

Heterobimetallic Cobalt/Rhodium Nanoparticle-Catalyzed Carbonylative Cycloaddition of 2-Alkynylanilines to Oxindoles

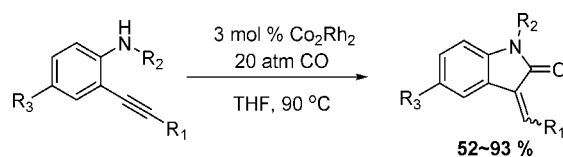
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ABSTRACT



The cobalt–rhodium heterobimetallic nanoparticle-catalyzed synthesis of oxindoles from 2-alkynylanilines in the presence of carbon monoxide is described.

The transition-metal-catalyzed carbonylative cyclization of unsaturated hydrocarbons using carbon monoxide¹ is among the most important and synthetically useful catalytic transformations. Recently, considerable research efforts have focused on the carbonylative cyclization to heterocycles.² However, in some cases, the usefulness of the transition-metal-catalyzed carbonylation is debased because of the requirement for high temperatures, high carbon monoxide pressure or specially designed ligands.³ It would be desirable to develop new carbonylation catalysts that can be carried out under mild reaction conditions.

Recently, transition metal nanoparticles have been widely used as catalysts for organic synthesis because to their high catalytic activity and recyclability.⁴ We recently found cobalt/rhodium nanoparticles (Co₂Rh₂) derived from Co₂Rh₂(CO)₁₂ to be useful catalysts in carbonylation related reactions.⁵ In the context of our studies on the use of transition metal nanoparticles in organic reactions, we found that Co₂Rh₂ was quite effective for the carbonylative cycloaddition of 2-alkynylanilines. This reaction permits the formation of oxindoles, which are versatile synthetic intermediates as well as important structural units in a variety of biologically active natural products.⁶ Many useful synthetic methods have been published.⁷ Among them, one of the most popular methods is based on a palladium-catalyzed arylation.⁸ A transition-metal-catalyzed carbonylation is highly recommendable in the synthesis of oxindoles. However, there has only been a limited amount of research in this area until now.^{9–11} In

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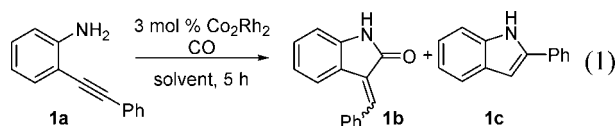
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1995, Takahashi et al. reported⁹ a Rh₆(CO)₁₆-catalyzed carbonylation of 2-alkynylanilines under water-gas shift reaction conditions (100 atm of CO) to give oxindoles in good yields along with a small amount of 2-quinolones. Here we report the Co₂Rh₂-catalyzed cyclization of 2-alkynylanilines in the presence of carbon monoxide to give oxindoles. This is the first use of transition metal nanoparticles as catalysts in the synthesis of oxindoles. The catalytic system does not require any additives or promoters and can be recycled several times without any significant loss of its catalytic activity. For the catalytic synthesis of oxindoles, the catalytic reaction can be carried out under relatively low CO pressure (20 atm).

A catalytic synthesis of oxindoles was studied using 2-alkynylaniline **1a** as a model substrate and Co₂Rh₂ as a catalyst. 2-Alkynylanilines were easily synthesized by the palladium-catalyzed cross-coupling between 2-haloanilines and acetylenes. The treatment of **1a** (58 mg, 0.3 mmol) with 20 atm of carbon monoxide in the presence of Co₂Rh₂ (3 mol %, 15 mg) in 5 mL of toluene at 100 °C for 5 h gave an oxindole **1b** in 29% with the concomitant formation of an indole **1c**¹⁰ in 71% yield (eq 1).¹¹ The formation of the oxindoles was confirmed by ¹H and ¹³C NMR and HRMS studies. We were pleased to find that the desired product **1b** was obtained in 29% in the initial study.



Encouraged by the formation of **1b**, we further optimized the reaction conditions. The representative optimization experiments are summarized in Table 1. The yield was highly

Table 1. Screening of Catalyst Systems for the Formation of **1b**^a

entry	CO (atm)	solvent	temp (°C)	isolated yield of 1b (%) ^b
1	1	toluene	100	0 (>99)
2	5	toluene	100	0 (>99)
3	20	toluene	130	13 (87)
4	20	toluene	100	29 (71)
5	20	THF	100	71 (29)
6	20	THF	130	52 (48)
7	20	THF	90	90 (10)

^a 0.3 mmol of **1a** and 5 mL solvent were used. ^b The numbers in parentheses are the isolated yields of the corresponding indole **1c**.

dependent upon the reaction temperature, the pressure of CO, and the reaction solvent. The best yield of **1b** was 90%. Compound **1b** was a mixture of *E/Z* isomers (ca. 10:1) with a slightly different isomer ratio for each experiment. The optimized reaction conditions were established as follows: 20 atm of CO, 90 °C, and 5 h.

To check for recyclability, the catalyst was separated and reused several times. The catalyst maintained its high level

of activity even after being recycled six times (90%, 89%, 91%, 92%, 89%, and 91%, respectively). In order to recycle the catalyst, it was filtered from the reaction mixture and dried in vacuum. It could then be reused for further catalytic reactions.

To examine the scope of the present reaction, various 2-alkynylanilines were screened under the optimized reaction conditions. The results are summarized in Table 2, which

Table 2. Co₂Rh₂-Catalyzed Synthesis of Oxindoles from 2-Alkynylanilines^a

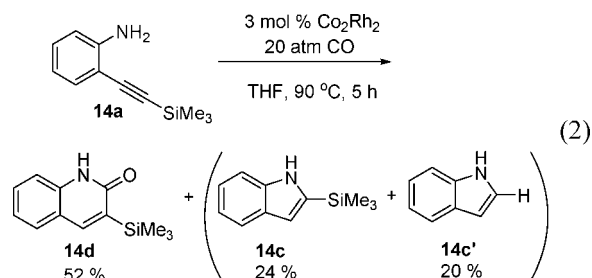
entry	2-ethynylaniline	product	yield(%) ^b
1	2a	2b	89
2	3a	3b	52
3	4a	4b	93
4	5a	5b	80
5	6a	6b	58
6	7a	7b	82
7	8a	8b	84
8	9a	9b	73
9	10a	10b	92
10	11a	11b	92
11	12a	12b	71
12	13a	—	0 ^c

^a 0.3 mmol of **a** and 3 mol % of Co₂Rh₂ catalyst were used in 5 mL THF for 5 h. ^b Isolated yield. ^c Decomposed.

shows that oxindoles **b** were obtained in satisfactory yields for all 2-alkynylanilines with an internal alkyne bearing a hydrogen, alkyl, or aryl substituent on the amine moiety. In addition to the formation of **b**, formation of **c** was observed for all the cases with slightly different yields (ca. 10–20%).

However, in the case of entries 2 and 5, **3c** and **6c** were obtained in 48% and 42% yields, respectively. When 2-alkynylaniline with a terminal alkyne was used as a substrate (entry 12), no characterizable compounds were isolated. Several years ago, Gabriel and co-workers reported¹² a palladium-catalyzed oxidative carbonylation of 2-alkynylanilines to oxindoles. However, when the reaction was applied to 2-alkynylanilines with internal triple bonds, carbamates were obtained as a product. Very recently, Li and co-workers reported¹³ the palladium-catalyzed carbonylative annulation of 2-(1-alkynyl)benzenamines to 3-(halomethylene)indolin-2-ones under mild reaction conditions. However, the N-substituted substrates were not suitable for their reaction conditions. Thus, our reactions are unique and can be used as a supplement to other methods.

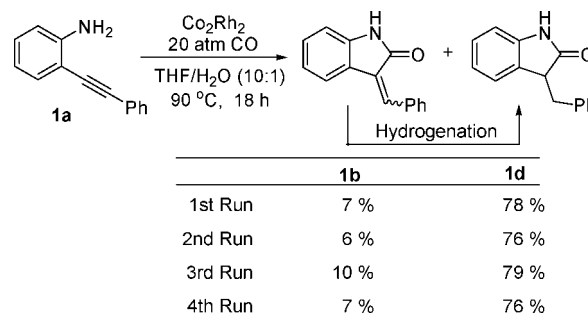
Interestingly, treatment of 2-alkynylaniline (**14a**) with bearing TMS under the optimized reaction conditions gave a quite different result (eq 2). Instead of an oxindole derivative, a quinolinone **14d** was isolated in 52% with a concomitant formation of indoles, **14c** and **14c'**. The formation of quinolinone from 2-alkynylaniline was quite unusual observation.



It has been well reported¹⁴ that a transition-metal-catalyzed carbonylation under water-gas shift reaction conditions (in the presence of carbon monoxide, water, and an amine) leads to a mixture of a carbonylated and a carbonylated/

hydrogenated product. Thus, a mixture of H₂O/Et₃N was added to the reaction mixture. However, no reaction was observed. Instead, when a wet THF was used a reaction medium, a reduced oxindole and oxindole were isolated in 78% and 7% yields, respectively (Scheme 1). However, the

Scheme 1. Reaction under Water-Gas Shift Reaction Condition



addition of water led to a slight decrease in the yield and a lengthening of the reaction time to up to 18 h. The maximum reusability of the catalytic system was not tested. The catalytic system can be reused at least three times without loss of catalytic activity.

In conclusion, we demonstrated that Co₂Rh₂ can be used as an effective catalyst in the carbonylative cycloaddition of 2-alkynylanilines in the presence of carbon monoxide. This reaction permits the formation of oxindoles, which are versatile synthetic intermediates as well as important structural units in a variety of biologically active natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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