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SYNTHESIS OF TRIAZOLE, INDOLE, AND FIVE OR SIX-MEMBERED SATURATED HETEROCYCLIC COMPOUNDS

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Abstract – Heterogeneously-catalyzed synthetic methods for the preparation of 1,2,3-triazoles, indolines, indoles, and saturated heterocyclic compounds, such as piperidine and pyrrolidine, are demonstrated. Triazoles are intermolecularly synthesized by the 1,3-dipolar cycloaddition of alkynes with azides using heterogeneous copper catalysts. Solvent-free triazole syntheses are also described. Inter- and intramolecular annulations as indole syntheses are summarized; e.g., a palladium on carbon (Pd/C)-catalyzed Yamanaka–Larock method affords 2- or 2,3-substituted indoles from 2-iodoaniline derivatives and mono- or di-substituted alkynes; an intramolecular Pd/C-catalyzed Buchwald–Hartwig reaction of 2-bromophenethylamine derivatives temperature-dependently affords indolines or indoles. Pd/C can also catalyze an intermolecular aromatic amination of bromoarenes with indoles to generate the corresponding *N*-arylindoles. The application of the hydrogenation technology using 10% Pd/C, 10% rhodium on carbon (Rh/C), or 10% ruthenium on carbon (Ru/C) as a catalyst is finally introduced for the synthesis of indole by the intramolecular hydrogenative *N*-alkylation of 2-cyanomethylaniline and piperidine, pyrrolidine, and tetrahydrofuran derivatives by the arene hydrogenation of pyrridine, pyrrole, and furan derivatives under relatively mild conditions, respectively.

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1. INTRODUCTION

Heterogeneous transition metal catalysts, such as palladium on carbon (Pd/C), have traditionally been used for the hydrogenation of a wide range of reducible functionalities including alkyne, alkene, and nitro functionalities, and most of them are embedded on some insoluble supports, such as activated carbon, CaCO₃, Al₂O₃, etc.¹ Recently, the use of such heterogeneous transition metal catalysts for organic synthesis is demanded from the environmental and cost-efficient points of view based on their recoverability, reusability, and property of preventing contamination of the metal residue in the products.² We have developed unique heterogeneous transition metal catalysts using industrially manufactured products³ as well as natural resources,⁴ such as a fibroin protein as a major component of raw silk, for the hydrogenation and cross-coupling reactions. Furthermore, novel synthetic methodologies for carbon–carbon,⁵ carbon–nitrogen,⁶ and carbon–oxygen⁷ bond forming reactions, hydrogen–deuterium exchange reactions,⁸ arene hydrogenation,⁹ hydrodehalogenation,¹⁰ and oxidation of hydrogen¹¹ using conventional activated carbon-supported transition-metal catalysts, such as Pd/C,¹² ruthenium on carbon (Ru/C), rhodium on carbon (Rh/C), and platinum on carbon (Pt/C), have been established. In this review, we focused on the heterogeneously catalyzed annulation as the 1,4-disubstituted 1,2,3-triazole^{13–15} and indole synthesis^{6a,6c,16,17} and an arene hydrogenation for the synthesis of saturated heterocyclic compounds.^{9b}

2. COPPER-CATALYZED HETEROGENEOUS HUISGEN CYCLIZATION FOR 1,2,3-TRIAZOLE SYNTHESIS

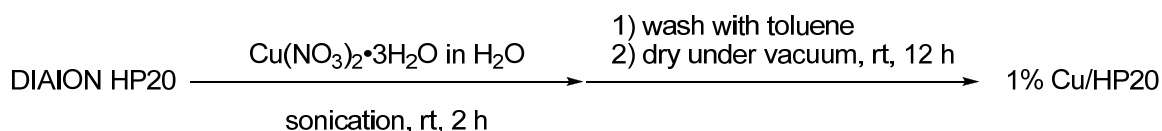
The Huisgen cyclization of azides to alkynes is a powerful tool for the construction of the 1,2,3-triazole nucleus,¹⁸ which is recognized as one of the important structural units in bioactive compounds.¹⁹ In particular, the copper-catalyzed reaction using mono-substituted alkynes and azides for the regioselective synthesis of 1,4-di-substituted 1,2,3-triazoles independently developed by Sharpless²⁰ and Meldal²¹ has been widely used for the preparation of a variety of functional materials because of its reliability, simplicity, and effectiveness.²² The current supports employed for the immobilized copper catalysts for the heterogeneous Huisgen cyclization are carbon materials,²³ amine- or imino-bound silica,²⁴ zeolite,²⁵ superparamagnetic mesoporous silica,²⁶ hydrotalcite,²⁷ AlO(OH),²⁸ metal oxides,²⁹ polysaccharide,³⁰

ligand-bound organic polymers,³¹ and ion exchange resins, such as Amberlyst A21³² and Dowex.³³ The preparation of supported copper catalysts on these materials requires multiple steps in most cases and centrifugation or decantation for their separation from the reaction mixture in some cases.

2.1. Cu on Synthetic Adsorbent-Catalyzed Azide–Alkyne Cycloaddition^{13,14}

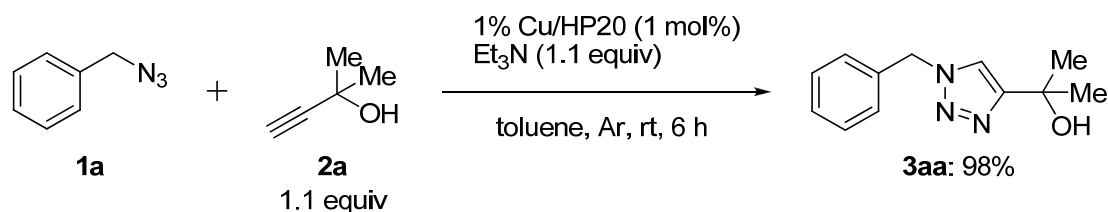
Industrially produced materials should be good candidates as supports of immobilized metal catalysts due to their reliable qualities and stable supply. DIAION[®] HP20 (HP20, Mitsubishi Chemical Corporation), which is a commercially available polystyrene-polyvinylbenzene-based synthetic adsorbent for chromatographic separation, possesses a large surface area (ca. 590 m²/g) and fine pore structure (30 nm of radius) on the particle (440 μm of average diameter) and is stable in organic solvents and in acidic and basic media.³⁴ These features encouraged us to use HP20 as a support for the heterogeneous transition-metal catalysts because of the possible efficient contact of organic substrates with active metal species on/in the organic adsorbent by a lipophilic enrichment effect. The palladium catalyst supported on HP20 was successfully prepared and used for the hydrogenation and cross-coupling reaction as expected.^{3a,3b}

The copper species were simply embedded on HP20 according to the modified preparation procedure of Lipshutz's Cu/C.^{23a} HP20 was immersed in an aqueous solution of Cu(NO₃)₂ and sonicated for 2 h. The resulting Cu/HP20 was filtered, washed with toluene, and dried. The immobilized copper species of Cu/HP20 was determined to be 1 weight % by measurement of the copper content in the filtrate and wash obtained during the catalyst preparation using an atomic absorption photometer (Scheme 1).¹³



Scheme 1. Preparation of 1% Cu/HP20

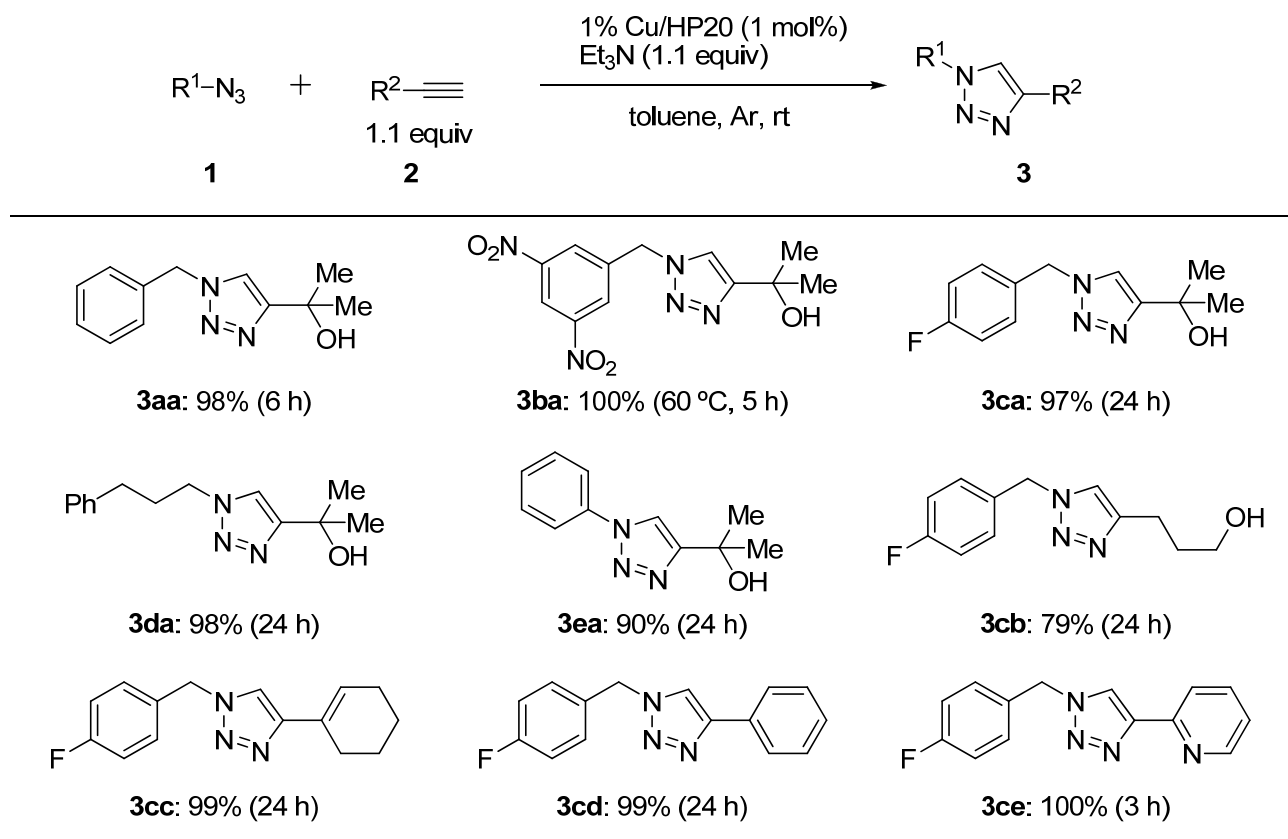
1% Cu/HP20 (1 mol%) effectively catalyzed the cycloaddition of benzylazide (**1a**) with 3-methyl-1-butyn-3-ol (**2a**) in the presence of Et₃N (1.1 equiv) to give the corresponding 1,4-disubstituted 1,2,3-triazole (**3aa**) in an excellent yield (Scheme 2).



Scheme 2. 1% Cu/HP20-catalyzed Huisgen cycloaddition

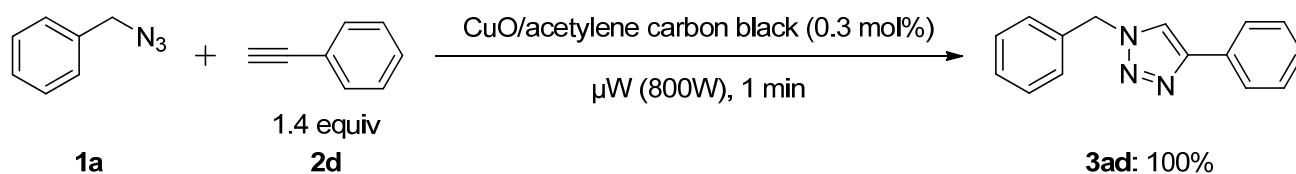
The 1% Cu/HP20-catalyzed Huisgen cycloaddition exhibits a broad substrate applicability. 3-Methyl-1-butyn-3-ol (**2a**) smoothly reacted with various azides (**1**) at room temperature, although the cycloaddition of 3,5-dinitrophenylmethylazide (**1b**) to the triazole (**3ba**) required the application of heat for the complete consumption of **1b** possibly because of its low solubility in toluene as an exception (Table 1). Such a problem could be solved by the solvent-free reaction as described below (Table 2). A wide range of alkynes (**2**) were also good substrates for the 1% Cu/HP20-catalyzed cycloaddition with 4-fluorobenzylazide (**1c**). Especially, the reaction of 2-ethynylpyridine (**2e**) was completed within 3 h probably because the nitrogen atom of the pyridine nucleus worked as a directing group of copper metal based on the coordination to facilitate its approach to the adjacent carbon-carbon triple bond. The 1% Cu/HP20 could be reused until at least the 3rd run for the cycloaddition to **3ca** without any significant loss of the catalyst activity, although a longer reaction time was required in the 4th and 5th runs to complete the reaction progress (from 5 h to 12 h and 24 h).

Table 1. 1% Cu/HP20-catalyzed Huisgen cycloaddition between various azides (**1**) and alkynes (**2**)

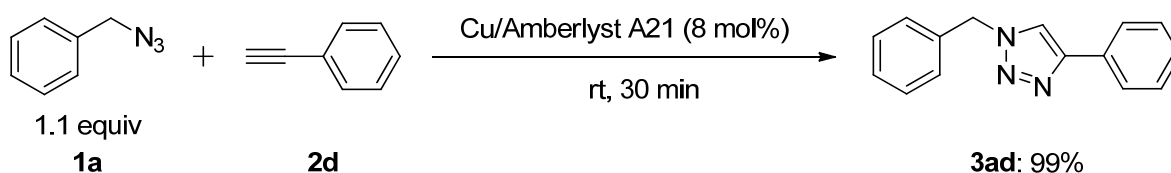


The elimination of solvents from organic reactions as well as the use of heterogeneous catalysts is recognized as one of the goals of green sustainable chemistry because it leads to the reduction of solvent wastes, size of the manufacturing plants, and cost.^{35,36} Only a couple of studies have reported the solvent-free heterogeneous Huisgen cycloaddition using copper oxide on acetylene carbon black^{23d} and

copper on Amberlyst A21^{32b} as catalysts (Schemes 3 and 4). These reactions proceeded without any base. The former catalyst could be reused for at least five cycles, but microwave conditions and centrifuging were required. The reuse of the catalyst is not mentioned in the latter case.

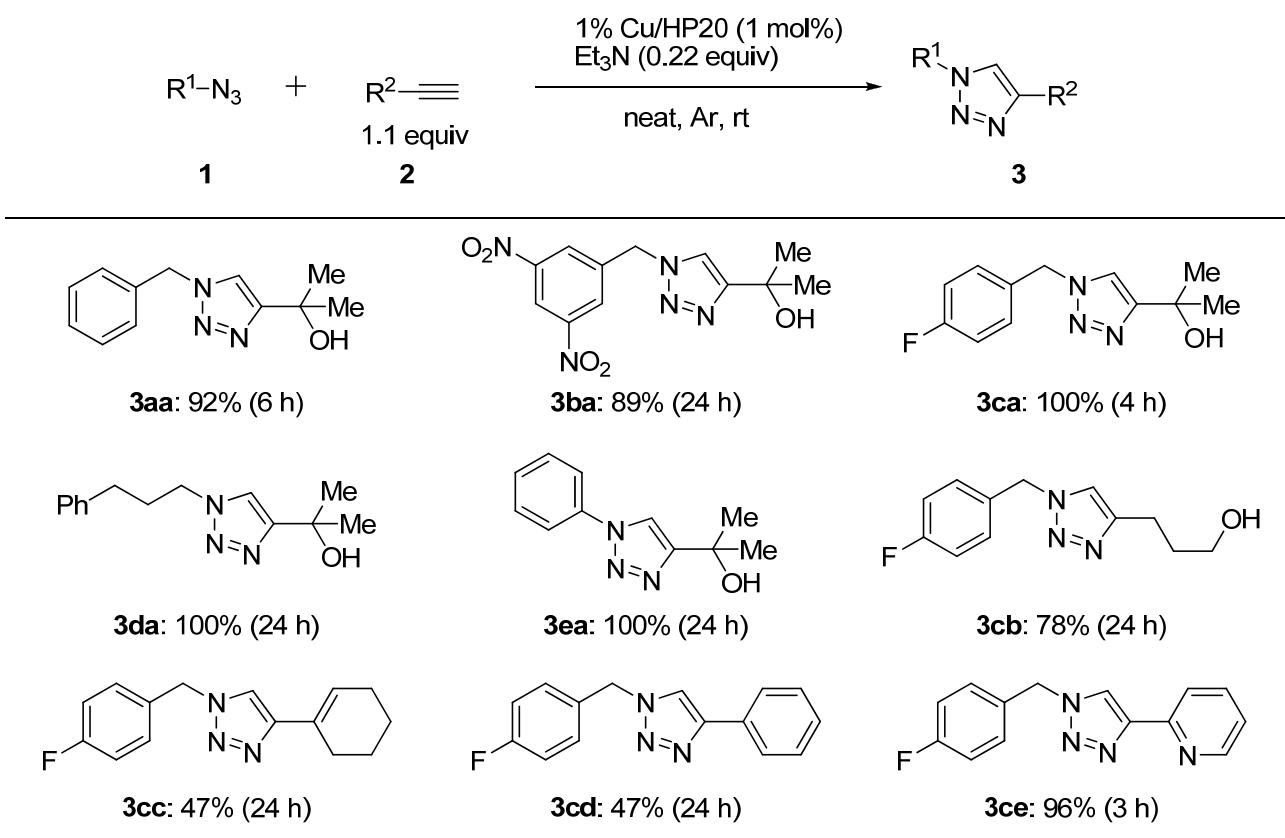


Scheme 3. Solvent-free heterogeneous Huisgen cyclization catalyzed by CuO/activated carbon black^{23d}



Scheme 4. Solvent-free heterogeneous Huisgen cyclization catalyzed by Cu/Amberlyst A21^{32b}

Table 2. 1% Cu/HP20-catalyzed solvent-free Huisgen cycloaddition between various azides (**1**) and alkynes (**2**)



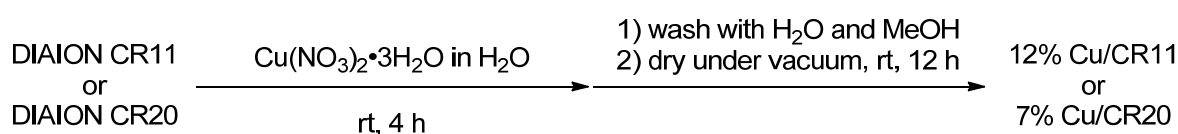
The 1% Cu/HP20-catalyzed Huisgen cycloaddition could also be carried out in the presence of a catalytic amount of Et₃N (0.22 equiv) under solvent-free conditions.¹⁴ A wide variety of azides (**1**) reacted with alkynes (**2**) at room temperature to give the corresponding triazoles (**3**) in good yields (Table 2). The huge advantage of the solvent-free conditions was to enhance the efficiency of the cyclization using the low soluble azide, 3,5-dinitrophenylmethylazide (**1b**), probably due to the substrates concentration effect on the lipophilic support, although the above-mentioned reaction in toluene in Table 1 never proceeded at room temperature and required heat at 60 °C for the completion. 2-Ethynylpyridine (**2e**) was also a good substrate for the preparation of **3ce** under the solvent-free conditions.

The reuse test of 1% Cu/HP20 under the solvent-free conditions indicated that the reaction efficiency was significantly reduced after each run (1st run, 100%; 2nd run, 88%; 3rd run, 34%). Approximately 19% copper leaching from 1% Cu/HP20 during the reaction of **1c** with **2a** was observed by inductively coupled plasma atomic emission spectrometry (ICP-AES), thus the leaching of copper species would cause the problematic reuse of the 1% Cu/HP20 as a catalyst.

2.2. Cu on Chelate Resin-Catalyzed Azide–Alkyne Cycloaddition¹⁵

Chelate resins, DIAION CR11 (CR11) and DIAION CR20 (CR20), both produced by the Mitsubishi Chemical Corporation, polystyrene-divinylbenzene-based polymers possessing iminodiacetic acid and polyamine moieties as ligands, respectively, have been used for water purification by their capturing ability of heavy metal ions based on chelation.^{34a,37} These resins should also be guaranteed as industrial products in quality and properties under strictly controlled regulations.

Copper ions were immobilized on the CR11 and CR20 in an improved manner for the preparation for 1% Cu/HP20, by simply immersing CR11 and CR20 in an aqueous solution of Cu(NO₃)₂ but without sonication, and highly loaded copper catalysts, 12% Cu/CR11 and 7% Cu/CR20, were obtained by the effective complexation of copper ions with ligands on the polymers (Scheme 5).¹⁵



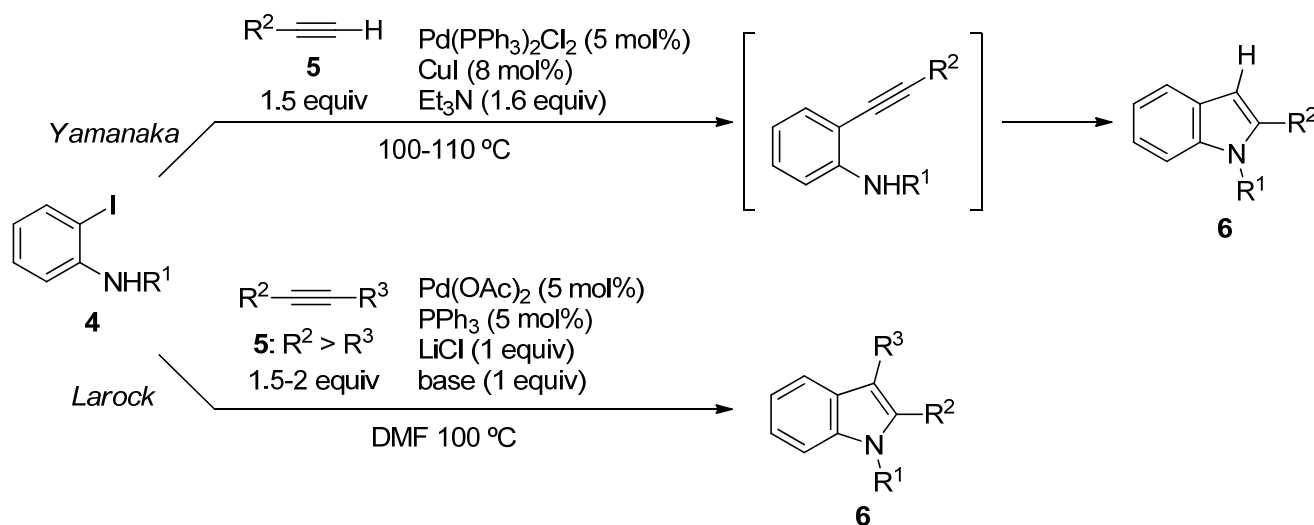
Scheme 5. Preparation of 12% Cu/CR11 and 7% Cu/CR20

The 1,3-dipolar cycloaddition of benzylazide (**1a**) with ethynylbenzene (**2d**) was found to effectively proceed at 70 °C under solvent-free conditions in the presence of catalytic amounts of 12% Cu/CR11 (1–5 mol%) and Et₃N (0.22 equiv), and the corresponding 1,2,3-triazole (**3ad**) was quantitatively obtained (Table 3). A wide range of azides (**1**) and alkynes (**2**) were good substrates for the solvent-free

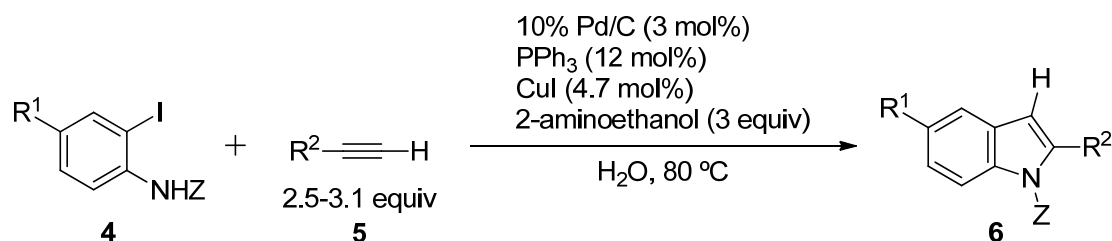
The indole framework is one of the most ubiquitous heterocyclic nuclei found in the chemical structure of biologically active compounds, such as serotonin, indometacin, sertindole, etc.³⁸ Various methods for the construction of the indole nucleus have been developed.³⁹

3.1. Yamanaka–Larock Indole Synthesis¹⁶

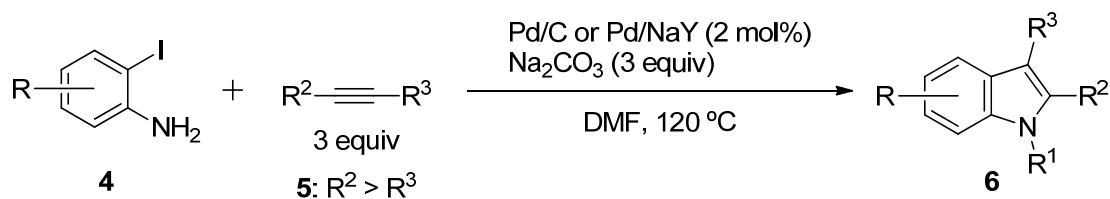
The one-pot direct synthesis of 2-substituted indoles from 2-haloanilines and mono-substituted alkynes by the Sonogashira reaction and the following cyclization in the presence of Pd(PPh₃)₂Cl₂, CuI, and Et₃N was first reported by Yamanaka et al.,⁴⁰ while Larock employed disubstituted alkynes with Pd(OAc)₂, LiCl, and K₂CO₃ to obtain 2,3-disubstituted indoles in a highly regioselective manner (Scheme 6).⁴¹ There are a few reports of the Yamanaka-type 2-substituted indole syntheses from mono-substituted alkynes using not commercially available heterogeneous palladium catalysts^{42,43} or palladium-copper combined catalysts.⁴⁴ The Pd/C-catalyzed Yamanaka-type annulation was also developed, but the combined use with triphenylphosphine as a ligand, CuI, and 2-aminoethanol was necessary (Scheme 7).⁴⁵ Djakovitch et al. reported the LiCl-free Larock-type annulation for the 2,3-disubstituted indole synthesis using heterogeneous palladium species including Pd/C (Scheme 8)⁴⁶ during the preparation of our paper for the Pd/C-catalyzed Yamanaka–Larock indole synthesis.¹⁶



Scheme 6. Palladium-catalyzed indole synthesis from iodoaniline (**4**) and alkyne (**5**)

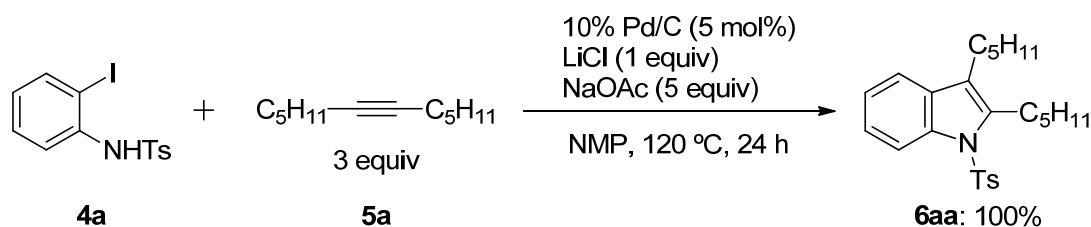


Scheme 7. Pd/C-catalyzed Yamanaka indole synthesis



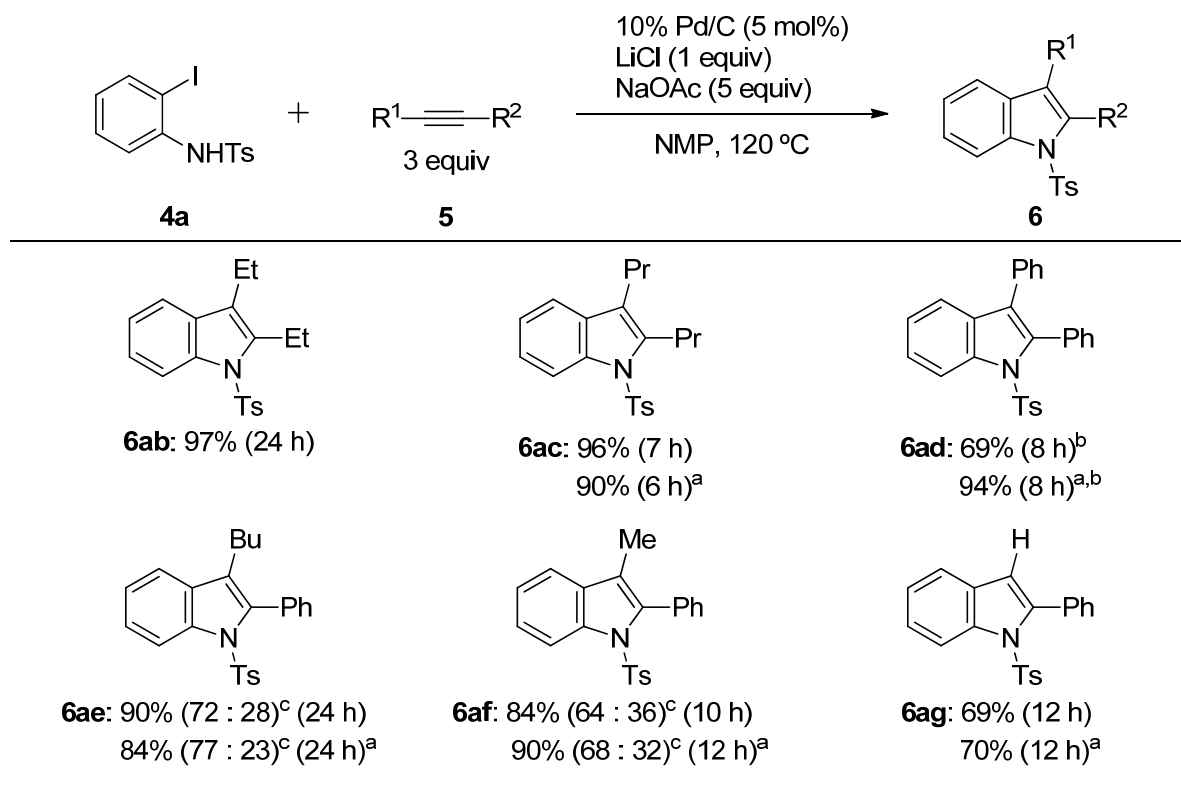
Scheme 8. Pd/C-catalyzed Larock indole synthesis

Our initial optimal conditions are shown in Scheme 9. The 10% Pd/C-catalyzed annulation between *N*-tosyl-2-iodoaniline (**4a**) and 6-dodecyne (**5a**) led to the quantitative formation of *N*-tosyl-2,3-dipentylindole (**6aa**) using an equimolar amount of LiCl and 5 equiv of NaOAc in heated *N*-methylpyrrolidone (NMP) (120 °C).



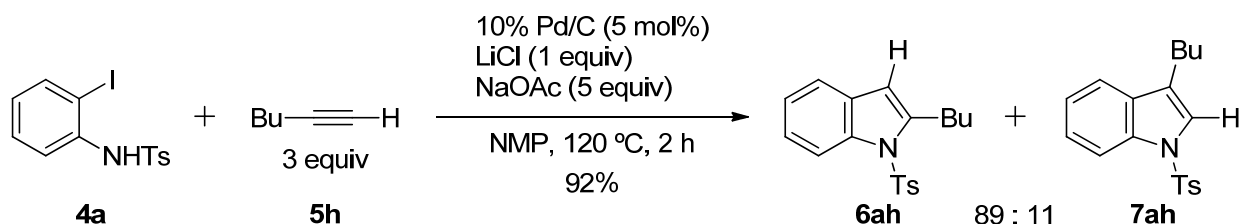
Scheme 9. 10% Pd/C-catalyzed annulation of 6-dodecyne (**5a**) with *N*-tosyl-2-iodoaniline (**4a**)

Table 5. 10% Pd/C-catalyzed annulation using *N*-tosyl-2-iodoaniline (**4a**) and various alkynes (**5**)

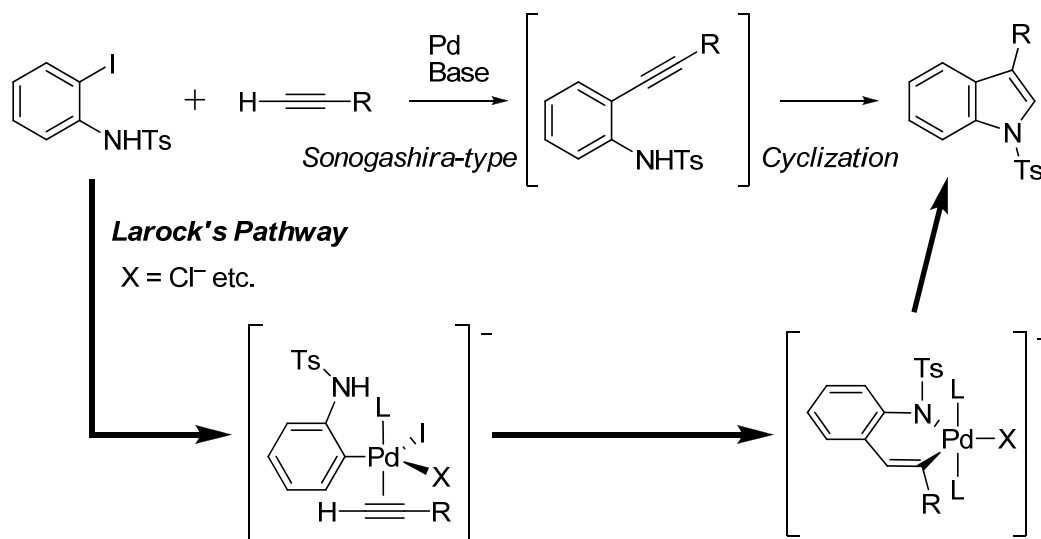


^a LiCl was not added. ^b 2 equiv of diphenylacetylene was used. ^c The ratio of **6** and its regioisomer (**7**) is indicated in parenthesis.

A wide range of alkynes (**5**: 3 equiv) could be used for the preparation of the indole derivatives from *N*-tosyl-2-phenylindole (**4a**) under the above-mentioned optimal conditions (Table 5). The reactions of symmetrical dialkylacetylenes gave the corresponding 2,3-disubstituted indoles [**6aa** (Scheme 9), **6ab**, **6ac**, and **6ad** (Table 5)] in good to quantitative yields, regardless of the alkyl chain length of **5**. Unsymmetrical disubstituted acetylenes, such as 1-phenyl-1-hexyne (**5e**) and 1-phenyl-1-propyne (**5f**), were also smoothly cyclized, but complete regioselectivities could not be achieved. The cyclization of ethynylbenzene (**5g**), a mono-substituted alkyne, proceeded in a complete regioselective manner to give *N*-tosyl-2-phenylindole (**6ag**) as the sole product, while the use of 1-hexyne (**5h**) as a substrate gave a mixture of regioisomers, i.e., the 2- and 3-butyl-1-tosylindoles (**6ah** and **7ah**) in the ratio of 89 : 11, respectively (Scheme 10). These results indicated that the pathway for the indole formation from mono-substituted alkynes would be the same as the proposed mechanism for the synthesis of 2,3-disubstituted indoles from disubstituted alkynes reported by Larock, which involves the insertion of an alkyne into the arene–palladium bond to form the vinylic palladium intermediate,⁴¹ although the two-step process including the Sonogashira-type coupling could not be thoroughly excluded (Scheme 11).⁴⁰ The Yamanaka–Larock indole synthesis requires no use of LiCl as does the Djakovitch's protocol (see the synthesis of **6ac**, **6ad**, **6ae**, **6af**, and **6ag** in Table 5).⁴⁶



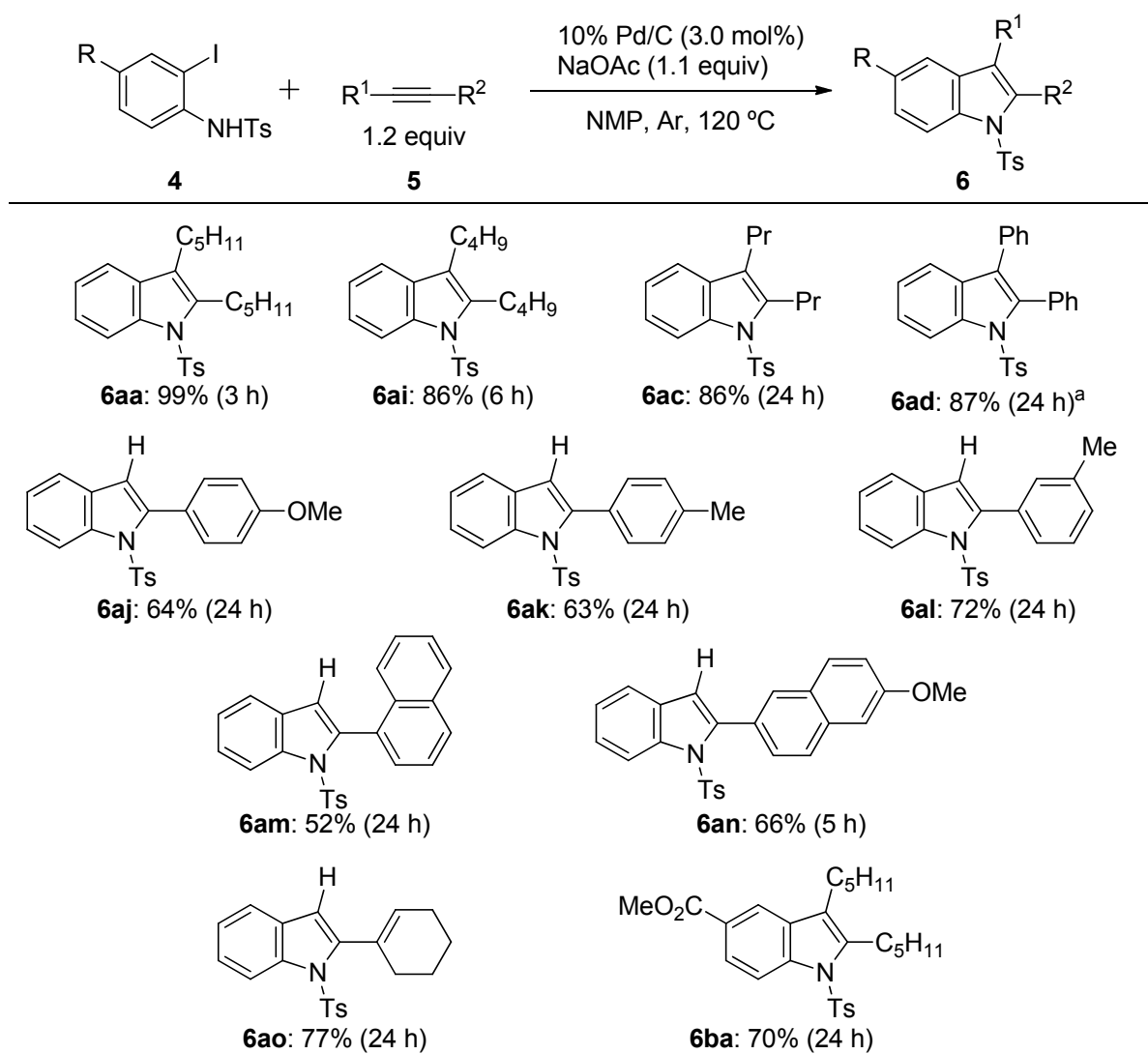
Scheme 10. Generation of regioisomers of indole (**6ah** and **7ah**) from monosubstituted alkyne (**5h**)



Scheme 11. Proposed reaction pathways for the annulation using the mono-substituted alkynes and 2-iodoaniline derivative

The optimal conditions for the LiCl-free 10% Pd/C-catalyzed Yamanaka–Larock indole synthesis using *N*-tosyl-2-iodoaniline (**4**) and alkyne (**5**) derivatives as substrates are summarized in the equation of Table 6. Various 2,3-di- and 2-monosubstituted indoles were successfully synthesized from alkynes (1.1 equiv) (**6**) and *N*-tosyl-2-iodoaniline derivatives (**4**) in the presence of 10% Pd/C (3 mol%) and NaOAc (1.1 equiv) in heated NMP (120 °C). Symmetrical alkynes (**5a**, **5i**, **5c**, and **5d**) were effectively reacted with **4a** to give the corresponding 2,3-disubstituted indoles (**6aa**, **6ai**, **6ac**, and **6ad**) in excellent yields. Phenylacetylenes bearing a methoxy (**5j**) or methyl (**5k** and **5l**) functionality on the benzene ring cyclized to the corresponding 2-arylindoles (**6aj**, **6ak**, and **6al**) in a completely regioselective manner. The reaction of the 1-naphthyl- (**5m**), 2-naphthyl- (**5n**) and 1-cyclohexenyl (**5o**) acetylene derivatives also gave the desired 2-naphth-1-yl- (**6am**), 2-naphth-2-yl- (**6an**), and 2-cyclohexenylindole (**6ao**) derivatives in

Table 6. LiCl-free 10% Pd/C-catalyzed Yamanaka–Larock indole synthesis from iodoaniline derivatives (**4**) and alkynes (**5**)



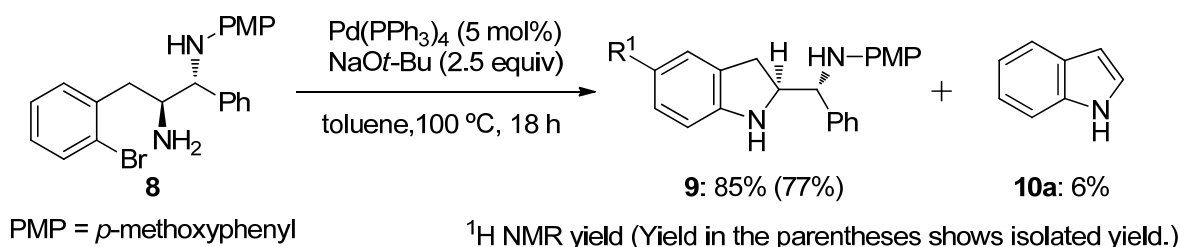
^a 130 °C.

practically applicable yields. Furthermore, *N*-tosyl-2-iodo-4-methoxycarbonylaniline (**4b**) was also a good substrate. The distinctive features of the protocol are typically for both the Yamanaka- and Larock-type reactions and a high efficiency with lower amounts of alkyne and base.¹⁶

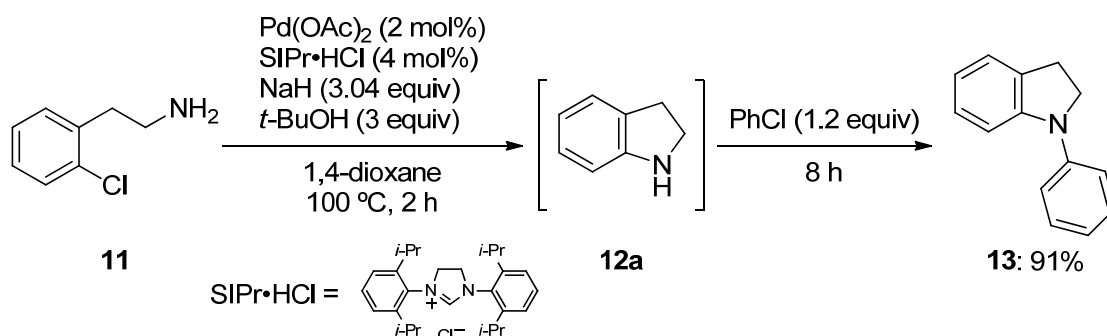
A practical, efficient, and general protocol for the 10% Pd/C-catalyzed Yamanaka–Larock indole synthesis in the absence of LiCl, was described. Symmetrical disubstituted alkynes reacted with *N*-tosyl-2-iodoaniline to give the corresponding 2,3-disubstituted indoles in excellent yields, and a variety of 2-mono-arylsubstituted indole derivatives were synthesized from the mono-arylalkynes in a completely regioselective manner. Easy deprotection of the *N*-tosyl group on the indole nucleus⁴⁷ is also an advantage of this protocol. The next section will introduce the heterogeneously catalyzed intramolecular cyclization for the syntheses of indole and dihydroindole (indoline) derivatives.

3.2. *N*-Arylindole Synthesis by Intramolecular Aromatic Amination¹⁷

2-Halophenethylamines have been used as the starting materials for construction of the indoline skeleton, which is readily found as a core structural unit of biologically active compounds, by the cyclization based on the copper-,⁴⁸ copper-iron-,⁴⁹ nickel-,⁵⁰ or palladium-catalyzed^{51,52} intramolecular carbon–nitrogen bond forming reaction. Tocher et al. reported that the intramolecular cyclization of a 2-bromophenethylamine derivative (**8**) using Pd(PPh₃)₄ as a catalyst afforded the desired 2-substituted indoline derivative (**9**) together with decomposed product, indole (**10a**) (Scheme 12).^{51a} 2-Chlorophenethylamine (**11**) was also applied by Schneider and Fort et al. for the one-pot synthesis of



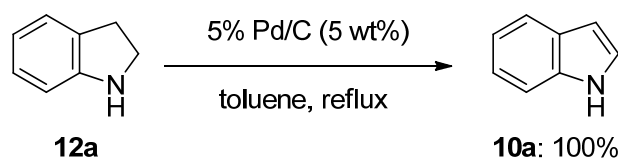
Scheme 12. Pd-catalyzed intramolecular aromatic amination of 2-bromophenethylamine derivative (**8**)



Scheme 13. One-pot synthesis of phenylindoline (**13**) via consecutive intra- and intermolecular aromatic aminations

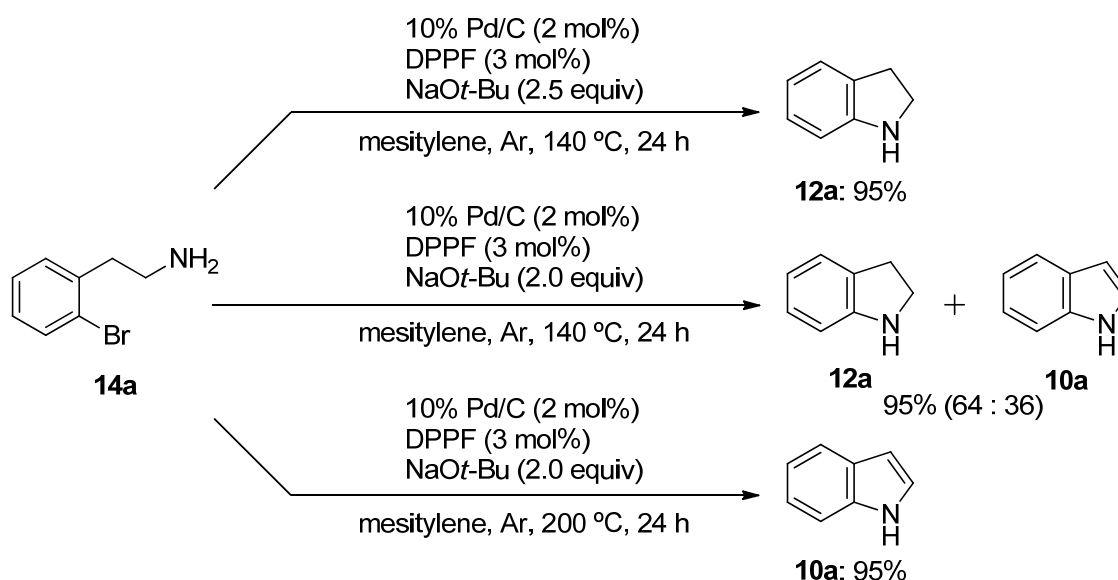
N-arylindoline (**13**) by the intramolecular annulation using Pd(OAc)₂ and active *N*-heterocyclic carbene and subsequent *N*-arylation of the resulting indoline (**12a**) with chloroarene (Scheme 13).^{51b}

The aromatization of indoline to the indole was achieved by a variety of oxidation methods.⁵³ Dehydrogenation reactions using heterogeneous transition metal catalysts, such as polymer-incarcerated gold,⁵⁴ gold on graphite,⁵⁵ ruthenium on alumina,⁵⁶ palladium on hydroxyapatite (PdHAP),⁵⁷ and palladium on carbon (Pd/C) (Scheme 14)⁵⁸ were also reported in the literature, although the direct or one-pot synthesis of the indole from 2-halophenethylamine has scarcely been reported.⁵⁹



Scheme 14. Pd/C-catalyzed aromatization of indoline (**12a**) to indole (**10a**)

We have recently developed a Pd/C-catalyzed Buchwald–Hartwig cross-coupling reaction between amines and bromoarenes forming a carbon–nitrogen bond with a very low level of palladium leaching.^{6b} 2-Bromophenethylamine (**14a**) was used for the intramolecular Buchwald–Hartwig aromatic amination in the presence of 10% Pd/C (2 mol%), 1,1'-bis(diphenylphosphino)ferrocene (DPPF, 3 mol%), and NaOt-Bu (2–2.5 equiv) in mesitylene. The cyclization temperature-dependently gave different products; i.e., indoline (**12a**) at 140 °C and indole (**10a**) at 200 °C, both in 95% yields (Scheme 15). The amount of NaOt-Bu is also an important factor for this selectivity, and a 64 : 36 mixture of **12a** and **10a** was

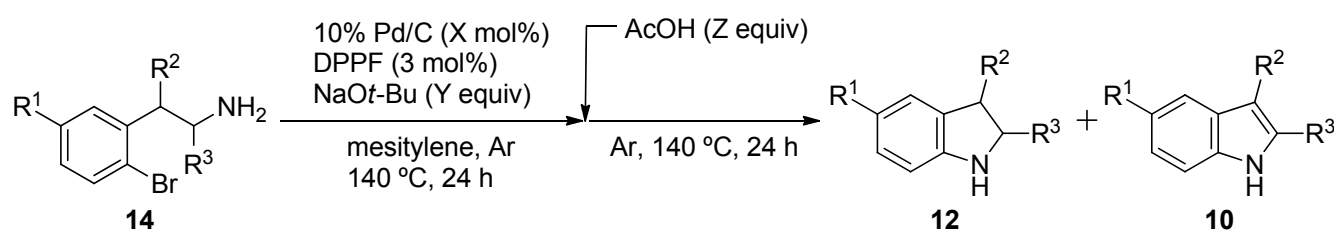


Scheme 15. Temperature-dependent selective synthesis of indoline (**12a**) and indole (**10a**) by the 10% Pd/C-catalyzed cyclization of 2-bromophenethylamine (**14a**)

obtained by using 2 equiv of NaOt-Bu even at 140 °C. These results indicated that the strongly basic conditions should be unfavorable for the aromatization of the indoline (**12a**) to indole (**10a**). Crabtree et al. achieved the Pd/C-catalyzed aromatization of **12a** in refluxing toluene under neutral conditions (Scheme 14).⁵⁸

Methyl-substituted indolines (**12b** and **12c**) were synthesized under the same conditions indicated for the synthesis of **12a** (Scheme 15 and Table 7, Entry 1) using 10% Pd/C (2 mol%), DPPF (3 mol%), and NaOt-Bu (2.5 equiv) in mesitylene at 140 °C (Table 7, Entries 3 and 5). Since the aromatization was not completed at 200 °C in the case of the methylated 2-bromophenethylamine derivatives (**14b** and **14c**) as substrates, 1.5 equiv of acetic acid was added to neutralize the reaction media after completion of the indoline formation (**12b** and **12c**). Methylated indoles (**10b** and **10c**) as well as non-substituted indole (**10a**) were selectively obtained in good yields by the addition of acetic acid after further stirring at 140 °C without raising the temperature for the aromatization (Entries 2, 4, and 6). Furthermore, 5-methoxyindole (**10d**) was also obtained from 2-bromo-5-methoxyphenethylamine (**14d**) by the minor tuning of the reaction conditions (Entry 7).

Table 7. One-pot selective indoline and indole synthesis from 2-bromophenethylamine derivatives (**14**)

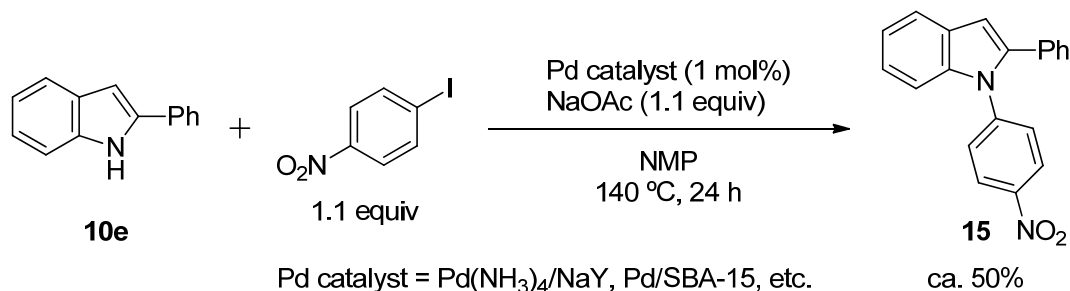


Entry	14	R ¹	R ²	R ³	X	Y	Z	Yield (%) (Ratio 13 : 11) ^a
1	14a	H	H	H	2	2.5	0	95 (100 : 0)
2	14a	H	H	H	2	2.5	1.5	92 (1 : 99)
3	14b	H	Me	H	2	2.5	0	69 (100 : 0)
4	14b	H	Me	H	4	2.5	1.5	77 (0 : 100)
5	14c	H	H	Me	2	2.5	0	70 (100 : 0)
6	14c	H	H	Me	4	2.5	1.5	75 (0 : 100)
7 ^b	14d	MeO	H	H	4	3	1	60 (0 : 100)

^a Obtained as a mixture after purification by column chromatography. Ratio in parentheses was determined by ¹H NMR. ^b The HCl salt of **14d** was used as a substrate. The reaction was carried out at 200 °C.

N-Arylindole derivatives are also expected to be potential bioactive compounds; e.g., sertindole has an antipsychotic activity.^{38b} Although the introduction of the aryl function to the N-1 position of the indole nucleus has been achieved by the aromatic amination of aryl halides using palladium catalysts,^{43,60,61} only a few heterogeneously catalyzed N-arylation reactions for indoles have been reported in the literature.

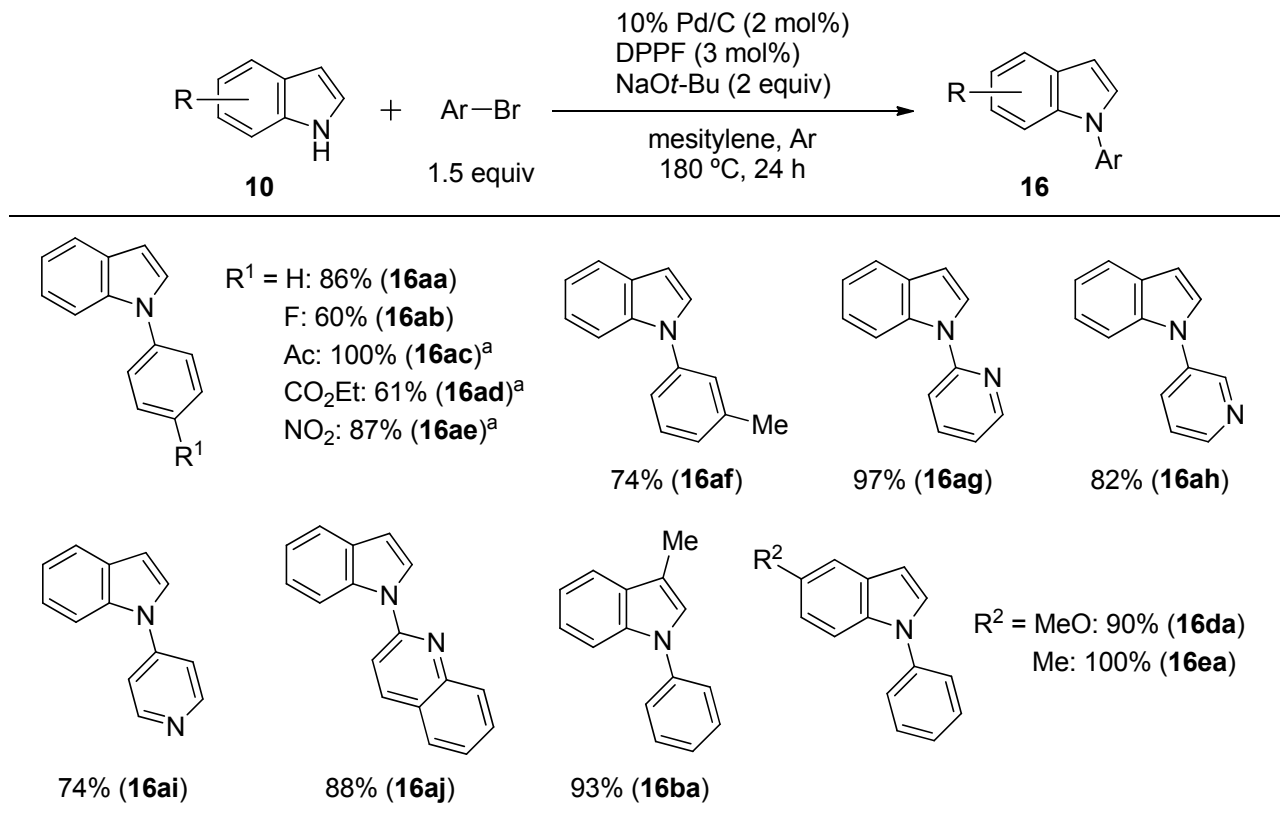
Djakovitch et al. achieved the heterogeneous palladium-catalyzed synthesis of *N*-arylated 2-phenylindole (**15**) by the cross-coupling between 2-phenylindole (**10e**) and 4-iodonitrobenzene (Scheme 16).⁴³



Scheme 16. Heterogeneous palladium-catalyzed *N*-arylation of indole derivative (**11e**)

Pd/C could catalyze the direct introduction of aryl groups into the *N*-1 position of the indole derivatives (**10**) under the conditions similar to those for the intramolecular aromatic amination of the 2-bromophenethylamines (**14**) (Table 8). *N*-Phenylindole and its derivatives (**16aa**, **16ab**, **16af**, **16ba**, **16da**, and **16ea**) were obtained in excellent yields from the *N*-1 free indole derivatives (**10a**, **10b**, **10d**, and **10e**) and aryl bromides. Although the alternative use of Cs₂CO₃ instead of NaOt-Bu was necessary

Table 8. 10% Pd/C-catalyzed intermolecular cross-coupling reaction of indoles (**10**) and bromoarenes

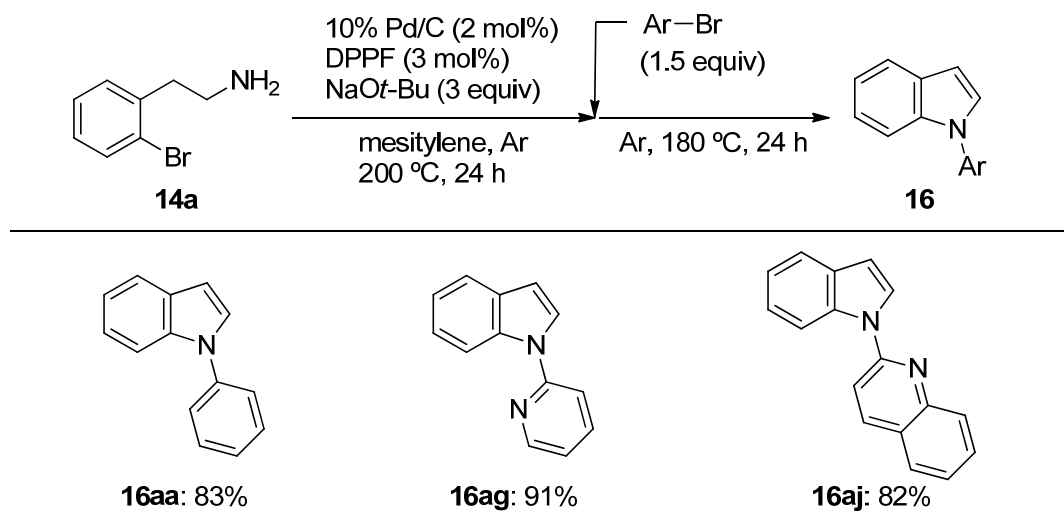


^a Cs₂CO₃ was used instead of NaOt-Bu. The reaction was carried out at 140 °C.

for the effective progress of the *N*-arylation of **10a** with bromobenzene derivatives bearing an electron-withdrawing group,^{6b} the corresponding *N*-arylindoles (**16ac**, **16ad**, and **16ae**) were generated in good yields. Bromopyridine derivatives as well as 2-bromoquinoline were also good substrates regardless of the substitution position of the bromine on the pyridine nucleus (**16ag**, **16ah**, and **16ai**).

A one-pot synthesis, which is a synthetic methodology for the multistep reaction conducted in one reaction vessel, is generally desired from the viewpoints of time-, effort-, cost-, and waste-reduction based on the avoidance of several purification and separation processes of the intermediates. The *N*-arylindoles (**16**) could be satisfactorily synthesized in a one-pot manner from 2-bromophenethylamine (**14a**) via the consecutive Pd/C-catalyzed intramolecular aromatic amination and aromatization at 200 °C, and subsequent *N*-arylation of the resulting indole with bromoarenes at 180 °C (Table 9).

Table 9. One-pot synthesis of *N*-arylindoles (**16**) from 2-bromophenethylamine (**14a**)

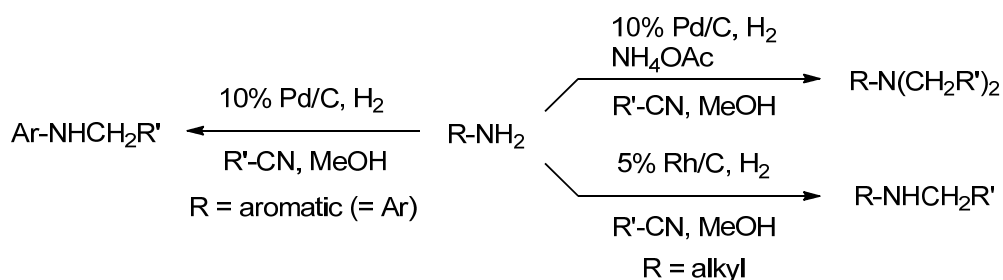


Both the indoline and indole derivatives could be temperature-dependently and distinctively synthesized from 2-bromophenethylamine under the Pd/C-catalyzed aromatic amination conditions. The pH control is an important factor for the Pd/C-catalyzed aromatization of indolines to indoles; the neutralization of the reaction media by the addition of acetic acid after the formation of indoline derivatives was effective for their aromatization to the corresponding indoles. Pd/C was found to be an effective heterogeneous catalyst for the intermolecular cross-coupling between the indole derivatives and bromoarenes to synthesis the *N*-arylated indoles.

In this section, both indole syntheses via the annulation and arene introduction to the N-1 position of indoles catalyzed by heterogeneous palladium catalysts were demonstrated. In the next section, the application of hydrogenation conditions using carbon-supported transition-metal catalysts to the synthesis of heterocyclic compounds is described.

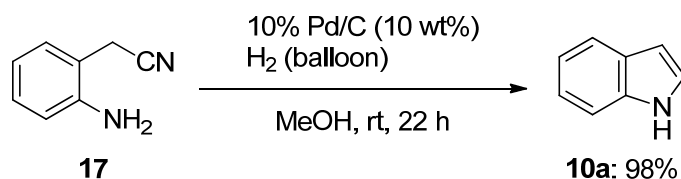
4. HYDROGENATION FOR THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

We recently reported that 10% Pd/C catalyzed either the dialkylation of primary alkylamines to the corresponding tertiary amines or monoalkylation to the corresponding secondary amines when using nitriles as the alkylating reagents under hydrogenation conditions. Furthermore, the use of 5% Rh/C instead of 10% Pd/C for the alkylation of primary alkylamines with nitriles leads to the selective synthesis of dialkylamines (Scheme 17).^{6a,6c}



Scheme 17. Hydrogenative alkylation of primary amines using nitriles for the selective synthesis of secondary and tertiary amines

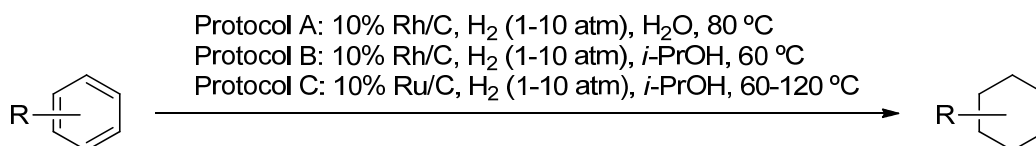
The nitrile-mediated *N*-monoalkylation of arylamines could be used for the intramolecular alkylation of 2-cyanomethylaniline (**17**). The reaction of **17** smoothly proceeded under Pd/C-catalyzed hydrogenation conditions at room temperature to quantitatively give the corresponding indole (**10a**) (Scheme 18).^{6a,6c} This method will be applied to the synthesis of various kinds of indole derivatives.



Scheme 18. 10% Pd/C-catalyzed intramolecular hydrogenative alkylation of primary amine

Arene hydrogenation is one of the most fascinating methods to access the saturated cyclic compounds bearing substituents because a variety of excellent methods for the introduction of substituents into aromatic rings rather than alicycles has been developed. However, arene hydrogenation typically requires harsh reaction conditions, such as a high hydrogen pressure and temperature, due to the resonance stabilization of arene nucleus.¹ We recently developed three protocols for the arene hydrogenation under relatively mild conditions (< 10 atm) using 10% Rh/C, H₂, in H₂O at 80 °C (protocol A), 10% Rh/C, H₂, in *i*-PrOH at 60 °C (protocol B), or 10% Ru/C, H₂, in *i*-PrOH at 60–120 °C (protocol C) (Scheme 19).^{9b}

Protocol A is most environmentally benign due to the use of water as the solvent, while protocol B was found to be the most efficient. Protocol C is an economically friendly procedure due to the use of the low-cost Ru/C. Therefore, these protocols could be appropriately selected taking into account the environmental burden, reactivity of substrates, and cost.



Scheme 19. 10% Rh/C- and 10% Ru/C-catalyzed arene hydrogenation under mild conditions

The protocols could be used for the hydrogenation of heteroarenes. Pyridine, pyrrole, and furan derivatives could undergo the hydrogenation under the mild 10% Rh/C- or 10% Ru/C-catalyzed hydrogenation conditions (protocol A–C) to afford the corresponding piperidine (**18** and **19**), pyrrolidine (**20**), and tetrahydrofuran (**21**) derivatives, respectively, in excellent yields (Figure 1).

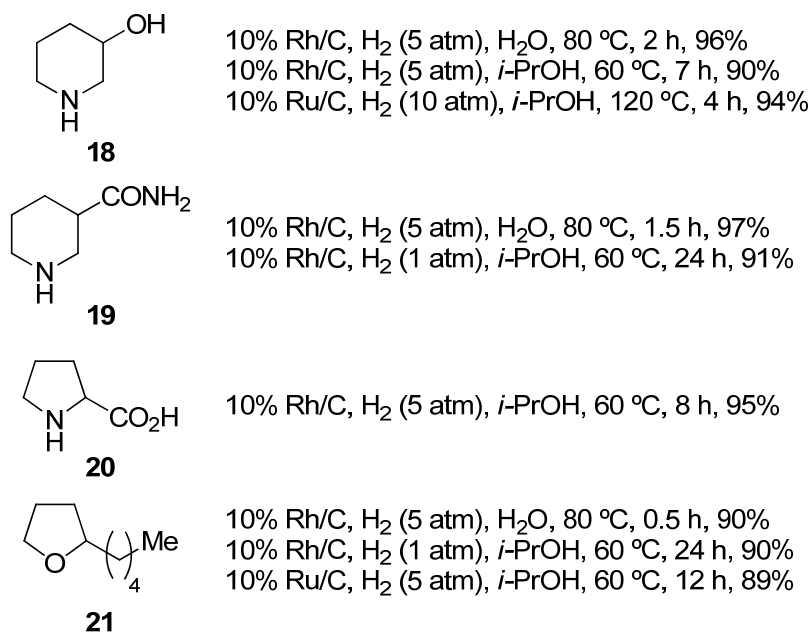


Figure 1. Synthesis of the saturated heterocyclic compounds (**18–21**) by arene hydrogenation

5. CONCLUSION

This review summarized the heterogeneously catalyzed syntheses of 1,4-disubstituted 1,2,3-triazoles by Huisgen cycloaddition and indoles by the Yamanaka–Larock annulation and intramolecular Buchwald–Hartwig aromatic amination. The copper catalysts embedded in an organic polymer could be used for the Huisgen cycloaddition due to the effective adsorption of organic substrates into the polymer

support based on its lipophilic nature; the solvent-free Huisgen cycloaddition proceeds using chelate resin-supported copper catalysts. The intra- and intermolecular annulations for the construction of indole nuclei are efficiently catalyzed by Pd/C. In the last part, the application of the activated carbon-supported transition-metal catalyzed hydrogenation conditions was introduced; 1) indole is synthesized by the 10% Pd/C-catalyzed intramolecular reductive alkylation of 2-cyanomethylaniline, 2) saturated heteroaromatic compounds, piperidine, pyrrolidine, and tetrahydrofuran derivatives, are obtained by the 10% Rh/C- or 10% Ru/C-catalyzed arene hydrogenation. The heterogeneous transition-metal catalysts would be more widely used for the synthesis of heterocyclic compounds due to their advantages, such as their good recovery, reuse, and decreased metal-contamination risk.

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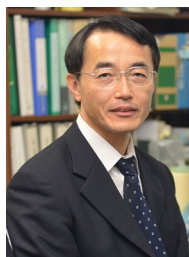
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