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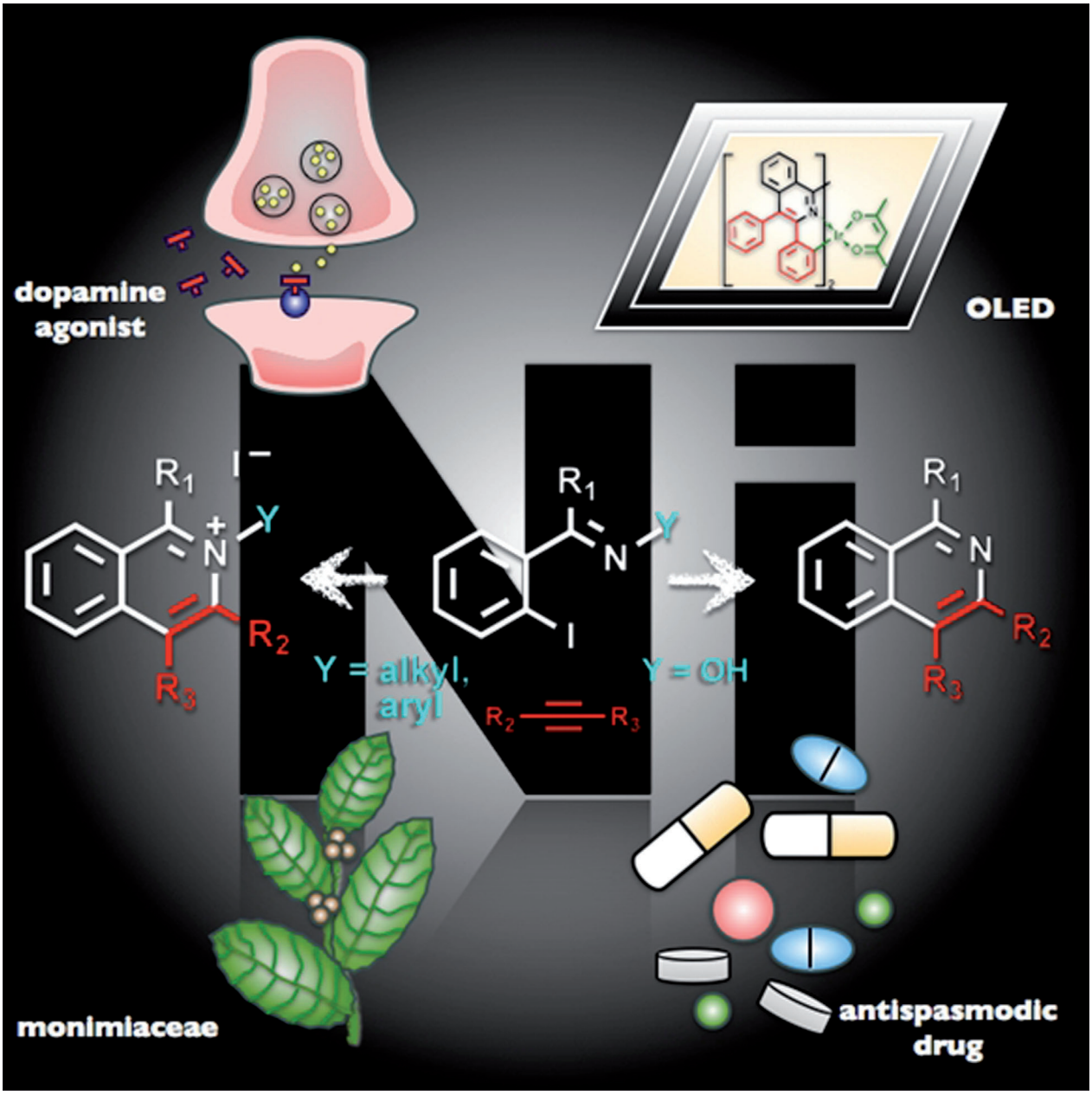
VIP

Nickel-Catalyzed Cyclization of *ortho*-Iodoketoximes and *ortho*-Iodoketimines with Alkynes: Synthesis of Highly Substituted Isoquinolines and Isoquinolinium Salts

Wei-Chun Shih, Chu-Chun Teng, Kanniyappan Parthasarathy, and Chien-Hong Cheng*[a]

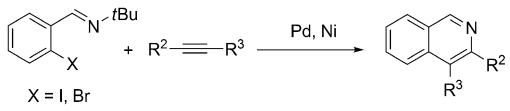


Abstract: A convenient method for the synthesis of highly substituted isoquinolines and isoquinolinium salts by the nickel-catalyzed cyclization of *ortho*-haloketoximes and -ketimines, respectively, with alkynes is described. The reaction of *ortho*-haloketoximes and various alkynes in the presence of [Ni-$(PPh_3)_2Br_2$] and zinc powder in a mixture of acetonitrile and tetrahydrofuran at 80 °C for 15 hours gave 1,3,4-trisubstituted isoquinoline products in moderate to excellent yields and high regioselectivity. The corresponding isoquinoline *N*-oxide was found to be the intermediate in the cyclization reaction pathway. In contrast, the reaction of *ortho*-haloketimines and alkynes under similar catalytic conditions in tetrahydrofuran at 70 °C for two hours gave 1,2,3,4-tetrasubstituted isoquinolinium salts in good to excellent yields.

Keywords: alkynes · cyclization · isoquinolines · ketimines · nickel

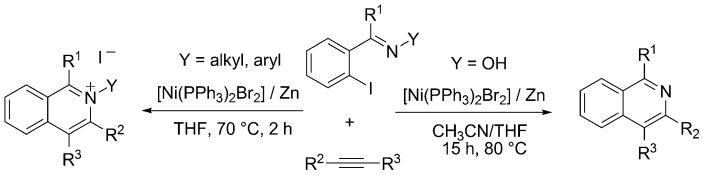
Introduction

Highly substituted isoquinolines and isoquinolinium salts are important classes of heterocycles. These types of skeletons are found in a wide range of naturally occurring compounds that show various biological activities, such as anti-HIV,[1,2] antimalarial,[3] ion-channel blocker,[4] and dopamine agonist.[5] Furthermore, these compounds are useful ligands in the synthesis of chiral compounds[6] and phosphorescent emitters for organic light-emitting diodes (OLEDs).[7] They are usually synthesized using the traditional Bischler–Napieralski, Pomeranz–Fritsch, and Pictet–Spengler reactions, which involve intramolecular cyclizations and require harsh conditions.[8] More recently, the synthesis of isoquinolines has gained much attention in metal-catalyzed organic synthesis.[9] Larock and co-workers developed a synthesis of isoquinolines that proceeds via the palladium-catalyzed annulation of *ortho*-haloaldemines with internal alkynes.[10] In 2006, we reported an efficient nickel-catalyzed synthesis of isoquinolines from alkynes and 2-iodobenzaldimines.[11] However, the above methods are only applicable for synthesizing 3,4-disubstituted isoquinoline derivatives (Scheme 1). To synthesize 1,3,4-trisubstituted isoquinolines by a similar method, we would need to prepare *N*-*tert*-butyl *ortho*-haloketimines. Unfortunately, we were unable to prepare any *N*-*tert*-butyl-*ortho*-haloketimines from *ortho*-bromoacetophenones or *ortho*-iodoacetophenones with *N*-*tert*-butylamine under various reaction conditions, probably owing to the steric hindrance of the *N*-*tert*-butyl group with substituents at the C1 and C3 positions. Therefore, the synthesis of 1,3,4-trisubstituted isoquinolines required a new method.



Scheme 1. Palladium- or nickel-catalyzed synthesis of 3,4-disubstituted isoquinolines.

Our continued efforts in nickel-catalyzed cyclization reactions and isoquinoline synthesis[11,12] prompted us to explore the reaction of *ortho*-halogenated ketoximes or ketimines with alkynes. Herein, we report the synthesis of 1,3,4-trisubstituted isoquinolines and 1,2,3,4-tetrasubstituted isoquinolinium salts by the nickel-catalyzed cyclization of *ortho*-iodoketoximes and -ketimines, respectively, with alkynes (Scheme 2).



Scheme 2. Nickel-catalyzed synthesis of isoquinolines and isoquinolinium salts from ketoximes and ketimines with alkynes.

Results and Discussion

The reaction of **1a** with diphenylacetylene (**2a**) in the presence of $[Ni(PPh_3)_2Br_2]$ and zinc powder in acetonitrile/tetrahydrofuran = 1:1 at 80 °C for 15 hours gave 1,3,4-trisubstituted isoquinoline **3a** in 87% yield (Table 1, entry 1). The structure of compound **3a** was confirmed by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. Substrate (*E*)-2-iodoacetophenone oxime was prepared from 2-iodoacetophenone and hydroxylamine hydrogen chloride in methanol, followed by recrystallization in dichloromethane and *n*-hexane.

To see the effect of solvent and catalyst on the formation of isoquinolines, various nickel complexes were investigated for the reaction of **1a** (0.20 mmol) with **2a** (0.40 mmol) in the presence of a nickel complex (3.0 mol%), and zinc powder (0.3 mmol) in acetonitrile/tetrahydrofuran (1:1, 2.0 mL) at 100 °C for 15 hours. First, we examined the catalytic activity of bidentate phosphine nickel(II) complexes $[Ni(dppm)Br_2]$, $[Ni(dppe)Br_2]$, $[Ni(dppp)Br_2]$, and $[Ni(dppb)Br_2]$, which provided the product **3a** in 30%, 32%, 40%, and 42% yield, respectively (dppm = 1,1-bis(diphenyl-

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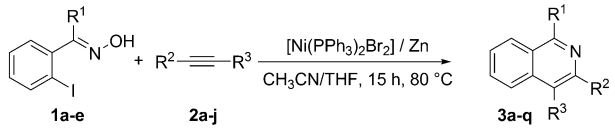
Supporting information for this article, including characterization data of the remaining compounds and copies of ^1H and ^{13}C NMR spectra of all compounds, is available on the WWW under http://dx.doi.org/10.1002/asia.201100834.

Table 1. The nickel-catalyzed synthesis of isoquinolines from ketoximes **1** and alkynes **2**.[a]



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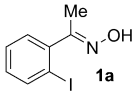
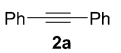
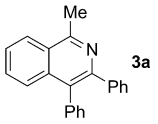
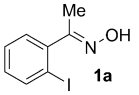
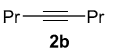
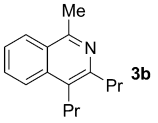
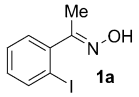
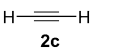
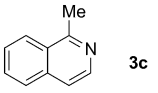
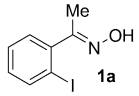
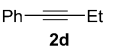
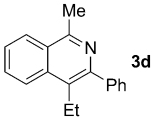
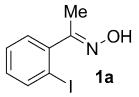
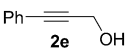
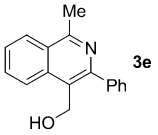
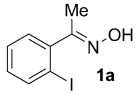
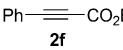
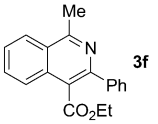
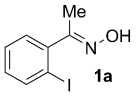
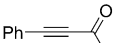
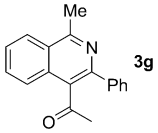
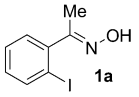
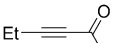
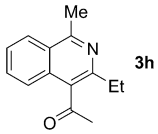
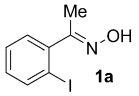
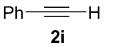
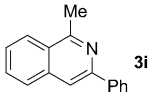
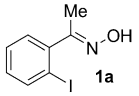
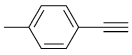
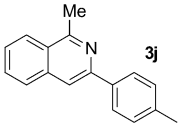
1				87
2				75
3				58
4				95[c]
5				83
6				99
7				84
8				67
9				88
10				80

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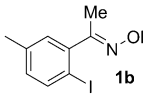
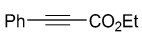
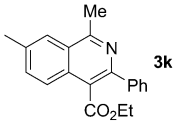
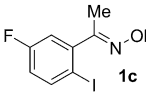
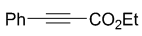
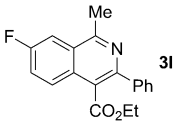
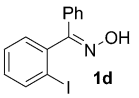
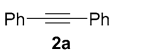
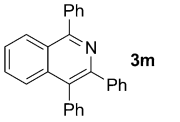
11				83
12				72
13				45[d]
	E-**1d**	**2a**	**3m**	82
14				35[d]
15				48[d]
16				64[d]
17				41[d]

[a] General conditions: ketoxime **1** (0.20 mmol), alkyne **2** (0.40 mmol), $[Ni(PPh_3)_2Br_2]$ (3.0 mol%), Zn powder (0.7 mmol), $CH_3CN/THF = 1:1$ (1.0 mL), 80 °C, 15 h. [b] Yield of isolated product. [c] PPh_3 (12 mol%) was added. [d] A mixture of *E*/*Z* isomers of substrates **1d**–**1g** were used and the reactions were performed for 24 h.

Abstract in Chinese:

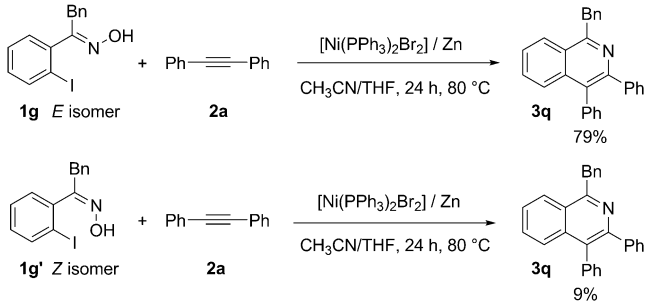
多取代異喹啉衍生物可以廣泛被應用在合成藥物、天然物以及有機發光二極體的材料上，如何以簡便的方式合成異喹啉衍生物是長久以來被關注的一件事情。本篇文章利用鎳金屬催化合環方法，以酮肟與酮亞胺化合物作為起始物，可以分別合成出具有不同官能基的異喹啉與異喹啉鹽類。

phosphino)methane, dppe = 1,2-bis(diphenylphosphino)-ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane). The nitrogen-containing nickel(II) complexes $[Ni(tmeda)Br_2]$, $[Ni(phen)Br_2]$, $[Ni(phen)Cl_2]$, and $[Ni(bpy)Cl_2]$, were completely inactive (tmeda = tetramethylethylenediamine, phen = phenanthroline, bpy = 2,2′-bipyridine). Monodentate-phosphine/nickel(II) complexes were then examined; $[Ni(PPh_3)_2Cl_2]$ gave compound **3a** in 42% yield, whilst $[Ni(PPh_3)_2(CO)_2]$ and $[Ni(PMePh_2)_2Br_2]$ afforded compound **3a** in 40% and 44% yield, respectively. Of the complexes examined, $[Ni(PPh_3)_2Br_2]$ was the most active, furnishing compound **3a** in 92% yield, as determined by integration of the crude NMR spectrum, and isolated in 87% yield (Table 1, entry 1). The solvent systems also played an important role in this reaction. The best solvent system using $[Ni(PPh_3)_2Br_2]$ as the catalyst was acetonitrile/tetrahydrofuran (1:1) in which compound **3a** was obtained in 87% yield. Toluene was also an

effective solvent, giving compound **3a** in 53% yield. Other solvent mixtures, such as acetonitrile with 1,2-dichloroethane, dimethyl sulfoxide, *N*,*N*-dimethyl formamide, and ethanol were less effective in the catalytic reaction (see the Supporting Information). Finally, $[Ni(PPh_3)_2Br_2]$ with zinc powder (0.7 mmol) in acetonitrile/tetrahydrofuran (1:1, 1.0 mL) at 80°C for 15 hours were found to be the most-suitable reaction conditions for the reaction of compounds **1a** and **2a**, thus forming product **3a** in 87% yield.

Under the optimized reaction conditions, various alkynes reacted smoothly with compound **1a** to give the corresponding substituted isoquinolines. Thus, symmetrical dialkyl alkyne **2b** and ethyne **2c** underwent cyclization with compound **1a** to give products **3b** and **3c** in 75% and 58% yield, respectively (Table 1, entries 2 and 3). The cyclization reaction also worked well with unsymmetrical alkynes. Accordingly, the reaction of ethyl phenyl acetylene **2d** with compound **1a** afforded the product **3d** in 95% yield with excellent regioselectivity (Table 1, entry 4). The regiochemistry of product **3d** was confirmed by NOESY experiments. Similarly, unsymmetrical alkynes such as 3-phenylpropargyl alcohol (**2e**), 3-phenylpropiolate (**2f**), 4-phenylbut-3-yn-2-one (**2g**), hex-3-yn-2-one (**2h**), phenylacetylene (**2i**), and 4-tolylacetylene (**2j**) reacted well with compound **1a** to afford substituted isoquinolines in good to excellent yields (Table 1, entries 5–10) and excellent regioselectivity. We have previously observed similar regioselectivities of the alkyne moieties in the products.[11] This nickel-catalyzed cyclization reaction was successfully extended to various substituted ketoximes **1b**–**1g**. It should be noted that ketoximes are easily prepared by the condensation of ketones with hydroxylamine hydrochloride. Thus, electron-donating 5-methyl-2-iodoacetophenone oxime (**1b**) and electron-withdrawing 5-fluoro-2-iodoacetophenone oxime (**1c**) reacted well with compound **2f** to afford the corresponding cyclized products **3k** and **3l** in 83% and 72% yield, respectively (Table 1, entries 11 and 12). Changing the methyl group in acetophenone oxime (**1a**) into other bulkier substituents had a dramatic effect on the yield of the reaction. Thus, 2-iodobenzophenone oxime (**1d**) and oxime **1e** reacted with compound **2a** to provide compounds **3m** and **3n** in only 45% and 35% yield, respectively (Table 1, entries 13 and 14). In a similar manner, (2-iodophenyl)pentanone oxime (**1f**) and 2-iodophenyl benzyl ketone oxime (**1g**) reacted with compounds **2a** and **2f** to give the corresponding isoquinolines **3o, 3p**, and **3q** in 48%, 64%, and 41% yields, respectively (Table 1, entries 15–17).

The above results indicate that oxime substrates **1d**–**1g** gave much-lower yields of the expected products (**3**) compared to those from 2-iodoacetophenone oxime derivatives **1a**–**1c**. We believe that the low product yields obtained from the reactions of oxime substrates **1d**–**1g** is due to the existence of *E*- and *Z* isomers, which are difficult to separate and which undergo very slow interconversion because of the presence of a relatively large substituent (R^1) at the C1 position of the substrates at the reaction temperature 80°C. It is expected that only the *E* isomer will react with the alkyne to give the corresponding isoquinoline, owing to the fact that the electron lone pair on the nitrogen atom should be in the *endo* position to form catalytic intermediate **A** and for the cyclization to proceed (see below). The *Z* isomer cannot react with an alkyne to give the cyclized product unless it undergoes isomerization into the *E* isomer. To clarify this concept, the *E*- and *Z* isomers of oxime **1g** were carefully separated and isolated. The *E*/*Z* ratio of compound **1g** based on the amount isolated was about 3:2. As expected, the *E* isomer of compound **1g** reacted well with compound **2a** in the presence of $[Ni(PPh_3)_2Br_2]$ and zinc powder in acetonitrile/tetrahydrofuran (1:1) at 80°C for 24 hours to give the isolated isoquinoline **3q** in 79% yield (Scheme 3). Under similar reaction conditions, the *Z* isomer of compound **1g** gave compound **3q** in only 9% yield

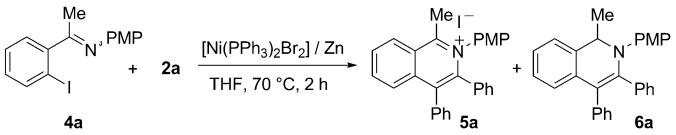


Scheme 3. The reactivity of the *E*- and *Z* forms of ketoxime **1g** with alkyne **2a**.

(Scheme 3). It is noteworthy that the use of oximes in related isoquinoline syntheses involving rhodium-catalyzed C–H activation and alkyne insertion[13] is also known.

This nickel-catalyzed cyclization reaction has been successfully extended to various ketimines, but the cyclization products observed are isoquinolinium salts and *N*-substituted-1,2-dihydroisoquinolines. For example, the reaction of ketimine (**4a**) with diphenylacetylene (**2a**) under similar reaction conditions gave isoquinolinium salt **5a** in 37% yield along with 1,2-dihydroisoquinoline **6a** in 43% yield (Table 2, entry 1). The latter is likely to have formed from the reduction of compound **5a** by zinc metal. A few reports have described the synthesis of isoquinolinium salts using the traditional coupling reaction of isoquinolines and alkyl halides and the stoichiometric metal-mediated addition reaction.[14] Until now, methods for the catalytic formation of isoquinolinium salts have been extremely limited. Very recently, we reported the synthesis of isoquinolinium salts using a nickel-catalyzed annulation of *ortho*-halobenzaldimines with alkynes.[15] In that report, we were unable to prepare isoquinolinium salts from the reaction of ketimines with alkynes. Our continued interest in the synthesis of various substituted isoquinolinium salts prompted us to search for optimal reaction conditions for the synthesis of isoquinoline salts from ketimines and alkynes. The amount of zinc used was found to be crucial for the formation of the ex-

Table 2. Effect of zinc on the formation of isoquinolinium salt **5a**.[a]



Entry	Zn [equiv]	Yield of **5a** [%][b]	Yield of **6a** [%][b]
1	2	37	43
2	1	80	12
3	0.5	97	0
4	0.2	77	0
5	0.1	41	0

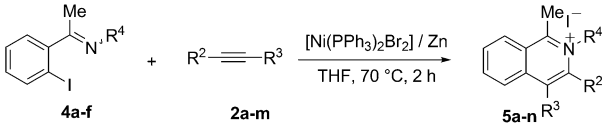
[a] General conditions: ketimine **4a** (0.20 mmol), diphenylacetylene **2a** (0.20 mmol), Zn powder (*x* equiv), $[Ni(PPh_3)_2Br_2]$ (5.0 mol%), THF (3.0 mL), 70°C, 2 h. [b] Yields were measured from integration of the ^1H NMR spectrum of the crude products using mesitylene as an internal standard.

pected isoquinoline salt. After examining different ratios of zinc dust in the reaction of substrate **4a** (see Table 2), we found that 0.5 equivalents of zinc powder in tetrahydrofuran at 70°C for 2 hours gave compound **5a** in 97% yield, as determined by integration of the NMR spectrum (Table 2, entry 3) and isolated in 92% yield (Table 3, entry 1).

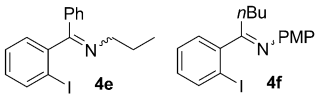
Under the above reaction conditions, various aliphatic alkynes reacted smoothly with compound **4a** to give the corresponding substituted isoquinolinium salts. Thus, oct-4-yne (**2b**) underwent cyclization with compound **4a** to give compound **5b** in 70% yield (Table 3, entry 2). Similarly, acetylene (**2c**) reacted well with compound **4a** to afford the corresponding salt product **5c** in 80% yield (Table 3, entry 3). To understand the regioselectivity of this reaction, unsymmetrical alkynes **2d, 2k**, and **2h** were investigated. 1-Phenyl-1-butyne (**2d**) and 3-hexyne-2-one (**2h**) reacted efficiently with compound **4a** to give two regioisomeric products in excellent yield and high regioselectivity (Table 3, entries 4 and 5). Interestingly, methyl propiolate **2k** gave a single regioisomer (**5f**) in 85% yield (Table 3, entry 6). Encouraged by the above results, various terminal alkynes were tested for this cyclization reaction. Under the standard catalytic conditions, phenylacetylene (**2i**) reacted successfully with compound **4a** to give the corresponding salt product (**5g**) in excellent yield and regioselectivity. Similarly, terminal alkynes **2l** and **2m** reacted smoothly with compound **4a** to afford mixtures of two regioisomers in good yields (Table 3, entries 8 and 9). It should be noted that this reaction appears to be the only method for the preparation of *N*-aryl-substituted isoquinolinium salts reported so far. This annulation reaction also worked well for the reaction of various ketimines with diphenylacetylene (**2a**) to give isoquinolinium salts in good to excellent yields (Table 3, entries 10–14).

Under similar reaction conditions, different regioselectivities were observed in the reaction of iodo-ketimines and bromo-ketimines with alkyne **2f**. Thus, ketimine **4a** reacted well with compound **2f** to give regioisomers **5o** and **5o′** (6:1) in 99% combined yield (Scheme 4). Interestingly, the

Table 3. Results of nickel-catalyzed synthesis of isoquinolinium salts from ketimines **4** with alkynes **2**.[a]



4a: R^4 = 4-$MeOC_6H_4$ (PMP)
4b: $R^4 = (CH_2)_3CH_3$
4c: R^4 = cyclohexyl
4d: $R^4 = (CH_2)_{2\text{-}3}$-$MeOC_6H_4$
2k: R^2 = Me, $R^3 = CO_2Et$
2l: R^2 = H, $R^3 = CO_2Et$
2m: R^2 = H, $R^3 = (CH_2)_2$-OH



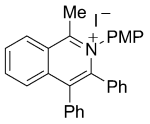
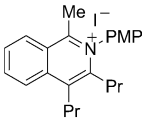
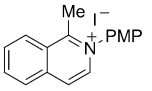
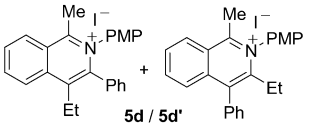
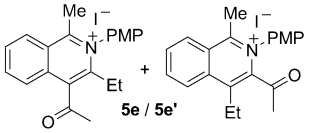
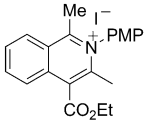
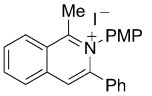
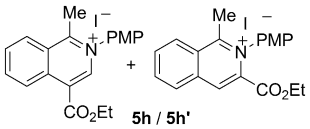
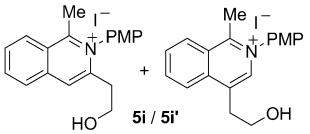
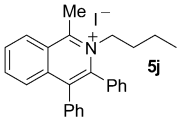
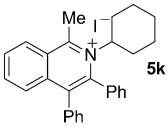
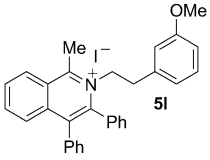
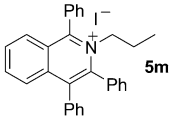
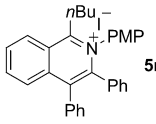
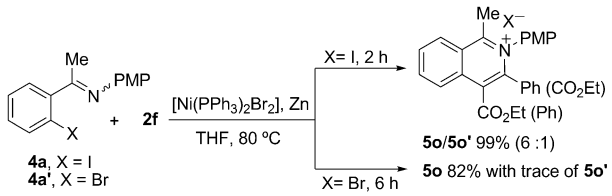
Entry	4	2	Product 5	Yield [%][b]
1	**4a**	**2a**	 **5a**	92[c]
2	**4a**	**2b**	 **5b**	70
3	**4a**	**2c**	 **5c**	80
4	**4a**	**2d**	 **5d / 5d'**	99 (8:1)
5	**4a**	**2h**	 **5e / 5e'**	99 (4:1)
6	**4a**	**2k**	 **5f**	85
7	**4a**	**2i**	 **5g**	94
8	**4a**	**2l**	 **5h / 5h'**	88 (1.5:1)
9	**4a**	**2m**	 **5i / 5i'**	80 (7.4:1)
10	**4b**	**2a**	 **5j**	95
11	**4c**	**2a**	 **5k**	87

Table 3. (Continued)

Entry	4	2	Product 5	Yield [%][b]
12	**4d**	**2a**	 **5l**	80
13	**4e**	**2a**	 **5m**	93
14	**4f**	**2a**	 **5n**	88

[a] General conditions: ketimine **4** (0.2 mmol), alkyne **2** (0.2 mmol), [Ni(PPh$_3$)$_2$Br$_2$] (5.0 mol%), Zn powder (0.10 mmol), THF (3.0 mL), 70°C, 2 h. [b] Yield of isolated product. [c] Reaction was carried out in CH$_3$CN/THF = 1:1 (3.0 mL).

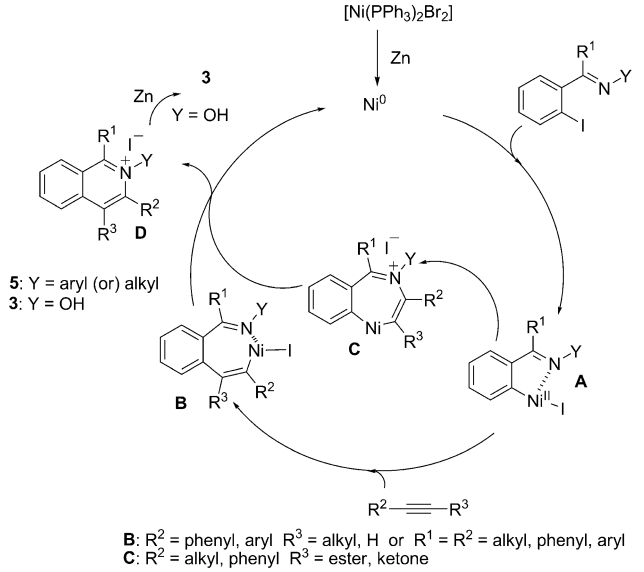


Scheme 4. The effect of iodo- and bromo-ketimines on the regioselectivity of product.

reaction of bromo-ketimine **4a′** with compound **2f** in the presence of [Ni(dppe)Br$_2$] and zinc powder in tetrahydrofuran at 80°C for 6 hours provided isoquinolinium salt **5o** in 82% yield with only a trace amount of **5o′** observed by ^{1}H NMR spectroscopy (Scheme 4). The observed different regiochemistry in the reactions of iodo-ketimines and bromo-ketimines with unsymmetrical alkyne **2f** to give different ratios of the products **5o** and **5o′** is interesting, but difficult to explain. The difference is likely related to the relative rate of insertion of the alkyne into the Ni–N or Ni–C bonds (intermediates **A**, **B**, and **C**, Scheme 5).

Proposed Mechanism

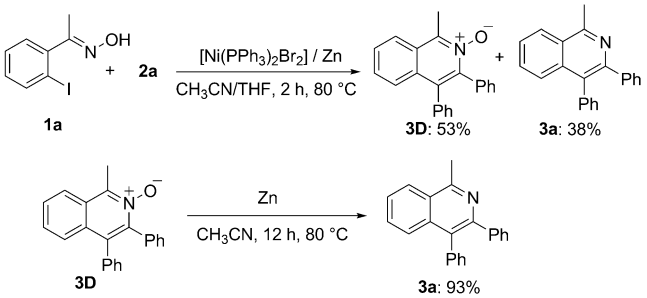
On the basis of known metal-catalyzed cyclization reactions,[9–11] a possible reaction mechanism is proposed to account for our nickel-catalyzed reaction (Scheme 5). The reaction likely starts with reduction of nickel(II) to nickel(0) with the aid of zinc powder. Oxidative addition of 2-iodoacetophenone oxime or 2-iodoketimine to nickel(0) leads to the formation of a five-membered nickelacycle **A**. Different coordinative insertions of the alkyne into the nickelacycle give intermediates **B** and **C**. This different coordinative insertion greatly depends on the nature of the alkyne.[10,14] Reductive elimination of intermediates **B** and **C** afforded the



Scheme 5. Possible mechanism for the nickel-catalyzed cyclization reaction.

isoquinoline-*N*-oxide or isoquinolinium salt and the regeneration of the nickel(0) catalyst for the next catalytic cycle. During the reaction, isoquinoline-*N*-oxide was reduced by the zinc powder to give the final product (**3**).

To support the proposed mechanism in Scheme 5, we tried to isolate the isoquinoline-*N*-oxide from (*E*)-2-iodoacetophenone oxime (**1a**) with diphenylacetylene (**2a**). Thus, the reaction of oxime (**1a**) with compound **2a** in the presence of [Ni(PPh$_3$)$_2$Br$_2$] and zinc powder in acetonitrile/tetrahydrofuran at 80°C for 2 hours gave isoquinoline-*N*-oxide **3D** in 53% yield along with isoquinoline **3a** in 38% yield (Scheme 6). It is surprising to note that we can isolate this



Scheme 6. Isolation of isoquinoline-*N*-oxide **3D** and its conversion into isoquinoline **3a**.

product that contains a relatively high energy and highly oxidizing *N*-oxide group in the presence of zinc metal. Furthermore, when compound **3D** was treated with zinc in acetonitrile at 80°C for 12 hours, the corresponding isoquinoline derivative **3a** was isolated in 93% yield (Scheme 6). The iso-

lation of compound **3D** and its conversion into product **3a** strongly supports the proposed mechanism in Scheme 5.

Conclusions

We have successfully developed a convenient and efficient method for the synthesis of highly substituted isoquinolines and isoquinolinium salts by the nickel-catalyzed annulation reaction of ketoximes and ketimines with various alkynes. Highly regioselective substituted isoquinolines were prepared in good to moderate yields. Further studies toward the synthesis of isoquinoline-*N*-oxide derivatives and applications of this methodology in natural product synthesis are in progress.

Experimental Section

*General procedure for the synthesis of isoquinolines **3***

A sealed tube (15 mL volume) initially fitted with a septum containing $[Ni(PPh_3)_2Br_2]$ (3.0 mol%), Zn (0.70 mmol), ketoxime **1** (0.20 mmol), and alkyne **2** (0.40 mmol) was evacuated and purged with N_2 three times. Freshly distilled CH_3CN (0.50 mL) and THF (0.50 mL) were added and the solution was stirred at 80°C for 15 h. The mixture was filtered through a Celite and silica-gel pad and the system was then washed with MeOH (50 mL). The combined filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexanes/EtOAc 9:1) to give the corresponding pure isoquinoline product.

*1-Methyl-3,4-diphenylisoquinoline (**3a**)*

White solid; m.p. 157–158°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.18 (m, 1H), 7.66–7.63 (m, 1H), 7.36–7.29 (m, 5H), 7.22–7.13 (m, 5H), 3.07 ppm (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 149.4, 140.9, 137.5, 135.9, 131.3, 130.2, 139.9, 129.1, 128.1, 127.5, 127.1, 126.9, 126.5, 126.2, 126.1, 125.5, 22.7 ppm; HRMS (EI$^+$): calcd for $C_{22}H_{17}N$: 295.1361; found: 295.1356. IR: $\tilde{\nu}$ = 3062, 1612, 1550, 1504, 1389 cm^{-1}.

*General procedure for the synthesis of isoquinolinium salts **5***

A sealed tube (15 mL volume) initially fitted with a septum containing $[Ni(PPh_3)_2Br_2]$ (5.0 mol%), Zn (0.1 mmol), ketimine **4** (0.20 mmol), and alkyne **2** (0.20 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled THF (3.0 mL) was added and the solution was stirred at 70°C for 2 h. The mixture was diluted with dichloromethane (ca. 15 mL), filtered through a Celite and silica-gel pad, and washed with MeOH (50 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (EtOAc/acetone 1:2) as eluent to give the corresponding pure isoquinoline salt.

*2-(4-Methoxyphenyl)-1-methyl-3,4-diphenylisoquinolinium iodide (**5a**)*

Yellow solid; m.p. 238.5°C; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 3.18 (s, 3H), 3.75 (s, 3H), 6.89 (d, J = 8.8 Hz, 2H), 7.02–7.03 (m, 3H), 7.18–7.20 (m, 2H), 7.28–7.32 (m, 5H), 7.48 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 8.05–8.08 (m, 2H), 8.73 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 1.55, 35.98, 95.72, 107.41, 107.57, 107.85, 108.51, 108.72, 109.04, 109.99, 110.85, 111.66, 111.77, 112.66, 113.15, 114.15, 117.15, 117.38, 118.16, 125.45, 140.53, 141.47 ppm; HRMS (FAB): calcd for $C_{29}H_{24}NO$: 402.1852; found: 402.1859; IR: $\tilde{\nu}$ = 1257, 1445, 1504, 1612, 2938, 2962 cm^{-1}.

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