 4-octyne in the presence of [$CoCl_2$(dppe)] and zinc powder in acetonitrile, the corresponding indenamine (**5a**; Scheme 1, $R^1=R^2=n$Pr) was obtained in 78% yield. This is in sharp contrast to the nickel-[4a] and palladium-catalyzed[4b–f] reactions that gave the corresponding isoquinoline derivative as product. The structure of the indenamine was established based on its ^{1}H, ^{13}C NMR, and MS spectral data.



Scheme 1. Nickel- and cobalt-catalyzed cyclization of *N*-*tert*-butyl-2-iodobenzaldimine with alkyne.

To simplify the reaction, we observed that by using the corresponding *o*-iodobenzaldehyde and amine to replace **1a**, the same indenamine product can be obtained. Thus, *o*-iodobenzaldehyde (**2a**), *p*-toluidine (**3a**), and 4-octyne underwent three-component reaction in the presence of [$CoCl_2$(dppe)] in an acetonitrile and THF mixture (optimization studies are given in the Supporting Information) to afford indenamine **5b** in essentially quantitative yield (entry1, Table 1). In a similar manner, diphenylacetylene (**4b**) afforded product **5c** in 78% yield. The three-component reactions of unsymmetrical alkynes with **2a** and **3a** were carefully studied by using the same catalyst system. Terminal alkyne **4c** gave a single regioisomer **5d** with the propyl group adjacent to the amino group in 82% yield (entry 3). For disubstituted unsymmetrical alkyne **4d**, two regioisomers **5e** (R^1=Ph, R^2=Et) and **5e'** (R^1=Et, R^2=Ph) in 60 and 36% yields, respectively, were observed. The application of alkynes with electron-withdrawing substituents **4e–g** in the cyclization reaction with **2a** and **3a** gave highly regioselective indene–enamine derivatives **6a–c** in moderate yields (entries 5–7, Table 1). It is worth noting that product **6** arises from a double-bond migration of the corresponding product **5**. Always, the electron-withdrawing ester or keto groups of alkynes are adjacent to the amine group. The re-

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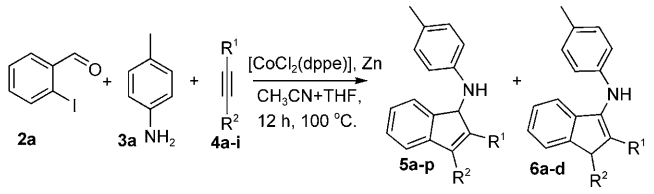
Table 1. Results of cobalt-catalyzed three-component reaction of *o*-iodobenzaldehyde, *p*-toluidine and alkynes.



Entry[a]	Alkyne	Product	Yield[b]
1	**4a**: $R^1=R^2=(CH_2)_2CH_3$	**5b**	99
2	**4b**: $R^1=R^2=Ph$	**5c**	78
3	**4c**: $R^1=(CH_2)_2CH_3$; $R^2=H$	**5d**	82
4	**4d**: $R^1=Ph$; $R^2=Et$	**5e+5e′**	60+36
5	**4e**: $R^1=CO_2Me$; $R^2=C_6H_{13}$	**6a**	73 (85)[c]
6	**4f**: $R^1=CO_2Et$; $R^2=Ph$	**6b**	64 (93)[c]
7	**4g**: $R^1=COMe$; $R^2=Ph$	**6c**	45 (90)[c]
8	**4h**: $R^1=Me$; $R^2=TMS$	**5f**	95
9	**4i**: $R^1=Ph$; $R^2=TMS$	**5g**	82

[a] All reactions were carried out under one nitrogen atmosphere using aldehyde **2** (0.30 mmol), amine **3** (0.30 mmol), alkyne **4** (0.60 mmol), $[CoCl_2(dppe)]$ (0.0210 mmol) and Zn (0.60 mmol) at 100 °C for 12 h. [b] Isolated yields. [c] Additional Hacac (penta-2,4-dione, 0.021 mmol) was added to the catalyst solution for the yield in the parenthesis.

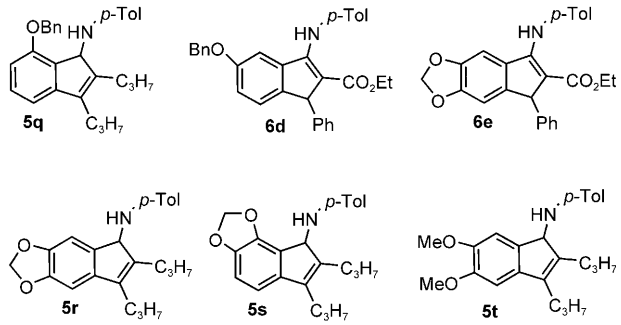
gioselectivity is opposite to the nickel-catalyzed annulation of *tert*-butyl-2-iodobenzaldimines with these alkynes to give the corresponding isoquinolines. The yields of products **6a–c** were greatly improved, when Hacac (Hacac = penta-2,4-dione) was added to the catalytic solutions. The regiochemistry of these products was determined based on their NOE data. In addition, the structure of compound **6c** was further confirmed by the X-ray crystallographic analyses. The reactions of TMS-substituted alkynes **4h** and **4i** gave indenamine derivatives **5f** and **5g** with excellent regioselectivity and yields. These yields were measured by the ^{1}H NMR integration method with mesitylene as the internal standard in the crude mixtures. These compounds are difficult to obtain in pure form from a silica gel column due to decomposition. The crude mixture was used for the removal of the TMS functionality (vide infra).

The scope of amine used for the present cobalt-catalyzed three-component reaction was carefully studied. The reactions of **2a** and **4a** with various aromatic amines, **3b–g**, proceed smoothly to give products **5h–m**, respectively, in good to excellent yields (entries 1–6, Table 2). 1-Napthylamine afforded the corresponding indenamine derivative **5h** in nearly quantitative yield, while sterically bulky 2,4,6-trimethylaniline provided **5i** in 73% yield. Other substituted anilines with electron-donating (**3d**,**e**) and electron-withdrawing substituents (**3f**,**g**) all gave the corresponding indenamines, **5j–m**, in excellent yields. However, the reaction with 8-aminoquinoline **3h** as the amine substrate failed to proceed to provide the expected product **5n**. Possibly, the chelation of both nitrogen atoms in **3h** inhibits the reactivity of the catalyst. For benzylamine (**3i**), the three-component reaction afforded indenamine **5o** in 68% yield, but *n*-butylamine failed to give the expected indenamine. It appears that other unknown products were produced and further investigation is necessary to unravel the reaction of *n*-butylamine with **2a** and **4a**. The cyclization reaction can be applied to various substituted 2-iodoaldehydes **2**. Treatment of benzoxyl-substituted *o*-iodobenzaldehyde **2b** with **3a** and **4a** and of **2c** with **3a** and **4f** afforded the expected indenamines **5q** and indene-enamine **6d** in 89 and 78% yields, respectively.

Table 2. Synthesis of indenamines using various amine derivatives and *o*-iodobenzaldehyde.[a]

Entry	2	R^3-NH_2	4	5	Yield
1	**2a**	**3b**: 1-napthylamine	**4a**	**5h**	99
2	**2a**	**3c**: 2,4,6-$(Me)_3C_6H_2NH_2$	**4a**	**5i**	73
3	**2a**	**3d**: 4-$OMeC_6H_4NH_2$	**4a**	**5j**	94
4	**2a**	**3e**: 3,4,5-$(OMe)_3C_6H_2NH_2$	**4a**	**5k**	92
5	**2a**	**3f**: 3,5-$(F)_2C_6H_3NH_2$	**4a**	**5l**	98
6	**2a**	**3g**: 4-$CF_3C_6H_4NH_2$	**4a**	**5m**	97
7	**2a**	**3h**: 8-aminoquinoline	**4a**	**5n**	0
8	**2a**	**3i**: Bn-NH_2	**4a**	**5o**	68
9	**2a**	**3j**: *n*$BuNH_2$	**4a**	**5p**	0

[a] The same reaction reaction conditions were used as those in Table 1.



Similarly, the reaction of 2-iodopiperonal (**2d**) with alkynes **4f** and **4a** gave the corresponding indene-enamine **6e** and indenamine **5r** in 79 and 68% yields, respectively. Even 2-bromo-5,6-(methylenedioxy)benzaldehyde (**2e**) gave indenamine derivative **5s** in 73% yield. Finally, the reaction of 2-iodo(4,5-dimethoxy)benzaldehyde (**2f**) with **4a** also resulted in the corresponding indenamine **5t** in 86% yield.

The indenamines prepared by the present three-component reaction can be readily converted to the corresponding indenimines (Scheme 2). Thus, the indenamines **5b**, **5c**, **5f**, and **5g** and indene-enamine **6b** gave the corresponding imine derivatives **7a–e** upon treatment with TBAF (tetrabutylammonium fluoride) in THF at 40 °C. The isolated yields of these imine derivatives after flash chromatography were essentially quantitative. The dehydrogenation of indenamines in the presence of TBAF is interesting, as this is a mild and convenient procedure, but the mechanism for the dehydrogenation is not yet clear.[5f] The structure of compound **7b** was confirmed by X-ray crystallographic data (see the Supporting Information). It is interesting to note that compound **5g** underwent both desilylation and dehydrogenation to give indenimine **7d** upon treatment with TBAF. These indenimines can be used for the preparation of substi-

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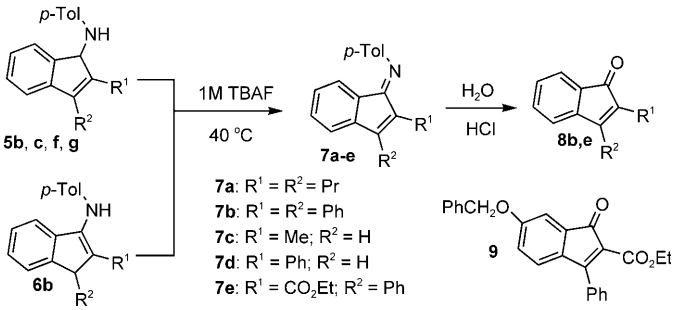
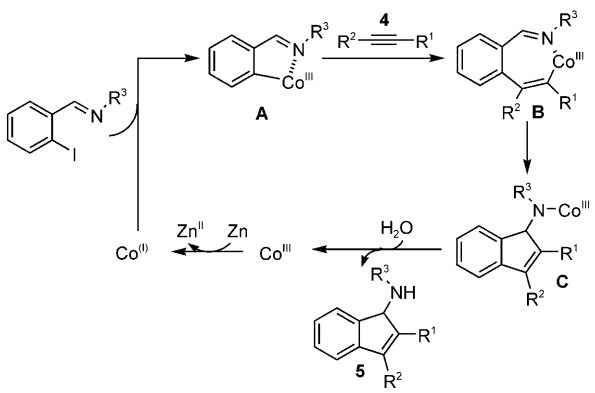


Scheme 2. Synthesis of indenimine derivatives and indenones from the corresponding amine and TBAF.

tuted indenones. Thus, acid hydrolysis of **7b** and **7e** gave indenones **8b** and **8e** in 96 and 92% yields, respectively.

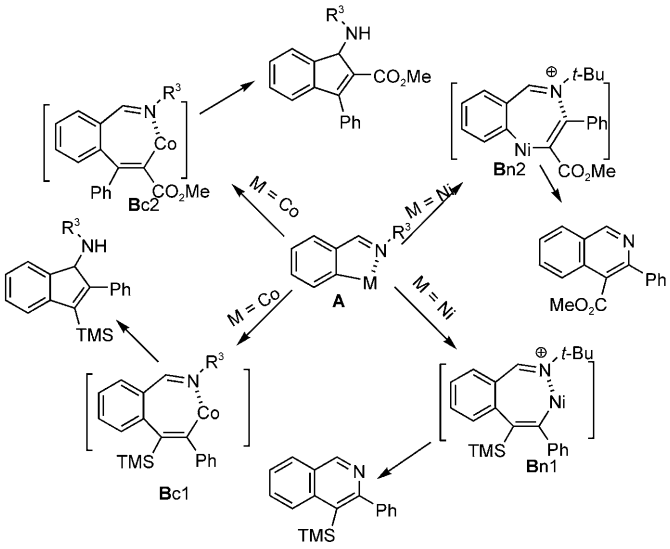
It is known that ester-substituted indenone derivatives are useful as agonists for peroxisome proliferator-activated receptor γ (PPARγ)[3b,6a]. One of these indenone derivatives, **9** (Scheme 2), can be prepared by the present oxidation method from indene-enamine **6d** in 95% yield. Previously these substrates were prepared by oxidizing the corresponding indene derivatives with SeO_2 in dioxane.[3b] Other biologically active 2,3-disubstituted indenone derivatives were also described in literature.[3c,6b]

A proposed mechanism for the present cobalt-catalyzed three component cyclization reaction was shown in Scheme 3. Chelation-assisted oxidative addition of 2-iodobenzaldimine **1** to Co^{I}, which is formed from the reduction of Co^{III} by zinc, gives a five-membered ring cobaltacycle **A**. Regioselective insertion of alkyne into C–Co bond of intermediate **A** yields a seven-membered[7] azacobaltacycle **B**. Subsequent intramolecular nucleophilic addition of the alkenyl group to C=N bond in **B** results in intermediate **C**. Upon hydrolysis, indenamine **5** and Co^{III} species were produced. The reduction of Co^{III} by zinc generates the Co^{I} needed for the next catalytic cycle. Generally, the alkyne insertion takes place in such a way that the electron-deficient carbon atom is near the metal.[8] Alternatively, intermediate **C** can be reduced by Zn to give Co^{I} and an intermediate similar to **C**, but with the Co^{III} replaced by Zn^{II}. During workup, this intermediate undergoes hydrolysis to give indenamine **5**.



Scheme 3. Proposed mechanism for the Co-catalyzed formation of indenamines.

It is worth noting that both cobalt and nickel complexes can catalyze the cyclization reaction of 2-iodobenzaldimine **1** with alkyne **4**, but the products, as shown in Scheme 4, are different. These two reactions are likely all through a five-membered azametalacycle **A** followed by insertion of alkyne into **A** to give **B**. For the cobalt-catalyzed reaction, intramolecular nucleophilic attack of the carbon anion at the imine carbon in **B** occurs to give finally the indenamine product. On the other hand, for the nickel-catalyzed reaction, reductive elimination probably takes place to afford an isoquinolinium salt and then the isoquinoline product. The observed different pathways are likely due to the difference of oxidation states of the two metals in intermediate **B**. One is Co^{III}, while the other is Ni^{II}. We think that in the cobalt-catalyzed reaction, the Co^{III} center in intermediate **B** (Scheme 3) is higher in Lewis acidity compared with Ni^{II}. The high acidity of Co^{III} greatly activates the imine group and enhances the intramolecular nucleophilic attack.



Scheme 4. Pathways for Ni- and Co-catalyzed insertion of alkynes.

Surprisingly, the regiochemistry for the cobalt-catalyzed indenamine and nickel-catalyzed isoquinoline formation is opposite to each other when alkynes with an electron-withdrawing group, such as COOR and COR, were used (Scheme 4). The observation may be explained based on the alkyne insertion into the M–C and M–N bonds in the five-membered metalacycle intermediate. In the cobalt-catalyzed reaction, the insertion of alkyne is all into the Co–carbon bond by Michael addition. Thus, the electron-withdrawing group is adjacent to the amine group of the indenamine product. However, for the nickel-catalyzed reaction, the alkyne insertion has two types. For normal alkynes such as TMSC≡CPh, the alkyne is inserted into the nickel–carbon

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bond of intermediate **A** to give intermediate **B**n1. For electron-withdrawing alkynes, the insertion is into the nickel–nitrogen bond of the five-membered nickelacycle by Michael addition (see intermediate **B**n2). As a result, for normal alkynes, both cobalt and nickel catalyst give the same regiochemistry, but for alkynes with an electron-withdrawing group, the two catalysts provides opposite regiochemistry for the products.

In conclusion, we have demonstrated a new methodology for the synthesis of substituted indenamines, indenimines, and indenones by a cobalt-catalyzed three-component reaction. The reaction is highly regioselective and many functionalized indenamine derivatives can be prepared. The interesting difference of products, regiochemistry, and mechanisms from those of the previous nickel-catalyzed *o*-halobenzaldimines and alkynes that gave isoquinoline products arises from the different natural properties of five-membered azametalcycles of cobalt and nickel.

Experimental Section

Procedure for the synthesis of 5a: A screw-cap seal tube initially fitted with septum containing **1a** (0.070 g, 0.30 mmol) was evacuated and purged with nitrogen gas three times. Then 4-octyne (0.066 g, 60 mmol), a mixture of freshly distilled CH_3CN and THF (2.0 mL, 1:1 by volume) were added to the system by syringe. The septum was removed and $[CoCl_2(dppe)]$ (0.012 g, 0.0210 mmol) and zinc (0.040 g, 0.60 mmol) were added to the system and the tube was quickly sealed with a screw cap. The resultant reaction mixture was stirred at 100 °C for 12 h. After completion of reaction, the mixture was cooled, diluted with dichloromethane, filtered through a small silica-gel pad, and then concentrated. Separation on a silica gel column using hexane/EtOAc as eluent gave pure indenamine derivative **5a** in 78% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 0.97–1.01 (m, 6H), 1.30 (s, 9H), 1.42–1.50 (m, 1H), 1.52–1.63 (m, 3H), 2.36–2.45 (m, 4H), 4.23 (s, 1H), 7.12 (t, $J = 7.0$ Hz, 1H), 7.16 (d, $J =$ 7.5 Hz, 1H), 7.23 (t, $J = 7.0$ Hz, 1H), 7.48 ppm (d, $J = 7.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 14.4$, 14.5, 22.0, 23.6, 27.6, 27.7, 30.9, 50.7, 60.7, 118.5, 123.0, 124.3, 127.0, 136.0, 145.1, 147.2, 148.5 ppm; HRMS (EI$^+$): *m*/*z* calcd for $C_{19}H_{29}N$: 271.2300; found: 271.2300; IR (KBr): $\tilde{\nu} = 1226$, 1465, 1604, 1704, 2869, 2931, 2954, 3355 cm^{-1}.

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Keywords: cobalt · nickel · nucleophilic addition · reaction mechanisms

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