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Iridium-Catalyzed [2 + 2 + 2] Cycloaddition of α,ω-Diynes with Nitriles

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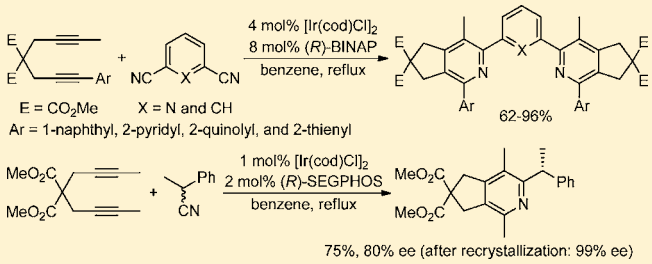
Supporting Information

ABSTRACT: $[Ir(cod)Cl]_2$/DPPF or BINAP efficiently catalyzed the cycloaddition of α,ω-diynes with nitriles to give pyridines. The reaction can accommodate a very wide range of nitriles. Both aliphatic and aromatic nitriles smoothly reacted with α,ω-diynes to give pyridines. Ten equivalents of unactivated aliphatic nitrile were enough to give the product in high yield. Aliphatic nitriles bearing an acetal or amino moiety could be used for the reaction. The highly regioselective cycloaddition of unsymmetrical diyne bearing two different internal alkyne moieties was achieved. The observed regioselectivity could be reasonably explained by considering the different reactivities of the α-position in iridacyclopentadiene. Regioselective cycloaddition was successfully applied to the synthesis of terpyridine and quinquepyridine. This chemistry was extended to a new and efficient synthesis of oligoheteroarenes. Five aromatic or heteroaromatic rings were connected in a single operation. $[Ir(cod)Cl]_2$/chiral diphosphine catalyst can be applied to enantioselective synthesis. Kinetic resolution of the racemic secondary benzyl nitrile catalyzed by $[Ir(cod)Cl]_2$/SEGPHOS gave a central carbon chiral pyridine in 80% ee. The mechanism was analyzed on the basis of the B3LYP level of density functional calculations.



INTRODUCTION

Heteroaromatic compounds play an important role in chemistry.[1] Moreover, heteroaromatic compounds are indispensable in recent far-reaching developments in material and biological science because they can be used as a substructure in functional materials, agrochemicals, and pharmaceuticals.[2] Traditionally, the synthesis of heteroaromatic compounds has been based on a condensation reaction that gives a byproduct as waste under strong acidic or basic conditions. A more environmentally benign synthesis of heteroaromatic compounds that does not give a waste byproduct under neutral conditions is needed. Transition metal catalysis continues to be a fruitful source of new methods for the synthesis of heteroaromatic compounds,[3] since transition metal catalysts can directly construct complex structures from easily accessible starting materials under neutral and mild reaction conditions. Among transition metal-catalyzed reactions, the cycloaddition of unsaturated molecules is one of the most straightforward and atom-economical reactions for constructing a substituted heteroaromatic ring.[4] Since Yamazaki and Wakatsuki pioneered the $CpCo(PPh_3)_2$-catalyzed reaction of alkynes with nitriles to give substituted pyridines,[5] much attention has been focused on the development of a Co-catalyzed cycloaddition to give pyridine.[6] Vollhardt developed $CpCo(CO)_2$-catalyzed partially intramolecular modes of the reaction using α,ω-diynes or cyanoalkynes as one component.[7] Recently, there have been extensive studies on the development of transition metal catalysts other than Co. Yamamoto and co-workers reported the RuCp*(cod)Cl-catalyzed cycloaddition of α,ω-diynes with activated nitriles such as electron-deficient nitriles and α-halonitriles.[8] Although the reaction conditions are mild, a major drawback of the RuCp*(cod)Cl-catalyzed reaction is the limited scope of nitriles. Simple nitriles such as acetonitrile and benzonitrile could not be used for the RuCp*(cod)Cl-catalyzed reaction. Saá and coworkers performed a mechanistic study in the same area.[9] With Cp or Cp* metal complexes, it can be difficult to control the reaction by tuning the steric and electronic effects of the Cp ligand, since the introduction of substituents to the Cp ligand requires considerable synthetic operations. A wide variety of electronically and sterically different phosphines are now commercially available. We can alter the catalytic activity both electronically and sterically by choosing a suitable phosphine ligand, which can lead to changes in product-, chemo-, regio-, and enantioselectivity. A metal phosphine complex-catalyzed pyridine synthesis is desired, since the reaction can be easily controlled by choosing the appropriate phosphine ligand. Rhodium catalyst has been reported to be a less-selective catalyst for pyridine synthesis due to the formation of an arene product by the cyclotrimerization of alkynes.[10] Tanaka reported

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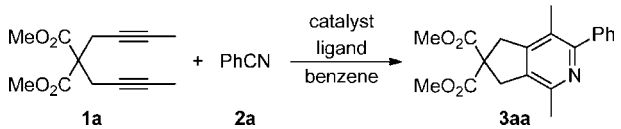
that $[Rh(cod)_2]BF_4$/BINAP was a more selective catalyst for pyridine synthesis.[11] In addition to these examples, the $Ni(cod)_2$-NHC catalyst has been reported by Louie.[12] These Rh and Ni catalysts require preactivation before diynes can be reacted with nitriles. In the case of Ni, air-sensitive $Ni(cod)_2$ and free NHC in dichloroethane must be stirred for at least 8 h before the reaction. In the case of Rh, COD ligand must be removed from the Rh center by hydrogenation before the reaction. Concentration of the solution after $[Rh(cod)_2]BF_4$ and phosphine ligand are stirred in CH_2Cl_2 under a hydrogen atmosphere gives catalytically active solution for use in pyridine synthesis. To expand the scope and selectivity, new catalysts that are suitable for a wide range of alkynes and nitriles including unactivated aliphatic nitriles are needed. Furthermore, a more convenient catalyst that does not require preactivation is desired. In the course of our study on the iridium-catalyzed carbon−carbon bond-forming reaction,[13] we first found that $[Ir(cod)Cl]_2$/DPPE is an efficient catalyst for the cycloaddition of alkynes to give arenes.[13d−f,i−k] Recently, we found that $[Ir(cod)Cl]_2$/BINAP is an efficient catalyst for the reaction of α,ω-diynes with isocyanates to give 2-pyridone.[13o] We have shown that Ir/diphosphine catalyst is a powerful tool in cycloaddition chemistry. To date, Ir-catalyzed pyridine synthesis has not yet been reported. In this paper, we report the full details of the iridium complex-catalyzed cycloaddition of α,ω-diynes with nitriles. We extend this chemistry to the synthesis of oligoheteroarenes. One of the advantages of the Ir catalyst described here is that even the reaction with unactivated aliphatic nitriles gives the corresponding pyridine in good to high yield. Another advantage is that the experimental procedure is more convenient than in the case of Rh or Ni. In particular, preactivation of the catalyst is not needed.

SCREENING OF THE CATALYST

2,7-Nonadiyne **1a** reacted with 3 equiv of benzonitrile (**2a**) to give a pentasubstituted pyridine derivative **3aa** in the presence of 2 mol % of $[Ir(cod)Cl]_2$ and 4 mol % of diphosphine ligand (P/Ir = 2). The catalytic activity depended on the ligand used. The results are summarized in Table 1. DPPF was found to be the most efficient ligand (entry 9). The reaction was completed in 3 h under refluxing benzene to give **3aa** in 91% yield. The catalyst loading could be reduced to 0.25 mol % without reducing the yield at 2 mol % (entry 18). Even a catalyst loading as low as 0.1 mol % gave **3aa** in 70% yield (entry 19). For most cyclotrimerization catalysts, more than 3 mol % of catalyst is needed for pyridine synthesis. These results show that the iridium complex has greater catalytic activity than any other transition metal complexes reported so far. $[Ir(cod)Cl]_2$ without any ligand did not give **3aa** (entry 1). PPh_3 was not effective (entry 2). We previously reported that DPPE was an efficient ligand for the cycloaddition of 1,6-diynes with monoynes to give indane derivatives. However, DPPE was far less efficient than DPPF for pyridine synthesis (entry 3). DPPE, DPPP, and DPPB were all inferior to DPPF (entries 3−5). DPPPentane was not effective at all (entry 6). DPPBenzene (1,2-bis(diphenylphosphino)benzene), which has a more rigid carbon framework than DPPE, gave the product in 2% yield (entry 7). The reaction with FDPPE as a ligand gave **3aa** in lower yield than in the reaction with DPPF (entry 8). (*R*)-BINAP was the second-best ligand. The reaction gave **3aa** in 84% yield (entry 10). BIPHEP was less effective than (*R*)-BINAP (entry 11). The use of Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) as a ligand inhibited the reaction (entry 12). The optimal reaction temperature was 50−80 °C. The reaction at 50 °C gave **3aa** in 89% yield (entry 14). The reaction at room temperature gave **3aa** in 12% yield and a substantial amount of the starting material was recovered (entry 15).

Table 1. Reaction of 1,6-Diyne (1a) with Benzonitrile 2a[a]



1a 2a 3aa

entry	catalyst (mol %)	ligand (mol %)	temperature	time (h)	yield (%)[b]
1	$[Ir(cod)Cl]_2$ (2)	none	reflux	24	0
2	$[Ir(cod)Cl]_2$ (2)	PPh_3 (8)	reflux	24	0
3	$[Ir(cod)Cl]_2$ (2)	DPPE (4)	reflux	2	6
4	$[Ir(cod)Cl]_2$ (2)	DPPP (4)	reflux	3	66
5	$[Ir(cod)Cl]_2$ (2)	DPPB (4)	reflux	3	73
6	$[Ir(cod)Cl]_2$ (2)	DPPPentane (4)	reflux	24	0
7	$[Ir(cod)Cl]_2$ (2)	DPPBenzene (4)	reflux	3	2
8	$[Ir(cod)Cl]_2$ (2)	FDPPE[c] (4)	reflux	24	78
9	$[Ir(cod)Cl]_2$ (2)	DPPF (4)	reflux	3	91
10	$[Ir(cod)Cl]_2$ (2)	(*R*)-BINAP (4)	reflux	2	84
11	$[Ir(cod)Cl]_2$ (2)	BIPHEP (4)	reflux	2	75
12	$[Ir(cod)Cl]_2$ (2)	Xantphos (4)	reflux	24	0
13	$[Ir(cod)_2]SbF_6$ (4)	DPPF (4)	reflux	24	0
14	$[Ir(cod)Cl]_2$ (2)	DPPF (4)	50 °C	2	89
15	$[Ir(cod)Cl]_2$ (2)	DPPF (4)	rt	24	12
16	$[Ir(cod)Cl]_2$ (1)	DPPF (2)	reflux	3	91
17	$[Ir(cod)Cl]_2$ (0.5)	DPPF (1)	reflux	3	89
18[d]	$[Ir(cod)Cl]_2$ (0.25)	DPPF (0.5)	reflux	3	90
19[e]	$[Ir(cod)Cl]_2$ (0.1)	DPPF (0.2)	reflux	24	70

[a]A mixture of **1a** (1 mmol), **2a** (3 mmol), $[Ir(cod)Cl]_2$ (2 mol %), ligand (4 mol %), and benzene (5 mL) was stirred under Ar. [b]Isolated yield. [c]FDPPE is $(C_6F_5)_2PCH_2CH_2P(C_6F_5)_2$. [d]A mixture of **1a** (1.5 mmol), **2a** (4.5 mmol), $[Ir(cod)Cl]_2$ (0.25 mol %), DPPF (0.5 mol %), and benzene (7.5 mL) was stirred under Ar. [e]A mixture of **1a** (2 mmol), **2a** (6 mmol), $[Ir(cod)Cl]_2$ (0.1 mol %), DPPF (0.2 mol %), and benzene (10 mL) was stirred under Ar.

REACTION OF 1a WITH VARIOUS AROMATIC NITRILES 2

Diyne **1a** reacted with various aromatic nitriles **2b−n** to give pyridine derivatives **3ab−an** under the reaction conditions optimized above. The results are summarized in Table 2. Diyne **1a** reacted with *p*-bromobenzonitrile (**2d**) and *p*-nitrobenzonitrile (**2e**) to give **3ad** and **3ae** in excellent yields, while the reactions with *o*-methylbenzonitrile (**2b**) and *p*-formylbenzonitrile (**2c**) gave **3ab** and **3ac** in moderate to good yields (entries 1−4). The reactions with *p*- and *m*-acetylbenzonitrile (**2f** and **2g**) gave pyridine derivatives **3af** and **3ag** in respective yields of 94% and 95%, but the reaction with *o*-acetylbenzonitrile (**2h**) gave no product (entries 5−7). *p*-(*p*-Tolyl)benzonitrile (**2i**) and 1-naphthonitrile (**2j**) reacted smoothly with **1a** to give the products **3ai** and **3aj** in good yields (entries 8 and 9). The reaction with 2-thiophenecarbonitrile (**2k**) gave **3ak** in 34% yield (entry 10). We next studied the cycloaddition of diyne **1a** with phenyl dicyanides **2*l*−n** to give 1:1 products and 2:1 products.

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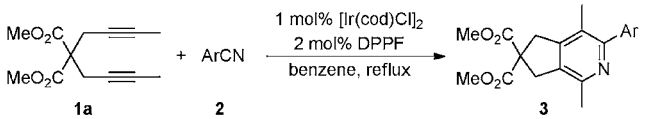
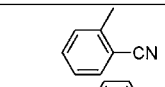
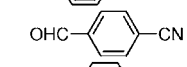
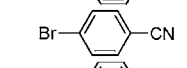
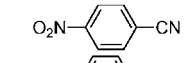
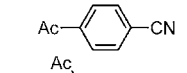
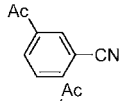
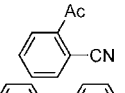
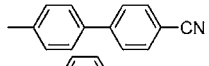
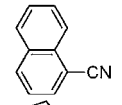
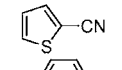
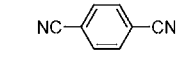
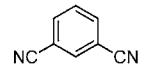
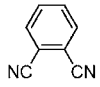
Table 2. Reaction of 1,6-Diyne (1a) with Various Aromatic Nitriles 2[a]

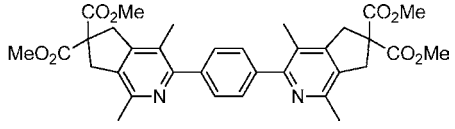


1a 2 3

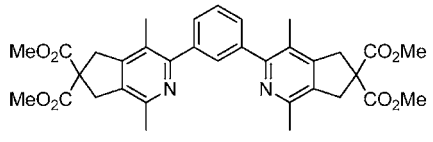
entry	2		1a/2	product	time (h)	yield (%)[b]
1		**2b**	1/3	**3ab**	2	56
2		**2c**	1/3	**3ac**	24	73
3		**2d**	1/3	**3ad**	2	>99
4		**2e**	1/3	**3ae**	2	>99
5		**2f**	1/3	**3af**	2	94
6		**2g**	1/3	**3ag**	2	95
7		**2h**	1/3	**3ah**	24	0
8		**2i**	1/3	**3ai**	2	92
9		**2j**	1/3	**3aj**	3	71
10		**2k**	1/3	**3ak**	24	34
11		**2l**	1/3	**3al**	2	>99
12[c]		**2l**	4/1	**4al**	3	95
13		**2m**	1/3	**3am**	2	80
14[c]		**2m**	4/1	**4am**	3	98
15		**2n**	1/3	**3an**	2	99
16[c]		**2n**	4/1	**3an**	3	92

[a]A mixture of **1a** (1 mmol), **2** (3 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar. [b]Isolated yield. [c]A mixture of **1** (2 mmol), **2** (0.5 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar.

4al:



4am:



The molar ratio of **1a** to **2** controlled the selectivity of 1:1 addition and 2:1 addition. The reactions of 1 mmol of **1a** with 3 mmol of *p*-, *m*-, and *o*-dicyanobenzene (**2*l*–n**) gave 1:1 products **3a*l***, **3am**, and **3an** in 80–99% yields (entries 11, 13, and 15). When an excess amount of dicyanide to diyne **1a** was used, only one of the two cyano groups participated in cyclization to give a product substituted with an intact cyano group. On the other hand, the reactions of 2 mmol of **1a** with 0.5 mmol of **2*l*** and **2m** gave only the 2:1 products in excellent yield (entries 12 and 14). When an excess amount of diyne to dicyanide was used, both of the cyano groups participated in cycloaddition to give a product with two pyridine rings. Aromatic nitrile **2n** was an exceptional case. The reaction of **2n** with 4 equiv of **1a** gave 1:1 product **3an** in 92% yield (entry 16). Only one of the two cyano groups participated in the cycloaddition even in the presence of an excess amount of **1a**. The steric hindrance by the cyano group at the ortho-position of **2n** would inhibit the second cycloaddition.

REACTION OF 1a WITH VARIOUS ALIPHATIC NITRILES 5

Several examples of pyridine synthesis with aliphatic nitriles have been reported. With the Cp*Ru(cod)Cl-catalyzed cycloaddition of diynes with nitriles, a major drawback is that applicable nitriles are limited to activated nitriles in which a cyano group or halogen is connected to a carbon–nitrogen triple bond by one or two methylene units.[8] The presence of another cyano group or halogen atom is essential for the Ru-catalyzed reaction, since they act as a coordinating group to the Ru center to induce cycloaddition.[8a,9] With $[Rh(cod)_2]BF_4$/BINAP-catalyzed cycloaddition, acetonitrile, the most common aliphatic nitrile, has been reported to participate in cycloaddition to give the product in 63% yield.[11b] However, acetonitrile was used as a solvent in the Rh-catalyzed reaction. To enhance the synthetic value of the reaction, the scope of suitable unactivated aliphatic nitriles has to be explored. In addition, the amount of unactivated nitrile required to give the product in high yield should be reduced. Encouraged by the good results with aromatic nitriles, we next examined the reaction with aliphatic nitriles. A wide range of unactivated aliphatic nitriles could be used for our cycloaddition. Ten equivalents of nitrile was enough to give the product in good yield. The results are summarized in Table 3. The reaction with 10 equiv of acetonitrile (**5a**) gave **6aa** in 75% yield (entry 2). Similarly, diyne **1a** smoothly reacted with *n*-butyronitrile (**5b**) to give **6ab** in 68% yield (entry 4). Especially noteworthy is that the reaction with 3 equiv of acetonitrile (**5a**) for 2 h gave the product in 64% yield (entry 1). Longer alkyl nitriles such as *n*-hexanenitrile (**5c**) and *n*-heptanenitrile (**5d**) underwent cycloaddition to give **6ac** and **6ad** in 67% and 71% yields, respectively (entries 5 and 6). The reactions with 10 equiv of benzyl cyanide (**5e**) and 3-phenylpropionitrile (**5f**) gave products **6ae** and **6af** in 90% and 84% yields, respectively (entries 8 and 10). Comparison of the product yields suggested that **5e** and **5f** were more reactive toward cycloaddition than **5a–d**. The reaction with **5g** bearing an acetal moiety gave **6ag** in 79% yield (entry 11). The acetal group remained intact during cycloaddition. While the use of aminonitrile in cycloaddition for pyridine synthesis has not been reported, our catalytic reaction can use aminonitrile. *α*-Aminonitrile (**5h**), *β*-aminonitrile (**5i–k**) and *γ*-aminonitrile (**5*l***) underwent cycloaddition to give products **6ah–a*l*** in 77–90% yields (entries 12–16). A pyrrolidine moiety, piperidine moiety, and morpholine moiety could be introduced at the side chain of the pyridine ring. When diyne **1a** was reacted with 3 equiv of aliphatic dicyanide (**5m**), only one of the two cyano groups participated in cycloaddition to give product **6am** bearing a single intact cyano group in 92% yield (entry 17). Secondary nitriles reacted with diyne **1a**. The reaction with isobutyronitrile (**5n**) gave product **6an** in 60% yield (entry 19). The reaction with cyclohexanecarbonitrile (**5o**) gave a product in a yield comparable to that in the reaction with

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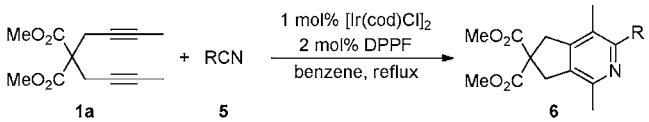
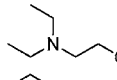
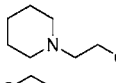
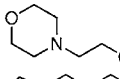
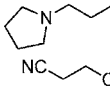
Table 3. Reaction of 1,6-Diyne (1a) with Various Aliphatic Nitriles 5[a]



1a 5 6

entry	5	equiv of 5	product	time (h)	yield (%)[b]
1	MeCN (**5a**)	3	**6aa**	2	64
2	MeCN (**5a**)	10	**6aa**	2	75
3	^{n}PrCN (**5b**)	3	**6ab**	2	56
4	^{n}PrCN (**5b**)	10	**6ab**	2	68
5	$CH_3(CH_2)_4CN$ (**5c**)	10	**6ac**	3	67
6	$CH_3(CH_2)_5CN$ (**5d**)	10	**6ad**	2	71
7	Ph(CH2)CN (**5e**)	3	**6ae**	1	82
8	Ph(CH2)CN (**5e**)	10	**6ae**	1	90
9	Ph(CH2)2CN (**5f**)	3	**6af**	2	71
10	Ph(CH2)2CN (**5f**)	10	**6af**	2	84
11	(MeO)2CH(CH2)2CN (**5g**)	10	**6ag**	1	79
12	 (**5h**)	3	**6ah**	1	86
13	 (**5i**)	10	**6ai**	1	79
14	 (**5j**)	10	**6aj**	1	79
15	 (**5k**)	10	**6ak**	1	90
16	 (**5l**)	10	**6al**	1	77
17	NC(CH2)CN (**5m**)	3	**6am**	2	92
18	^{i}PrCN (**5n**)	3	**6an**	2	47
19	^{i}PrCN (**5n**)	10	**6an**	2	60
20	 (**5o**)	10	**6ao**	1	54
21	 (**5p**)	10	**6ap**	1	73
22	 (**5q**)	3	**6aq**	2	88
23	^{t}BuCN (**5r**)	10	**6ar**	2	0
24	EtO_2CCN (**5s**)	3	**6as**	2	>99
25	(**5t**)	3	**6at**	24	11
26	ClCH2CN (**5u**)	10	**6au**	24	0
27	NC(CH2)CN (**5v**)	3	**6av**	24	0

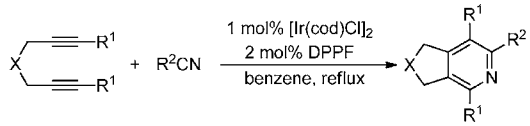
[a]A mixture of **1a** (1 mmol), **5**, $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar. [b]Isolated yield.

isobutyronitrile (**5n**) (entry 20). The reaction with 3-cyclohexene-1-carbonitrile (**5p**) gave a product in higher yield than that with cyclohexanecarbonitrile (**5o**) (entry 21). The reaction with cyclopropanecarbonitrile (**5q**) gave cyclopropyl-substituted pyridine **6aq** in 88% yield (entry 22). Cleavage of the cyclopropyl ring did not occur during the reaction. The reaction with pivalonitrile (**5r**) gave no product due to steric hindrance (entry 23). Activated aliphatic nitrile was also a good substrate for the reaction. Diyne **1a** reacted smoothly with ethyl cyanoformate (**5s**) to give **6as** in quantitative yield (entry 24). The reaction with acrylonitrile (**5t**) gave **6at** in 11% yield (entry 25). When chloroacetonitrile (**5u**) and malononitrile (**5v**) were used, no corresponding product was obtained (entries 26 and 27).

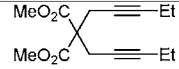
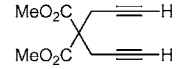
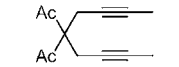
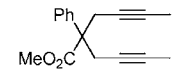
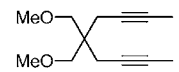
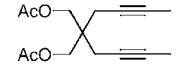
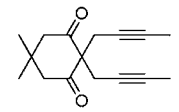
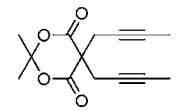
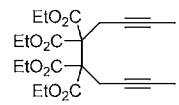
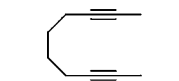
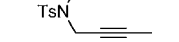
REACTIONS OF VARIOUS DIYNES 1 WITH NITRILES 2 AND 5

Various diynes (**1b**–*l*) were subjected to cycloaddition with nitriles. Three equivlents of benzonitrile (**2a**) or 10 equiv of acetonitrile (**5a**) was used as a nitrile component. The results are summarized in Table 4. Et-substituted diyne **1b** reacted with benzonitrile (**2a**) and acetonitrile (**5a**) to give the corresponding products **3ba** and **6ba** in respective yields of 71% and 21% (entries 1 and 2). The reaction of terminal diyne **1c** with **2a** gave dimers and trimers of **1c** instead of pyridine

Table 4. Reaction of Various 1,6-Diynes (1) with Nitriles 2 or 5[a]



1 2 or 5 3 or 6

entry	1		2 or 5		3 or 6	time (h)	yield (%)[b]
1		**1b**	PhCN	**2a**	**3ba**	2	71
2[c]		**1b**	MeCN	**5a**	**6ba**	2	21
3[d]		**1c**	PhCN	**2a**	**3ca**	2	0
4		**1d**	PhCN	**2a**	**3da**	1	82
5[c]		**1d**	MeCN	**5a**	**6da**	3	63
6		**1e**	PhCN	**2a**	**3ea**	1	85
7[e]		**1e**	PhCN	**2a**	**3ea**	2	86
8[c]		**1e**	MeCN	**5a**	**6ea**	3	79
9		**1f**	PhCN	**2a**	**3fa**	3	83
10[c]		**1f**	MeCN	**5a**	**6fa**	4	77
11[d]		**1g**	PhCN	**2a**	**3ga**	2	86
12[c,d]		**1g**	MeCN	**5a**	**6ga**	24	89
13		**1h**	PhCN	**2a**	**3ha**	1	77
14[c]		**1h**	MeCN	**5a**	**6ha**	3	75
15		**1i**	PhCN	**2a**	**3ia**	1	50
16[c]		**1i**	MeCN	**5a**	**6ia**	2	34
17		**1j**	PhCN	**2a**	**3ja**	1	95
18[c]		**1j**	MeCN	**5a**	**6ja**	24	70
19		**1k**	PhCN	**2a**	**3ka**	24	0
20		**1l**	PhCN	**2a**	**3la**	2	11

[a]A mixture of **1** (1 mmol), **2a** (3 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar. [b]Isolated yield. [c]10 mmol of **5a** was used instead of **2a**. [d]2 mol % of $[Ir(cod)Cl]_2$ and 4 mol % of DPPF were used. [e](*R*)-BINAP was used instead of DPPF. Product **3ea** was obtained in 7% ee. Enantiomeric excess was determined by HPLC.

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3ca (entry 3). Cycloaddition with a terminal alkyne moiety was preferred over cycloaddition with nitrile **2a**. The substituent at the 5-position in 2,7-nonadiyne affected the reaction, indicating that a Thorpe−Ingold effect was important for the cyclization.[14] Diketone **1d** reacted with **2a** and **5a** to give **3da** and **6da** in respective yields of 82% and 63% (entries 4 and 5). The reaction of **1a** gave higher product yields than those with **1d**. Diyne substituted with a phenyl group at the 5-position of 2,7-nonadiyne reacted with **2a** and **5a** to give **3ea** and **6ea** in respective yields of 85% and 79% (entries 6 and 8). These yields were comparable to those with **1a**. When (*R*)-BINAP was used as a ligand, **3ea** was obtained in 86% yield with 7% ee (entry 7). A substituent other than a carbonyl group was also effective for the cycloaddition. Methoxymethyl-substituted diyne (**1f**) reacted with **2a** and **5a** to give **3fa** and **6fa** in respective yields of 83% and 77% (entries 9 and 10). Similarly, acetoxymethyl-substituted diyne **1g** smoothly underwent cycloaddition (entries 11 and 12). Diyne **1h** bearing a methone moiety reacted with **2a** and **5a** to give **3ha** and **6ha** in respective yields of 77% and 75% (entries 13 and 14). Diyne **1i** bearing Meldrum's acid was a less efficient substrate than **1h** (entries 15 and 16). As mentioned above, the $[Ir(cod)Cl]_2$/DPPF catalyst system is efficient for the formation of bicyclic pyridines with a five-membered ring from both 2,7-nonadiyne derivatives (**1a** and **1d**−**i**) and 3,8-undecadiyne **1b**. We next examined the possibility of the formation of a six-membered ring from 2,8-decadiyne **1j**. The reaction of **1j** with **2a** and **5a** gave 5,6,7,8-tetrahydroisoquinoline derivatives **3ja** and **6ja** in respective yields of 95% and 70% (entries 17 and 18). Thus, the $[Ir(cod)Cl]_2$/DPPF catalyst system is effective for the formation of both five- and six-membered bicyclic pyridines. The reaction of 2,8-decadiyne (**1k**) with **2a** gave no product (entry 19). Tosylamide-tethered diyne **1*l*** reacted with **2a** to give **3*l*a** in 11% yield (entry 20).

REGIOSELECTIVE CYCLOADDITION OF UNSYMMETRICAL DIYNE WITH NITRILES

The reaction of unsymmetrical diyne with nitrile can give two regioisomeric pyridines. With an unsymmetrical diyne possessing a terminal alkyne moiety and internal alkyne moiety, the regioselectivity of the Ru-catalyzed reaction was studied in detail.[8] The reaction of malonate-derived diyne possessing a terminal alkyne moiety and methyl-substituted internal alkyne moiety with cyanoformate **5s** has been reported to give 2,3,4,6- and 2,3,4,5-substituted pyridines in a ratio of 88:12.[8b] Unsymmetrical diyne bearing two internal alkyne moieties is a more challenging substrate for regioselective pyridine synthesis. The reaction of such unsymmetrical diynes was limited.[8b,11b] We examined two types of unsymmetrical diyne: diyne with a sterically different substituent and diyne with an electronically different substituent. The results are summarized in Table 5. The structure of the products was determined on the basis of 2D-NMR analysis (see the Supporting Information, S115−S126 and S203−S266). We first examined the reaction of malonate-derived diynes possessing two different internal alkyne moieties. Ph-substituted diyne **1m** underwent cycloaddition with **5a** and **5e** to give **6ma** and **6me** in 94% yield as a single product in which the phenyl group was substituted at the α-position (entries 1 and 2). The reaction of **1m** with **5s** gave an 88:12 mixture of **6ms** and **6′ms** in 95% yield, favoring pyridine substituted with a Ph group at the α-position (entry 3). Naphthyl-substituted diyne **1n** reacted smoothly with **2a** to give **3na** in 96% yield (entry 4). The regioselectivity of the reaction of **1n** with **2a** was the same as that of the reaction of **1m** with **5a** and **5e**. The reactions of Me_3Si-substituted diyne **1o** with **5a** and **5e** gave the product in moderate yields, while the reaction with **5s** gave the product in 93% yield (entries 5, 6, and 7). The reactions were completely regioselective and gave a product in which the trimethylsilyl group was substituted at the β-position. The regioselectivity of the reaction of **1o** was opposite those of **1m** and **1n**. The reaction of **1p** bearing terminal alkyne moiety and iternal alkyne moiety with **2a** gave no corresponding product (entry 8). We next examined the reaction of ester tethered-diyne **1q** in which an ester group is conjugated with one of the two internal alkyne moieties. In contrast to the reaction of **1m**−**o**, the slow addition of **1q** to a reaction mixture containing a catalyst and nitrile over 2 h was needed to give the product in high yield. Self-dimerization and -trimerization of **1q** competed with pyridine ring formation. The reactions of ester tethered-diyne **1q** with **2a**, **5a**, and **5e** gave **3qa**, **6qa**, and **6qe** in 74−62% yields as a single product in which a carbonyl group was substituted at the β-position (entries 9−11). The reaction of **1q** with **5s** gave **6qs** in 56% yield without the slow addition of **1q** (entry 12). Ester tethered-diyne **1r** in which a phenyl group and carbonyl group are conjugated with the same alkyne moieties was also a good substrate for regioselective pyridine synthesis. Ester tethered-diyne **1r** reacted with **2a**, **5a**, **5e**, and **5s** to give the respective products in 72−91% yields (entries 13−16). The regioselectivity of the reaction of **1r** was the same as that of **1q**. Slow addition of ester diyne **1r** to the reaction mixture was needed for the reactions with **2a**, **5a**, and **5e**. Ester tethered-diyne **1s** bearing one alkyne moiety conjugated with a carbonyl group and another alkyne moiety conjugated with a Ph group. Although the reaction of ester tethered-diyne **1s** gave the product in low yields, the reaction was regioselective and gave a single product favoring a pyridine substituted with a carbonyl group at the β-position (entries 17−20). Our iridium catalyst system is the most regioselective of any other transition metal catalyst for cycloaddition to give pyridine.

REGIOCHEMICAL AND MECHANISTIC CONSIDERATIONS

The regioselectivity observed here should be explained based on mechanistic considerations. A plausible mechanism is as follows (Scheme 1). Diyne oxidatively adds to the iridium active species to give iridacyclopentadiene.[15] Nitrile reacts with iridacyclopentadiene to give pyridine. The regioselectivity observed here can be explained by considering the different reactivities of the α-carbon in iridacyclopentadiene formed by the oxidative cyclization of diyne. Two different substituents on terminal alkyne carbons lead to the different reactivities of the α-carbons in iridacyclopentadiene. When the steric effect is predominant, the less-hindered α-carbon preferentially reacts with a nitrile carbon atom. When the electronic effect is predominant, the more electron-rich α-carbon preferentially reacts with a nitrile carbon atom. These two effects determine the regioselectivity (Scheme 2). A methyl group is electron-donating, while phenyl and naphthyl groups are electron-withdrawing.[16] When diyne **1m** and **1n** were used, the methyl-substituted α-carbon in intermediates **7m** and **7n** is more electron-rich than the phenyl- or naphthyl-substituted α-carbon to react preferentially with a nitrile carbon to give **6ma**, **6me**, **6ms**, and **3na**. Phenyl and 1-naphthyl groups are more bulky than a methyl group. The less-hindered α-position in iridacyclopentadiene **7m** and **7n** preferentially reacts with the

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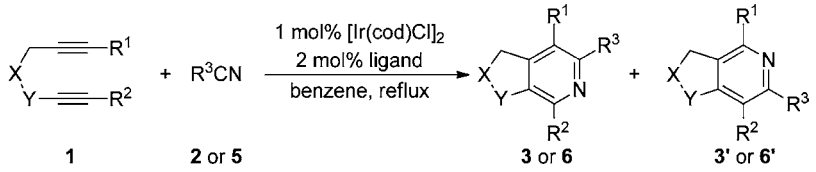
Table 5. Reaction of Unsymmetrical Diynes (1) with Nitriles 2 or 5[a]



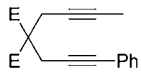
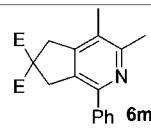
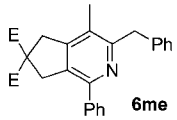
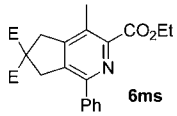
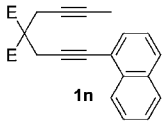
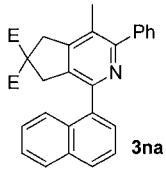
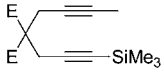
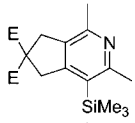
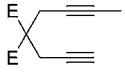
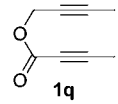
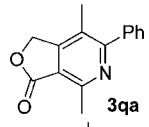
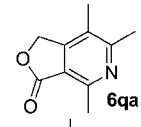
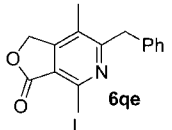
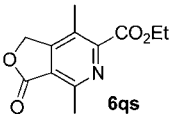
entry	1	2 or 5	ligand	major product[b]	time (h) addition[c]	time (h) stirring	yield (%)[d]	3/3' or 6/6'[e]
1	 1m	5a	(*R*)-BINAP	 6ma	–	1	94	>99/1
2	1m	5e	(*R*)-BINAP	 6me	–	1	94	>99/1
3[f]	1m	5s	(*R*)-BINAP	 6ms	–	4	95	88/12
4[g]	 1n	2a	(*R*)-BINAP	 3na	–	8	96	>99/1
5	 1o	5a	(*R*)-BINAP	 6'oa	–	24	49	1/>99
6	1o	5e	DPPF	 6'oe	–	4	59	1/>99
7[f]	1o	5s	DPPF	 6'os	–	2	93	1/>99
8	 1p	2a	(*R*)-BINAP	–	–	2	0	–
9[h]	 1q	2a	(*R*)-BINAP	 3qa	2	2	73	>99/1
10[h]	1q	5a	(*R*)-BINAP	 6qa	2	2	62	>99/1
11[h]	1q	5e	(*R*)-BINAP	 6qe	2	2	74	>99/1
12[h,i]	1q	5s	BIPHEP	 6qs	–	4	56	>99/1

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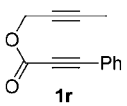
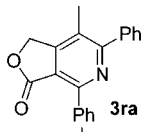
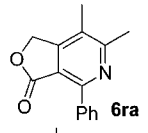
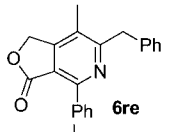
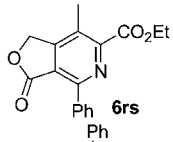
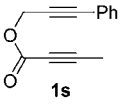
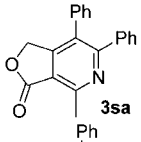
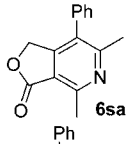
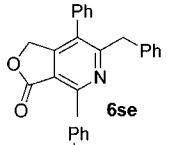
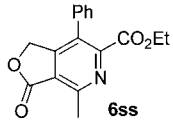
Table 5. continued

entry	1	2 or 5	ligand	major product[b]	time (h) addition[c]	time (h) stirring	yield (%)[d]	3/3' or 6/6'[e]
13[h]	 1r	2a	(*R*)-BINAP	 3ra	2	2	91	>99/1
14[h]	1r	5a	(*R*)-BINAP	 6ra	2	2	74	>99/1
15[h]	1r	5e	(*R*)-BINAP	 6re	2	2	83	>99/1
16[h,i]	1r	5s	BIPHEP	 6rs	–	1	72	>99/1
17[h]	 1s	2a	(*R*)-BINAP	 3sa	4	20	23	>99/1
18[h]	1s	5a	(*R*)-BINAP	 6sa	4	20	13	>99/1
19[h]	1s	5e	(*R*)-BINAP	 6se	4	20	38	>99/1
20[h,i]	1s	5s	(*R*)-BINAP	 6ss	–	1	35	>99/1

[a]A mixture of **1** (1 mmol), **2a** (3 mmol) or **5** (10 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), ligand (0.02 mmol), and benzene (5 mL) was stirred under Ar. [b]The structure of product except for **3na** was determined by 2D NMR (see Supporting Information S115−S126 and S203−S266). [c]Addition time of diyne **1** in the case of using a syringe pump. [d]Isolated yield. [e]Determined by ^{1}H NMR. [f]3 mmol of **5s** was used. [g]The structure of **3na** was determined by X-ray analysis (Figure 1). [h]2 mol % of $[Ir(cod)Cl]_2$ and 4 mol % of ligand were used. [i]2 mmol of **5s** was used.

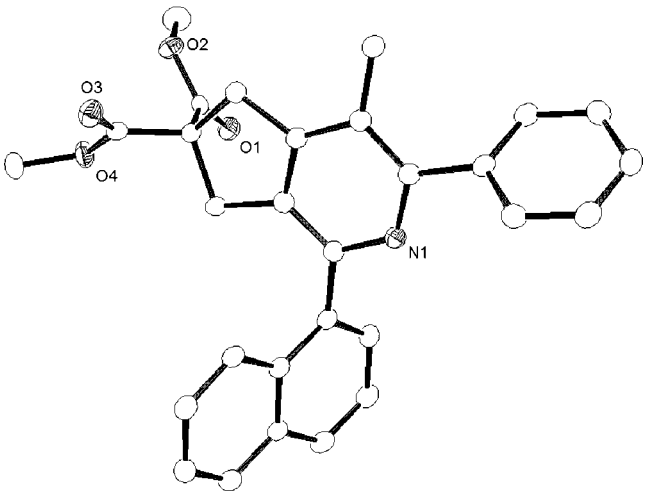


Figure 1. ORTEP drawing of **3na**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

nitrile carbon. The regioselectivity given by an electronic effect is the same as that given by a steric effect in the case of **1m** and **1n**. A trimethylsilyl group is more electron-donating than a methyl group.[16] With diyne **1o**, the trimethylsilyl-substituted α-carbon in intermediate **7o** is more electron-rich than the methyl-substituted α-carbon to react preferentially with the nitrile carbon atom to give **6′oa**, **6′oe**, and **6′os**. A trimethylsilyl group is more bulky than a methyl group. If steric effect is predominant, the methyl-substituted α-carbon in intermediate **7o** should react with the nitrile carbon to give **6oa**, **6oe**, and **6os**. The regioselectivity given by the electronic effect is opposite to that given by the steric effect. The results in the reaction of **1o** showed that the electronic effect was predominant over the steric effect to determine the regioselectivity. Ester-tethered diyne **1q** is a good substrate for evaluating the electronic effect of an internal carbonyl group on regioselectivity, since, with regard to steric considerations, diyne **1q** possesses the same alkyne terminus. The steric hindrance at each α-carbon in iridacyclopentadiene **7q** is the same in this

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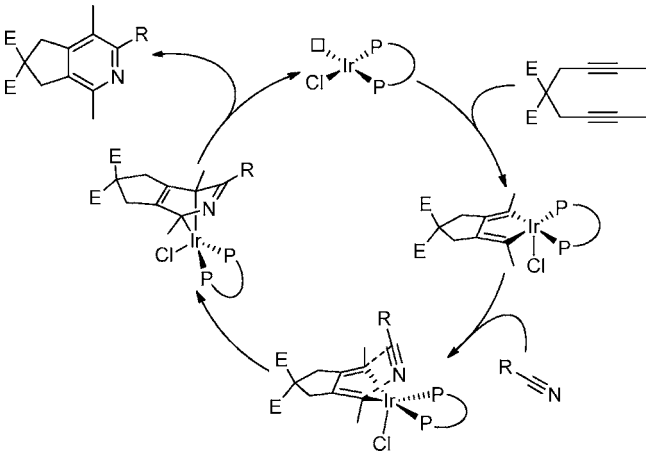
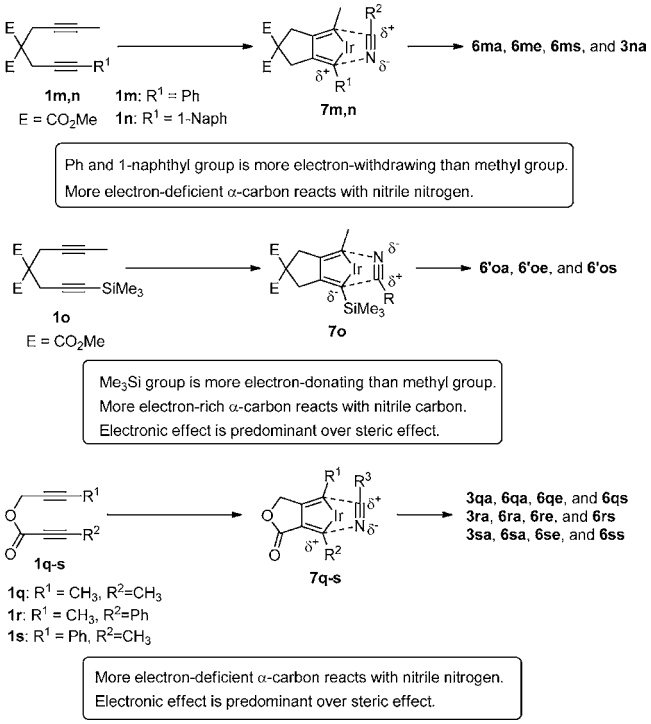
Scheme 1



Scheme 2



case. Consequently, the electronic effect plays a decisive role in determining the regioselectivity. With iridacyclopentadiene **7q**, an α-carbon conjugated with an internal carbonyl group is more electron-deficient than an α-carbon that is not conjugated with a carbonyl group. The nitrile nitrogen atom reacts at the more electron-deficient α-carbon to give **3qa**, **6qa**, **6qe**, and **6qs**. With ester diyne **1r**, an ester group and phenyl group were substituted on the same alkyne. The electron-withdrawing properties of these groups influence the same α-carbon. Phenyl-substituted α-carbon conjugated with an internal carbonyl group in intermediate **7r** preferentially reacts with a nitrile nitrogen atom to give **3ra**, **6ra**, **6re**, and **6rs**. With regard to the steric effect, the less-hindered methyl-substituted α-carbon reacted with the nitrile carbon atom to give the same product directed by the electronic effect. In the case of **1r**, the regioselectivity given by the electronic effect is the same as that given by the steric effect. On the other hand, in the case of ester-tethered diyne **1s**, the regioselectivity given by the electronic effect is opposite to that given by the steric effect. The methyl-substituted α-carbon should react with the nitrile carbon atom when the steric effect is predominant over the electronic effect. Since an ester group is more electron-withdrawing than a phenyl group, the phenyl-substituted α-carbon should react with the nitrile carbon atom when the electronic effect is predominant over the steric effect. The results of the reaction of **1s** showed that the electronic effect was predominant over the steric effect, and an internal ester group played a decisive role in determining the regioselectivity. In all cases, the regioselectivity was directed by the electronic effect.

THE REACTION OF DIYNE WITH HETEROAROMATIC NITRILES

On the basis of these results, we studied the reactions of diynes with heteroaromatic nitriles. The reaction with cyanopyridine is expected to give bipyridines.[17] The bipyridine framework is important for the synthesis of biologically active compounds such as pharmaceuticals and agrochemicals.[18] In particular, 2,2′-bipyridine compounds are of great importance as ligands that can attach to various metal atoms.[19] An atom-economical synthesis of bipyridines is needed. Cyanopyridines were good substrates for the cycloaddition. The results are summarized in Table 6. Cyanopyridines **2o**−**q** reacted with **1a** to give bipyridines **3ao**−**3aq** in yields of 88−99% (entries 1−3). Cyanopyridine **2r**, which is more hindered than **2o**, gave **3ar** in 94% yield (entry 4). A more electron-deficient heteroaromatic ring than pyridine decreased the yield. The reaction with 2-cyanopyrazine (**2s**) gave product **3as** in 60% yield (entry 5). 2-Cyanoquinoline (**2t**) gave **3at** in 98% yield (entry 6). As with diyne **1a**, Et-substituted diyne **1b** reacted with **2o** to give **3bo** in 70% yield (entry 7). Regioselective cycloaddition to give terpyridine was possible. Diyne **1t** bearing a 2-pyridyl terminus reacted with 2-cyanopyridine (**2o**) to give 2,2′:6′,2″-terpyridine **3to** as a single product in 93% yield (entry 9). The structure of **3to** was determined by X-ray analysis (Figure 2). (*R*)-BINAP was more efficient than DPPF for the reaction of **1t** with **2o** (entries 8 and 9). We developed another version of terpyridine synthesis. The reaction of dicyanobenzene with an excess amount of diyne **1a** gave benzene substituted with two pyridine rings (Table 2, entries 12 and 14). These results prompted us to study the reaction of 2,5-dicyanopyridine (**2u**) with an excess amount of diyne. The reaction of 4 equiv of **1a** with **2u** gave 2,2′:6′,2″-terpyridine **8au** in 85% yield (entry 10). Similarly, diynes **1b** and **1d** reacted with **2u** to give the corresponding terpyridines **8bu** and **8du** in nearly quantitative yields (entries 11 and 12). Six-membered ring formation was possible in terpyridine synthesis. The reaction of 2,8-decadiyne **1j** with **2u** gave terpyridine **8ju** with two six-membered rings in quantitative yield (entry 13). Our iridium catalyst could be successfully applied to the synthesis of bipyridines and terpyridines.

SYNTHESIS OF OLIGOHETEROARENES

Oligoarenes and oligoheteroarenes are useful molecules in various research areas that involve functional molecules, self-assembling molecules, and biologically active compounds.[20] One of the most reliable methods for the construction of these structures is the transition metal-catalyzed cross-coupling reaction.[21] Suginome reported a masking strategy in the Suzuki−Miyaura coupling as a new route to oligoarenes with a defined structure.[22a] However, a cross-coupling methodology

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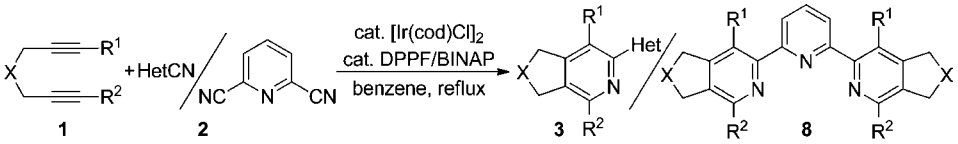
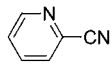
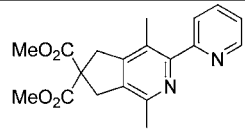
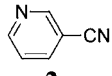
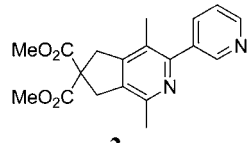
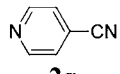
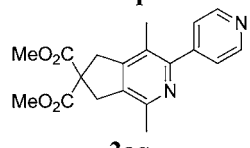
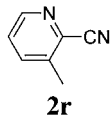
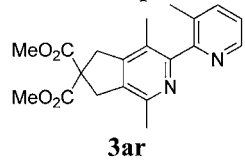
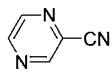
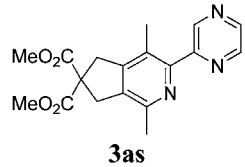
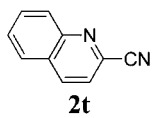
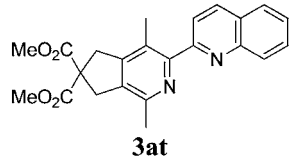
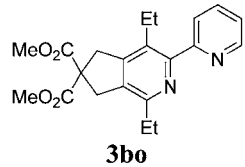
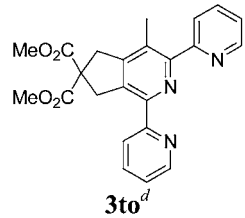
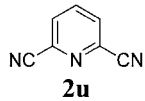
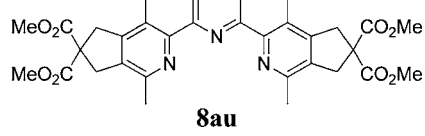
Table 6. Reaction of Diynes (1) with Heteroaromatic Nitriles 2[a]



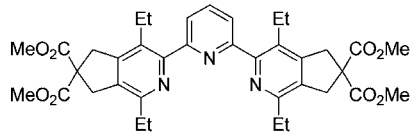
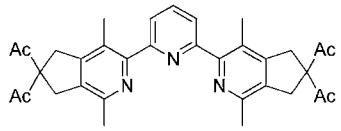
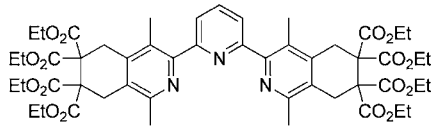
1 2

Het = heteroaryl

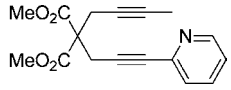
entry	1	2	product	time (h)	yield (%)[b]
1	**1a**	 **2o**	 **3ao**	2	>99
2[c]	**1a**	 **2p**	 **3ap**	5	88
3[c]	**1a**	 **2q**	 **3aq**	3	91
4	**1a**	 **2r**	 **3ar**	2	94
5	**1a**	 **2s**	 **3as**	24	60
6	**1a**	 **2t**	 **3at**	2	98
7	**1b**	**2o**	 **3bo**	6	70
8	**1t**	**2o**	 **3to**[d]	24	18
9[e]	**1t**	**2o**	**3to**[d]	4	93
10[f]	**1a**	 **2u**	 **8au**	3	85

dx.doi.org/10.1021/ja3028394 | J. Am. Chem. Soc. 2012, 134, 10515−10531

Table 6. continued

11[f]	**1b**	**2u**	 **8bu**	7	99
12[f]	**1d**	**2u**	 **8du**	3	97
13[f]	**1j**	**2u**	 **8ju**	3	>99

[a]A mixture of **1** (1 mmol), **2** (3 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar. [b]Isolated yield. [c]2 mol % of $[Ir(cod)Cl]_2$ and 4 mol % of DPPF were used. [d]With complete regioselectivity. [e](*R*)-BINAP was used as a ligand. [f]A mixture of **1** (2 mmol), **2** (0.5 mmol), $[Ir(cod)Cl]_2$ (0.01 mmol), DPPF (0.02 mmol), and benzene (5 mL) was stirred under Ar.

1t: 

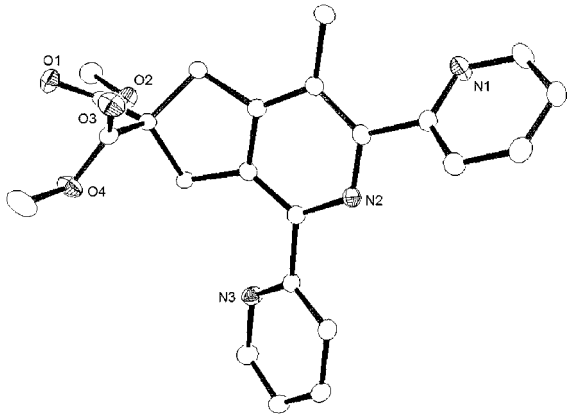


Figure 2. ORTEP drawing of **3to**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

for the synthesis of oligoarenes and oligoheteroarenes is a tedious multistep synthesis. Moreover, the installation of a metal group into heteroaromatic compounds is often difficult because of problems with the stability of the resulting heteroaromatic metal reagent.[23] For example, 2-pyridyl boronic acid and its esters are easily decomposed by proton.[23] In addition to the stability problem, the transmetalation of an electron-deficient heteroaromatic boron reagent to palladium is relatively slow.[24] There are still problems to overcome in the cross coupling of heteroaromatic compounds. A more efficient and convenient route to oligoarenes and oligoheteroarenes with a defined structure is needed. We extended the regioselective cycloaddition of unsymmetrical diyne bearing a heteroaromatic terminus with 2,5-dicyanopyridine or 1,3-dicyanobenzene to give a new synthetic route to oligoheteroarenes. An advantage of this methodology is that construction and connection of the ring can be performed in a single operation. We attempted to construct oligoheteroarenes in one step by our Ir-catalyzed regioselective cycloaddition. In the synthesis of the starting diynes, various aromatic or heteroaromatic rings can be introduced to the diyne terminus by Sonogashira coupling. Diynes **1n** and **1t**−**v** were prepared in high yields. As described in Table 2, the use of 4 equiv of diyne was needed to cyclize both of the cyano groups. The results are summarized in Scheme 3. Unsymmetrical diyne **1n** bearing a naphthyl terminus reacted with **2u** to give terpyridine **8nu** bearing two naphthyl rings in 96% yield with the use of (*R*)-BINAP as a ligand. The reaction was completely regioselective and gave a single product. This result prompted us to attempt the synthesis of 2,2′:6′,2″:6″,2‴:6‴,2⁗-quinquepyridine. As expected, the reaction of diyne **1t** bearing a 2-pyridyl terminus with **2u** gave quinquepyridine **8tu** in 86% yield with complete regioselectivity. We introduced a 2-quinolyl group and 2-thienyl group to the diyne terminus to extend the scope of this methodology. Diyne **1u** bearing a 2-quinolyl terminus reacted with **2m** and **2u** to give **8um** and **8uu** in respective yields of 86% and 84%. Similarly, diyne **1v** bearing a 2-thienyl terminus reacted with **2m** and **2u** to give **8vm** and **8vu** in respective yields of 79% and 62%. The structure of **8nu**·CH_2Cl_2, **8tu**, and **8vm** was determined by X-ray analysis (Figures 3, 4, and 5, respectively). The structure of **8um**, **8uu**, and **8vu** was determined on the basis of 2D-NMR analysis (see the Supporting Information, S281−S288 and S291−S294). Notably, a terpyridine with two heteroaromatic termini was obtained. The cycloaddition strategy is more efficient than a sequential cross-coupling strategy, since this method can connect five heteroaromatic rings in a single operation. As described above, symmetrical oligoheteroarenes were obtained in high yields. If this method can be successfully applied to the synthesis of unsymmetrical oligoheteroarene, it should be quite valuable for organic synthesis. Unsymmetrical oligoheteroarene could be obtained by stepwise cyclization using two different diynes (Scheme 4). When an excess amount of **2m** to **1t** was used, only one of the two cyano groups participated in

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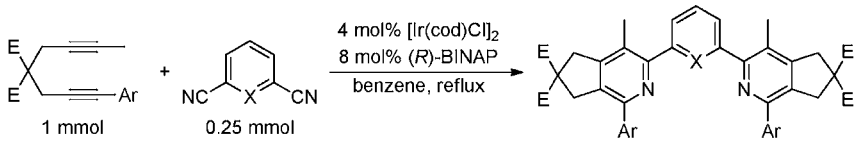
Scheme 3



[a] $[Ir(cod)Cl]_2$ (2 mol%) and DPPF (4 mol%) were used.
[b] 2 mmol of **1** and 0.5 mmol of **2u** were used.
[c] At 50 °C.

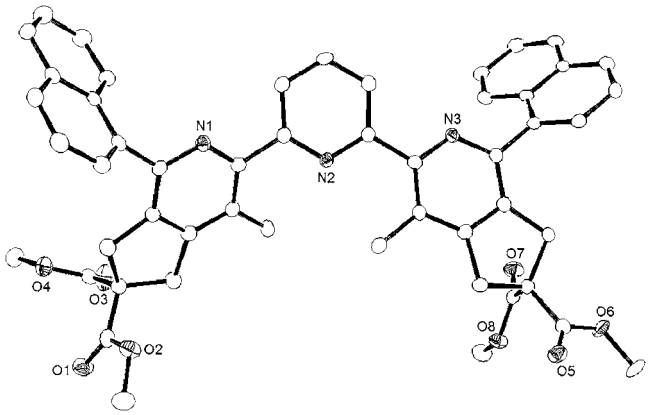


Figure 3. ORTEP drawing of **8nu**·CH_2Cl_2. Hydrogen atoms and CH_2Cl_2 are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

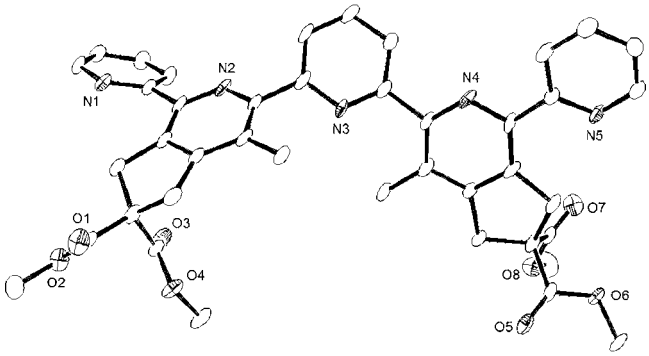


Figure 4. ORTEP drawing of **8tu**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

cyclization. Diyne **1t** reacted with 3 equiv of **2m** to give **3tm** bearing an intact cyano group in 92% yield. An excess amount of diyne **1v** to **3tm** was used to complete the second cyclization. Two equivalents of **1v** reacted with **3tm** to give unsymmetrical oligoheteroarene **9** bearing a pyridine terminus and thiophen terminus in 84% yield. The structure of **9** was determined by X-ray analysis (Figure 6).

■ ENANTIOSELECTIVE [2 + 2 + 2] CYCLOADDITION TO GIVE PYRIDINE BY THE KINETIC RESOLUTION OF A RACEMIC NITRILE

Much attention has been paid to enantioselective [2 + 2 + 2] cycloaddition to give pyridine, since chiral pyridines have been

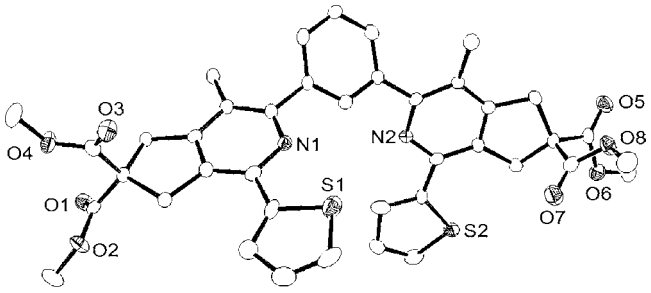


Figure 5. ORTEP drawing of **8vm**. Hydrogen atoms and minor parts of disorder are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

established as an important class of chiral building blocks not only in natural products[25] but also in asymmetric synthesis.[19a,26] A limited number of examples of enantioselective cycloaddition to give chiral pyridine have been reported. Axially chiral pyridine and central carbon chiral pyridine have been reported. Axially chiral pyridine given by the chiral Cp-cobalt complex-catalyzed cycloaddition of a sterically demanding diyne has been reported.[6e,g] Pyridine bearing a chiral quaternary stereocenter was synthesized in 64% ee by the Rh-catalyzed enantioselective desymmetrization of substituted malononitrile with diyne.[11b] The synthesis of chiral spirobipyridine by the Rh-catalyzed double cycloaddition of bisalkynenitrile has been reported.[11a] Co-catalyzed cycloaddition with chiral nitrile to give a central carbon chiral pyridine has been reported.[27] However, cycloaddition to give a chiral pyridine by the kinetic resolution of racemic nitriles has not been reported. We examined the reaction of diyne **1a** with racemic secondary nitrile **5w** in the presence of a catalytic amount of $[Ir(cod)Cl]_2$/(*R*)-SEGPHOS. (Optimization of the reaction conditions for the kinetic resolution of a racemic nitrile: see the Supporting Information, S2-S3). We chose secondary nitrile **5w** as a nitrile component because a benzyl nitrile is more reactive than an aliphatic nitrile. The corresponding product **6aw** was obtained in 75% with 80% ee (Scheme 5). Recrystallization of **6aw** with 67% ee from isopropyl alcohol gave **6aw** with 99% ee. The absolute configuration was determined to be *R* by the anomalous dispersion method (Figure 7). Since the absolute configuration of the product was (*R*), it is clear that (*R*)-**5w** reacts with diyne **1a** faster than (*S*)-**5w**.

■ THEORETICAL CALCULATIONS FOR THE REACTION MECHANISMS

There have already been several theoretical studies on transition metal-catalyzed [2 + 2 + 2] cyclotrimerizations.[28]

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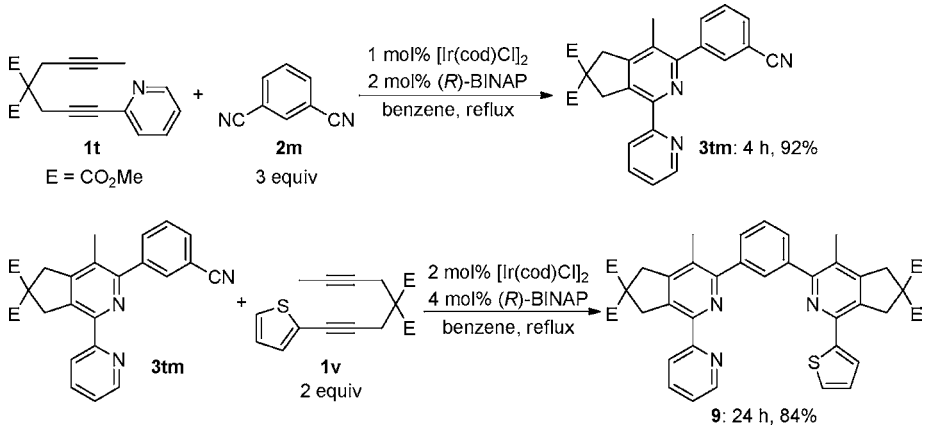
Scheme 4



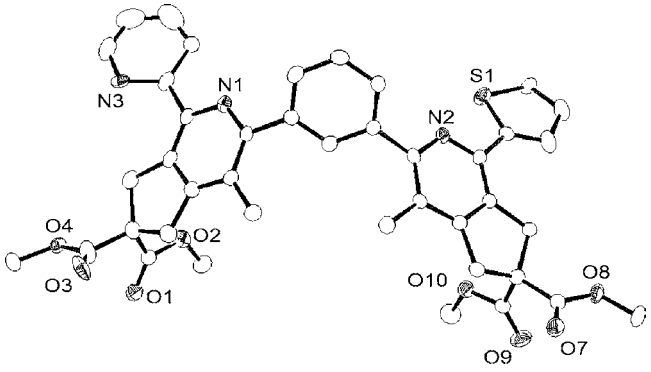
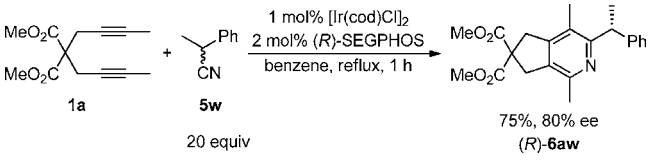


Figure 6. ORTEP drawing of **9**. Hydrogen atoms and minor parts of disorder are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

Scheme 5



However, the detailed mechanisms of these reactions have not been fully clarified. To the best of our knowledge, there has been no theoretical study on the reaction mechanism of iridium-catalyzed cycloaddition with nitrile. To shed light on the reaction mechanism of the cycloaddition between 1,6-diyne and acetonitrile, density functional theory (DFT) calculations using the B3LYP hybrid functional[29] with the Gaussian09 program[30] (LANL2DZ[31] for Ir atom and 6-31G*[32] for other atoms) were carried out for the model reaction of 1,6-diyne (**I**) with acetonitrile catalyzed by the iridium complex (**II**) (Scheme 6). Since the DPPP ligand is more efficient than DPPE (Table 1), the DPPP model ligand in which the phenyl group at DPPP is replaced by a hydrogen atom was used for the iridium complex **II**.

The optimized structures and energy diagrams are shown in Figures 8 and 9, respectively. The reaction pathways are shown in Scheme 7. The initial complex **III** generated by the complexation of **I** with **II** is transformed into complex **IV** through transition state **TSI**. The activation energy from **III** to **TSI** is 4.6 kcal/mol and the reaction energy from **III**

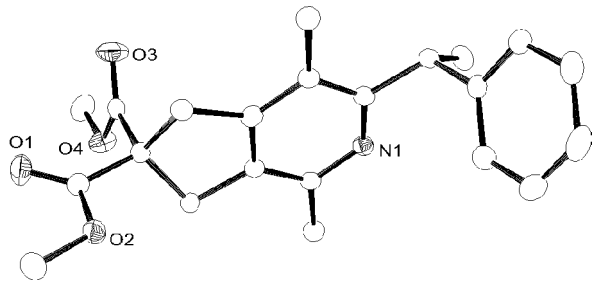
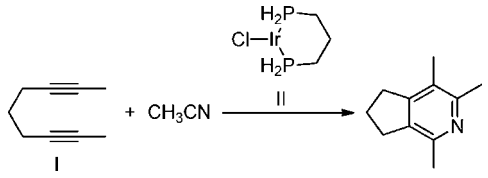
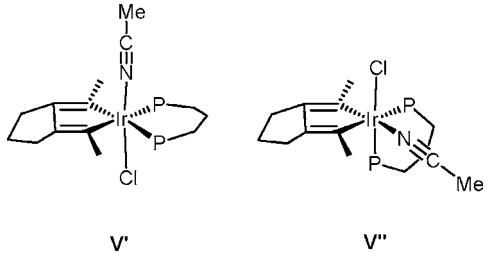


Figure 7. ORTEP drawing of **6aw**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

Scheme 6



to **IV** is −40.8 kcal/mol. Thus, this step provides a large degree of stabilization. As shown in Figure 8, the lengths of the C^2-C^3, C^3-C^4, and C^4-C^5 bonds in **IV** are 1.347, 1.464, and 1.349 Å, respectively. The lengths of the C^2-C^3 and C^4-C^5 bonds show a double bond character. Complex **IV** is considered to be a metallacyclopentadiene rather than a metallacyclopentatriene. The end-on coordination of acetonitrile to the iridium atom in **IV** gives complex **V**. The complexation energy is calculated to be 18.2 kcal/mol and complex **V** is more stable than complexes **V′** (complexation energy: 1.2 kcal/mol) and **V″** (complexation energy: 12.3 kcal/mol). On the other hand, no side-on complex was found in the present study.[33]



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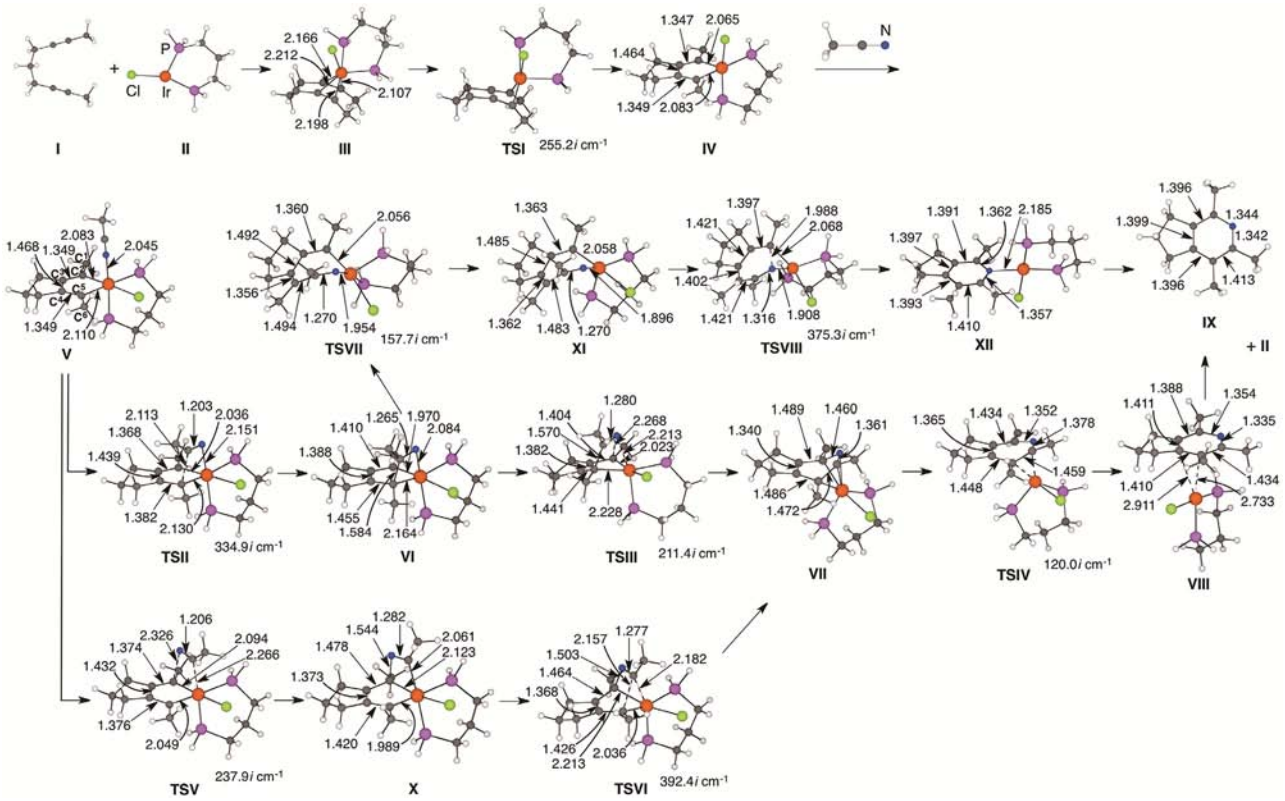

Figure 8. Optimized structures of stationary points for the model reaction between **I** and acetonitrile catalyzed by iridium complex **II**. Bond lengths are in angstroms.

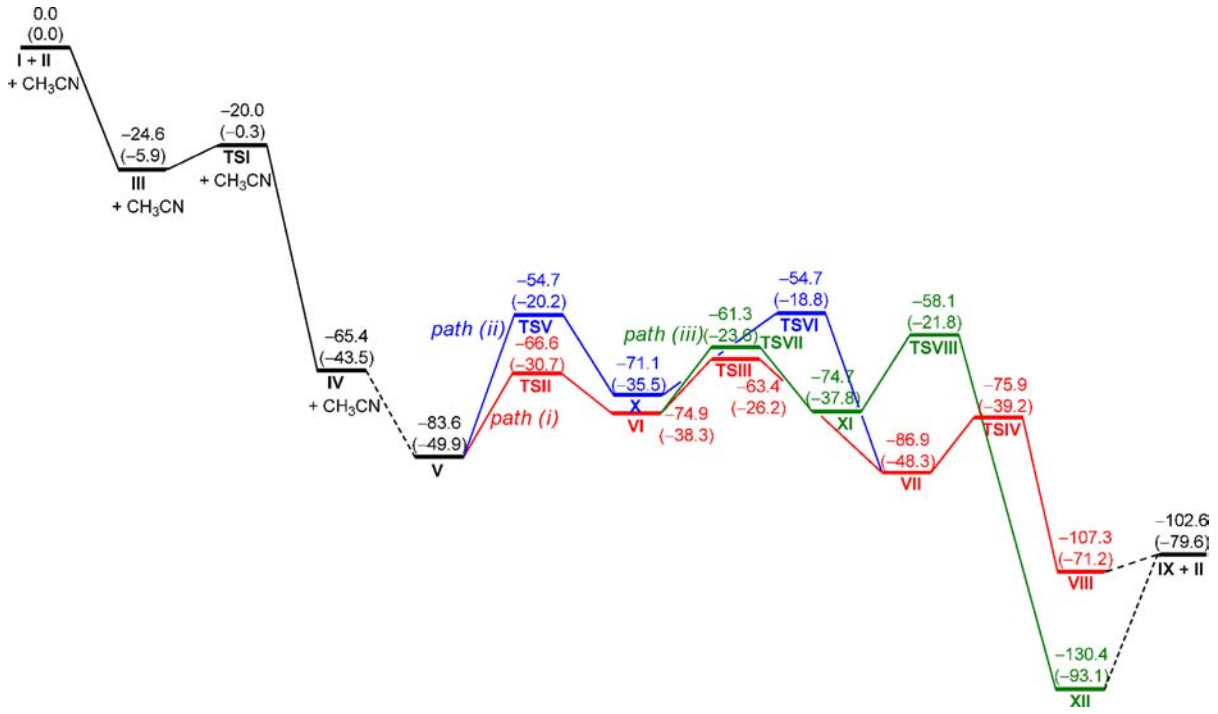

Figure 9. Relative energy diagram (kcal/mol) for the model reaction. Values in parentheses are relative Gibbs free energies at 298.15 K in the gas phase.

Three pathways (i, ii, and iii) from **V** to the final state (**IX** + **II**) are possible (Scheme 7). In pathway i, the first bond formation occurs between the nitrile carbon and the C^5 atom to give complex **VI** via **TSII**. The Ir−C^2 and C^3−C^4 bonds become shorter, from 2.083 and 1.468 Å to 1.970 and 1.388 Å, respectively, as a result of transformation from **V** to **VI**. In contrast, the Ir−C^5 bond lengthens from 2.110 Å to 2.164 Å. The length of the Ir−C^2 bond of 1.970 Å in **VI** shows a double

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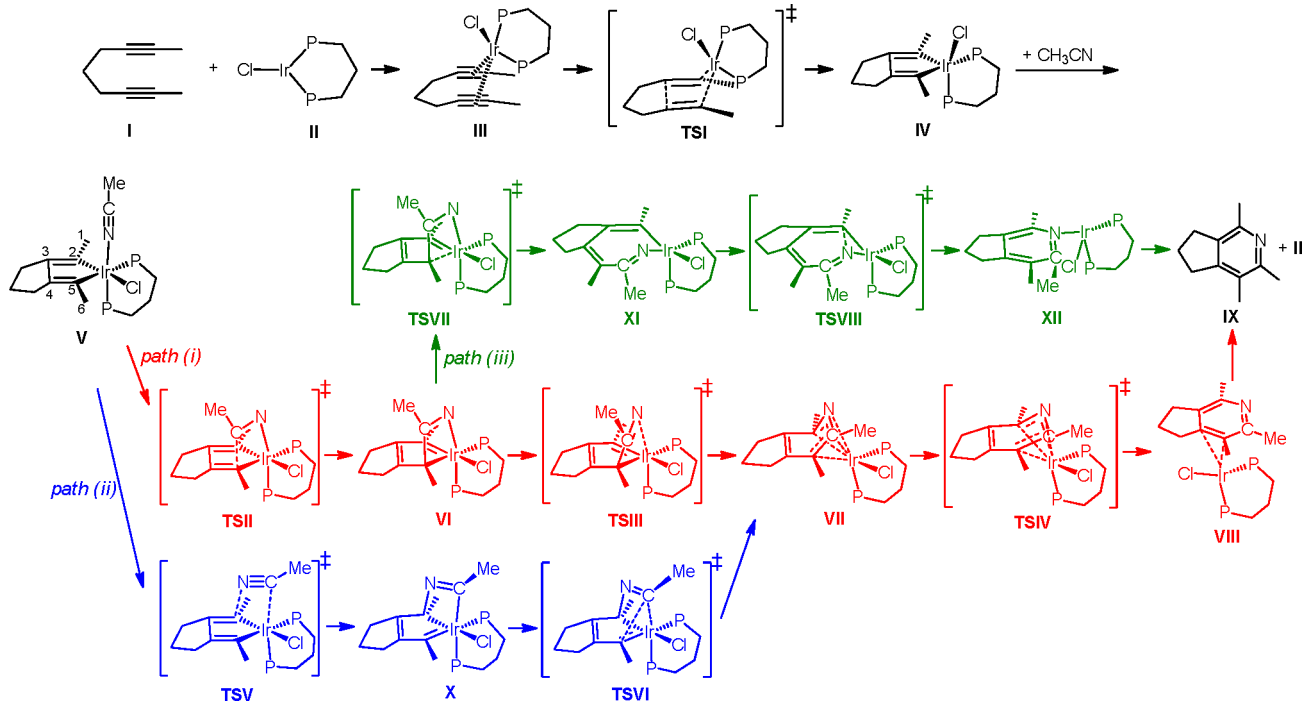
Scheme 7



bond character. Complex **VI** has an azairidabicyclo[3.2.0]-heptatriene structure. Related iridabicyclo[3.2.0]heptatriene was recently isolated by Paneque.[34] A process similar to that for the formation of azaruthenabicyclo[3.2.0]heptatriene is proposed based on the DFT calculation for the CpRuCl-mediated cyclotrimerization of acetylene with CF_3CN.[8b] Subsequent bond formation occurs between the nitrile nitrogen and C^2 via **TSIII** to give **VII**, in which the Ir−C^2 (2.141 Å), Ir−N(nitrile) (2.214 Å), Ir−C(nitrile) (2.227 Å), and Ir−C^5 (2.268 Å) bonds are almost the same length. Complex **VII** can be considered to be a η^4-pyridine Ir (+1) complex. A similar η^4-benzene Rh (+1) complex has been proposed in a theoretical study on the cyclotrimerization of acetylene catalyzed by Wilkinson's catalyst.[28t] η^4-Benzene Ir (+1) complex has been isolated.[35] The η^4-complex **VII** is transformed into the η^2-complex **VIII** via **TSIV**, and **VIII** readily dissociates into **IX** and **II**. Overall, the reaction system is highly exothermic.

In pathway ii, the first bond formation occurs between nitrile nitrogen and C^2 atom to give **X** via **TSV**. Subsequent bond formation occurs between nitrile carbon and C^5 atom to give **VII** via **TSVI**. Since transition states **TSV** and **TSVI** are at higher energies than **TSII** and **TSIII**, as shown in Figure 9, pathway ii is unfavorable compared to pathway i.

Pathway iii starts with complex **VI**. Transformation of **VI** to azairidacycloheptatriene **XI** via **TSVII** proceeds with cleavage of the Ir−C^5 bond of complex **VI**. A process similar to that for the formation of azaruthenacycloheptatriene is proposed in CpRuCl-mediated cyclotrimerization.[8b] **TSVII** is at a slightly higher energy than **TSIII** in pathway i, as shown in Figure 9. Reductive elimination from **XI** via **TSVIII** gives complex **XII**, in which the pyridine nitrogen atom coordinates to iridium (+1). According to the energy diagram shown in Figure 9, the transition states in pathway i, **TSII**, **TSIII**, and **TSIV**, are at lower energies than those in the other pathways. On the basis of these results, pathway i is preferred to the other pathways. The reaction proceeds via asynchronous addition of a carbon−nitrogen triple bond to iridacyclopentadiene to give azairidabicyclo[3.2.0]-heptatriene.

CONCLUSION

We have developed a new and efficient catalyst for the cycloaddition of alkynes with nitriles to give pyridines. Our catalyst system offers considerable advantages compared to previously reported catalyst systems: (1) The experimental procedure is more convenient than any previously reported. Pretreatment of the catalyst system is not necessary. The procedure simply requires mixing of $[Ir(cod)Cl]_2$ and an appropriate diphosphine ligand in solvent before the addition of substrates. (2) The catalytic activity can be altered at will through the use of various commercially available phosphines. (3) Aliphatic nitriles as well as aromatic nitriles can be used. The product was obtained in good to high yield. (4) Unsymmetrical diyne undergoes highly regioselective cycloaddition with nitrile to give a single product in high yield. (5) Oligoheteroarenes, including bipyridines and terpyridines, can be obtained by regioselective cycloaddition. Construction and connection of the heteroaromatic rings are performed in a single step. (6) Enantioselective [2 + 2 + 2] cycloaddition by the kinetic resolution of a racemic nitrile gives a centro chiral pyridine with high enantiomeric excess. (7) The reaction proceeds via asynchronous addition of a carbon−nitrogen triple bond to iridacyclopentadiene to give azairidabicyclo[3.2.0]heptatriene, which gives a η^4-pyridine Ir (+1) complex.

EXPERIMENTAL SECTION

Representative Procedure for the [2 + 2 + 2] Cycloaddition of Diyne (1) with Nitrile (2) (1:1 Reaction). A flask was charged with $[Ir(cod)Cl]_2$ (7.2 mg, 0.01 mmol) and DPPF (11.3 mg, 0.02 mmol). The flask was evacuated and filled with argon. To the flask

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were added benzene (5 mL) and benzonitrile (**2a**) (325 mg, 3.2 mmol). Diyne **1a** (235 mg, 1.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 3 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated in vacuo. Column chromatography of the residue gave **3aa** (*n*-hexane/AcOEt = 70/30, 305 mg, 0.9 mmol, 91% yield).

Representative Procedure for the [2 + 2 + 2] Cycloaddition of Diyne (1) with Dinitrile (2) (2:1 Reaction). A flask was charged with $[Ir(cod)Cl]_2$ (7.0 mg, 0.01 mmol), DPPF (11.8 mg, 0.02 mmol), and 1,4-dicyanobenzene (**2l**) (65 mg, 0.5 mmol). The flask was evacuated and filled with argon. To the flask was added benzene (5 mL) and diyne **1a** (473 mg, 2.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 3 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated in vacuo. Column chromatography of the residue gave **4al** (*n*-hexane/AcOEt = 30/70, 290 mg, 0.48 mmol, 95% yield).

Representative Procedure for the Synthesis of Oligoheteroarene. A flask was charged with $[Ir(cod)Cl]_2$ (7.7 mg, 0.01 mmol), (*R*)-BINAP (12.6 mg, 0.02 mmol), and 2,6-dicyanopyridine (**2u**) (65 mg, 0.5 mmol). The flask was evacuated and filled with argon. To the flask was added benzene (5 mL) and diyne **1n** (741 mg, 2.1 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 24 h. The solvent was evaporated in vacuo. Column chromatography of the residue gave **8nu** (*n*-hexane/AcOEt = 60/40, 397 mg, 0.48 mmol, 96% yield).

Procedure for the Enantioselective Cycloaddition of 1a with 5w. A flask was charged with $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol) and (*R*)-SEGPHOS (13.0 mg, 0.02 mmol). The flask was evacuated and filled with argon. To the flask were added benzene (5 mL) and nitrile (**5w**) (2658 mg, 20 mmol). Diyne **1a** (236 mg, 1.0 mmol) was added to the reaction mixture. The mixture was stirred under reflux for 1 h. The progress of the reaction was monitored by GLC. After the reaction was complete, the solvent was evaporated in vacuo. Column chromatography of the residue gave **6aw** (*n*-hexane/AcOEt = 70/30, 275 mg, 0.75 mmol, 75% yield, 80% ee). The ee value was determined by HPLC analysis with a Chiralcel OZ-H column (eluent: *n*-hexane/2-propanol = 99.65/0.35; flow rate: 1.0 mL/min; column temperature: 35 °C; retention time: 27.9 min (*R*) and 34.3 min (*S*)).

Recrystallization of 6aw. Two cycles of recrystallization of **6aw** (277.2 mg, 67% ee) from hot 2-propanol gave the enantiomerically pure **6aw** (123.9 mg, 99% ee). $[\alpha]^{29}_{D}$ −64.4 (*c* 0.49, $CHCl_3$) (99% ee (*R*)).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectroscopic data and high-resolution mass spectra data of **3**, **4**, **6**, **8**, and **9**, single-crystal X-ray diffraction data of compounds **3na**, **3to**, **8nu**·CH_2Cl_2, **8tu**, **8vm**, **9**, and **6aw**, computational details, total energy and free energy at 298 K, and Cartesian coordinates of stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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