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

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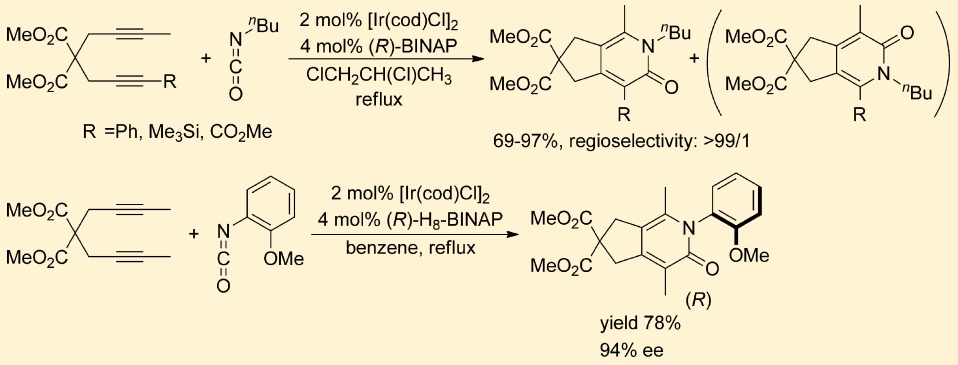
Supporting Information



ABSTRACT: [Ir(cod)Cl]$_2$/BINAP was found to be an efficient catalyst for the [2+2+2] cycloaddition of α,ω-diynes with isocyanates to give 2-pyridones. A wide range of isocyanates can be used for this reaction. Both aliphatic and aromatic isocyanates smoothly reacted with α,ω-diynes to give 2-pyridones in high yields. Aliphatic isocyanates were more reactive than aromatic isocyanates. For aromatic isocyanates, the electronic properties of the substituents affected the reactivity: electron-donating substituents enhanced the reaction. The reaction of unsymmetrical α,ω-diynes possessing two different internal alkyne moieties with isocyanates was regiospecific and gave a single product. This regioselectivity could be explained by the reaction of iridacyclopentadiene with a nitrogen−carbon double bond. The regioselectivity of the reaction of malonate-derived diyne was controlled by a steric effect, while that of the reaction of ester-tethered diyne was controlled by an electronic effect. [Ir(cod)Cl]$_2$/chiral diphosphine catalyst could be used for the enantioselective synthesis of C−N axially chiral 2-pyridone. The reaction of diyne **1a** with *o*-methoxyphenyl isocyanate (**7a**) gave C−N axially chiral 2-pyridone (*R*)-**8aa** in 78% yield with 94% ee.

INTRODUCTION

The transition metal-catalyzed reaction of heterocumulenes that would be either difficult or impossible with a Lewis acid catalyst or under thermal conditions represents a new approach to heterocyclic compounds.[1] Due to its ready availability and stability, isocyanate is especially important among heterocumulenes. Recently, Rovis developed a [2+2+2] cycloaddition of alkenylisocyanates with alkyne to give lactam and vinylogous amide.[2] This reaction has been applied to the enantioselective total synthesis of (+)-Lasubine II.[2f] On the basis of this success, isocyanates are becoming an increasingly important substrate. The cumulative structure of the carbon−nitrogen double bond and the carbon−oxygen double bond is attractive as a starting material.[3] The transition metal-catalyzed [2+2+2] cycloaddition of two molecules of alkyne with one molecule of isocyanate is an atom-economical and environmentally benign reaction for the synthesis of 2-pyridone, which is a valuable heterocycle for the production of pharmaceuticals and agrochemicals[4] because the reaction proceeds under mild and neutral conditions without giving a metal salt as waste. Since the pioneering work by Yamazaki[5] and Hoberg,[6] there have been several studies on the [2+2+2] cycloaddition of alkyne with isocyanate to give 2-pyridone. Vollhardt also reported Co-catalyzed reaction.[7] Recently, Ru,[8] Rh,[9,19] and Ni-NHC[10] complexes have been reported to be new catalysts for the cycloaddition of α,ω-diynes with isocyanates to give 2-pyridones. However, each catalyst has drawbacks. With Cp*Ru(cod)Cl, it can be difficult to change the selectivity of 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. These Rh[9a,19a,b] and Ni[10] catalysts require preactivation before diynes can be reacted with isocyanates. [Rh(ethylene)$_2$Cl]$_2$ is a relatively unstable complex.[2,9b,c] A more convenient and stable catalyst that does not require preactivation is needed to expand the scope of the reaction and improve the selectivity.

We have been studying iridium-catalyzed carbon−carbon and carbon−heteroatom bond formation[11] since we first found that an iridium complex was an efficient catalyst for highly branched-product selective allylic alkylation in 1997.[11a] We have also found that [Ir(cod)Cl]$_2$/diphosphine was an efficient

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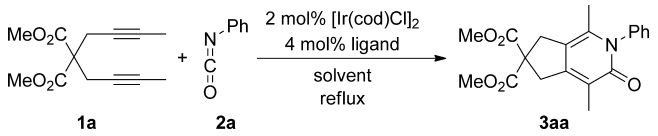
Table 1. Reaction of 1,6-Diyne (1a) with Phenyl Isocyanate (2a)[a]



1a 2a 3aa

entry	ligand	solvent	time (h)	yield (%)[b]
1	DPPE	$ClCH_2CH(Cl)CH_3$	24	0
2	DPPP	$ClCH_2CH(Cl)CH_3$	24	16
3	DPPB	$ClCH_2CH(Cl)CH_3$	24	32
4	DPPPentane	$ClCH_2CH(Cl)CH_3$	24	51
5	DPPF	$ClCH_2CH(Cl)CH_3$	24	54
6	BIPHEP	$ClCH_2CH(Cl)CH_3$	24	67
7	(*R*)-H_8–BINAP	$ClCH_2CH(Cl)CH_3$	24	63
8	(*R*)-BINAP	$ClCH_2CH(Cl)CH_3$	18	96
9[c]	PPh_3	$ClCH_2CH(Cl)CH_3$	24	41
10[c]	$P(OPh)_3$	$ClCH_2CH(Cl)CH_3$	24	4
11	(*R*)-BINAP	$ClCH_2CH_2Cl$	24	44
12	(*R*)-BINAP	THF	24	28
13	(*R*)-BINAP	benzene	24	40
14	(*R*)-BINAP	toluene	18	75
15	(*R*)-BINAP	$CH_3CH_2COCH_2CH_3$	24	80
16[d]	(*R*)-BINAP	$ClCH_2CH(Cl)CH_3$	1	97
17[d]	*rac*-BINAP	$ClCH_2CH(Cl)CH_3$	1	96

[a]Reaction condition: **1a** (1 mmol) and **2a** (3 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and a ligand (0.04 mmol) in solvent (5 mL). [b]Isolated yield. [c]8 mol % of ligand was used. [d]1.2 mmol of **2a** was used.

catalyst for the cycloaddition of unsaturated compounds to give cyclic compounds.[12] We have extended this iridium chemistry to cycloaddition with isocyanates. The iridium-catalyzed cycloaddition of alkynes with isocyanates has not yet been reported. In this paper, we report the full details of the $[Ir(cod)Cl]_2$/diphosphine-catalyzed [2+2+2] cycloaddition of α,ω-diynes with isocyanates to give 2-pyridones. In addition, we report the construction of C–N axial chirality catalyzed by $[Ir(cod)Cl]_2$/chiral diphosphine. An Ir catalyst is more convenient than Rh and Ni catalysts because the catalyst does not require preactivation. We can use various phosphines as a ligand for $[Ir(cod)Cl]_2$. It is easy to alter the catalytic activity by choosing an appropriate phosphine, which can lead to changes in product-, chemo-, regio-, and enantioselectivity.

RESULTS AND DISCUSSION

Screening of the Catalyst. Diyne **1a** reacted with phenyl isocyanate (**2a**) in the presence of 2 mol % of $[Ir(cod)Cl]_2$ and ligand to give 2-pyridone **3aa**. Phosphine ligand had a profound effect on the reaction. The effect of phosphine ligand was screened under refluxing 1,2-dichloropropane, and the results are summarized in Table 1. Although DPPE has been reported to be an efficient ligand for the Ir-catalyzed cycloaddition of alkynes to give benzene,[12b,d,e] DPPE was totally ineffective for the reaction of **1a** with **2a** (entry 1). As the number of methylene groups between the two diphenylphosphino groups increased from two to five, the yield of **3aa** increased from 0% to 51% (entries 1–4). Biaryl diphosphines were more efficient than 1,*n*-bis(diphenylphosphino)alkane (entries 6–8). (*R*)-BINAP was the most efficient ligand for this reaction. The reaction of **1a** with **2a** using (*R*)-BINAP for 18 h gave **3aa** in 96% yield (entry 8). PPh_3 and $P(OPh)_3$ were less efficient than (*R*)-BINAP (entries 9 and 10). We examined the effect of solvent on the reaction by using (*R*)-BINAP (entries 11–15). The optimal conditions were determined to be the use of (*R*)-BINAP under refluxing 1,2-dichloropropane. A reduction in the amount of **2a** to 1.2 mmol accelerated the reaction rate (entry 16). *rac*-BINAP gave essentially the same result as that with (*R*)-BINAP (entry 17).

Reaction of 1a with Various Isocyanates 2b–u. We examined the reaction of **1a** with various isocyanates under the optimized reaction conditions described above. The results are summarized in Table 2. The substituent at the para position on the aromatic ring affected the reaction. An electron-donating substituent such as a methoxy or methyl group gave a good result (entries 1 and 2). These reactions went to completion in 1 h. A weak electron-donating group such as halogen also gave a good result (entries 4 and 5). Although various transformations of an aromatic carbon–halogen bond catalyzed by transition metal are possible,[13] the aromatic carbon–halogen bond was compatible under the reaction conditions. The presence of an electron-withdrawing group at the para position decreased the yield. The reaction with *p*-trifluoromethylphenyl isocyanate (**2g**) and *p*-acetylphenyl isocyanate (**2h**) gave **3ag** and **3ah** in respective yields of 72% and 71% (entries 6 and 7). Strong electron-withdrawing groups such as a cyano or nitro group gave the corresponding products in low yields (entries 8 and 9). Aromatic isocyanates required heating to give the product, and aliphatic isocyanate was more reactive than aromatic isocyanate. The reaction with *n*-butyl isocyanate (**2k**) at room temperature went to completion in 20 min to give **3ak** in 98% yield (entry 10). A longer alkyl isocyanate similarly underwent cycloaddition at room temperature (entry 11). Benzyl isocyanate was a good substrate as an aliphatic isocyanate (entry 12). The reaction with phenethyl isocyanate (**2n**) gave the product in somewhat lower yield than that with benzyl isocyanate (**2m**) (entry 13). An isocyanate bearing a heteroaromatic ring could be used for the reaction. In contrast to the reaction with benzyl isocyanate, which proceeded at room temperature, the reaction with furfuryl isocyanate (**2o**)

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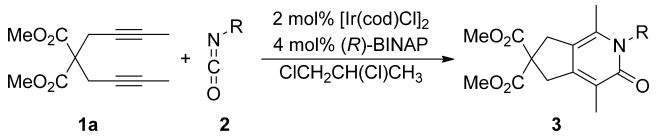
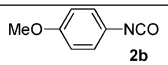
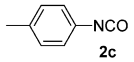
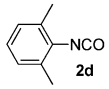
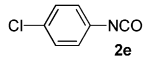
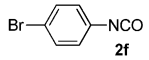
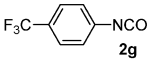
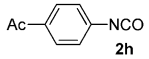
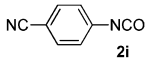
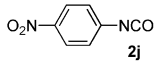
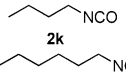
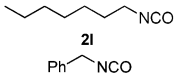
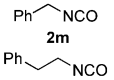
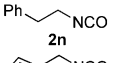
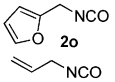
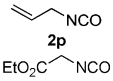
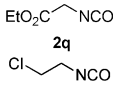
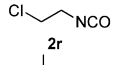
Table 2. Reaction of 1,6-Diyne (1a) with Various Isocyanates 2[a]



entry	2	product	temperature	time (h)	yield (%)[b]
1	 2b	**3ab**	reflux	1	99
2	 2c	**3ac**	reflux	1	95
3	 2d	**3ad**	reflux	1	0
4	 2e	**3ae**	reflux	18	94
5	 2f	**3af**	reflux	4	87
6[c]	 2g	**3ag**	reflux	24	72
7	 2h	**3ah**	reflux	24	71
8	 2i	**3ai**	reflux	24	24
9[d]	 2j	**3aj**	reflux	24	33
10	 2k	**3ak**	rt	0.3	98
11	 2l	**3al**	rt	0.3	98
12	 2m	**3am**	rt	0.3	98
13	 2n	**3an**	rt	0.3	89
14	 2o	**3ao**	reflux	1	92
15	 2p	**3ap**	reflux	24	80
16	 2q	**3aq**	rt	0.3	99
17	 2r	**3ar**	reflux	24	0
18	 2s	**3as**	rt	0.3	94
19	 2t	**3at**	rt	0.3	96
20	 2u	**3au**	reflux	8	0

[a]Reaction condition: **1a** (1 mmol) and **2** (1.2 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and (*R*)-BINAP (0.04 mmol) in 1,2-dichloropropane (5 mL). [b]Isolated yield. [c]Reaction condition: **1a** (1.5 mmol) and **2g** (1 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and (*R*)-BINAP (0.04 mmol) in 1,2-dichloropropane (5 mL). [d]3-Pentanone was used as a solvent.

required heating to give 2-pyridone **3ao**. Furfuryl isocyanate (**2o**) reacted with diyne **1a** under refluxing 1,2-dichloropropane for 1 h to give **3ao** in 92% yield (entry 14). The reaction of allyl isocyanate (**2p**) required heating to give *N*-allyl-2-pyridone **3ap** in 80% yield (entry 15). The introduction of an allyl group on nitrogen is valuable for further functionalization of the 2-pyridone ring because the carbon−carbon double bond can be transformed to another functional group. A functionalized isocyanate such as ethyl isocyanatoacetate (**2q**) smoothly reacted with diyne **1a** at room temperature to give **3aq** in 99% yield (entry 16). An ester group was compatible under the reaction conditions. On the other hand, 2-chloroethyl isocyanate (**2r**) did not give 2-pyridone at all (entry 17), and the starting material was recovered in quantitative yield. Both acyclic and cyclic secondary isocyanates gave results as good as primary isocyanates (entries 18 and 19). In contrast to these successful results with primary and secondary aliphatic isocyanates, tertiary aliphatic isocyanate **2u** failed to react even under refluxing 1,2-dichloropropane (entry 20). This lack

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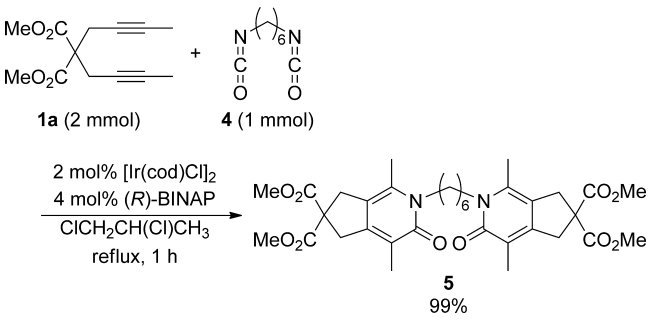
of reactivity is considered to be due to steric hindrance by the tertiary butyl group.

We examined the reaction of diisocyanate **4**, and expected the formation of two 2-pyridone rings in the same molecule when an excess amount of diyne **1a** was used. Both isocyanate groups participated in cycloaddition to give **5** in 99% yield under refluxing 1,2-dichloropropane when 2 equiv of **1a** was used (Scheme 1).

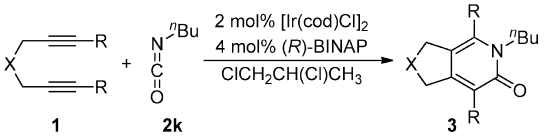
Scheme 1. Reaction of 1,6-Diyne 1a with Diisocyanate 4

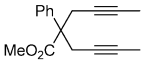
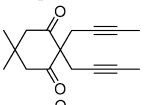
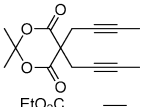
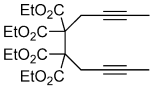
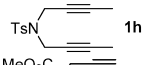
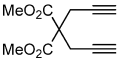


Reactions of Various Diynes with *n*-Butyl Isocyanate 2k. We examined the reactions of various diynes with *n*-butyl isocyanate (**2k**) because primary alkyl isocyanate was the most reactive isocyanate among the isocyanates surveyed. The results are summarized in Table 3. The substituent at the 5-position in 2,7-nonadiyne affected the reaction conditions to give 2-pyridone **3** in high yield. The reaction was compatible with various functional groups. Similar to 1,3-diester (**1a**), cyclic 1,3-diketone (**1d**) and acyclic 1,3-diketone (**1b**) gave good results. These reactions proceeded at room temperature to give **3bk** and **3dk** in nearly quantitative yields (entries 1 and 3). The reaction of monoester diyne (**1c**) gave **3ck** in 96% yield, which was comparable to the yield of 1,3-diester **1a** (entry 2). The reaction of diyne **1e** bearing Meldrum's acid at the 5-position required heating to give **3ek** in 89% yield (entry 4). As shown above, 2-pyridones fused with a five-membered ring were obtained in high yields from 2,7-nonadiynes. The reaction was successfully applied to the synthesis of 2-pyridones fused with a six-membered ring. The reaction of 2,8-decadiyne **1f** under refluxing 1,2-dichloropropane gave **3fk** in 94% yield (entry 5). However, the reaction of 2,8-decadiyne **1g** did not give 2-pyridone at all (entry 6). These results clearly showed that a Thorpe–Ingold effect[14] was indispensable for cyclization. Pyrrolidine is an important *N*-heterocycle as a biologically active compound because various substituted pyrrolidines are used as pharmaceuticals. 2-Pyridone fused with pyrrolidine was obtained with this reaction. *N*,*N*-Dipropargyl sulfonamide, **1h**, smoothly underwent cycloaddition with **2k** to give 2-pyridone fused with pyrrolidine **3hk** in 96% yield (entry 7). The reaction of 1,6-heptadiyne, **1i**, gave **3ik** in 56% yield (entry 8). Monoyne could not be used for the reaction in place of diyne. The reaction of monoyne with isocyanate gave no product.

Regioselective Cycloaddition of Unsymmetrical Diyne with *n*-Butyl Isocyanate 2k. Regioselective cycloaddition is important for the synthesis of substituted 2-pyridones. There have been few studies on the regioselective cycloaddition of unsymmetrical α,ω-diynes with isocyanates, and only Ru[8a] and Rh[9a] complexes have been examined as catalysts. In most of the cases examined so far, the substrates were unsymmetrical diynes with an internal alkyne moiety and a terminal alkyne moiety. We examined the regioselectivity of the reactions of unsymmetrical diynes with isocyanates. The results are

Table 3. Reaction of Various 1,6-Diynes (1) with Isocyanate 2k[a]



entry	1	product	temperature	time (h)	yield (%)[b]
1	 1b	**3bk**	rt	0.5	98
2	 1c	**3ck**	rt	0.3	96
3	 1d	**3dk**	rt	0.3	99
4	 1e	**3ek**	reflux	18	89
5	 1f	**3fk**	reflux	24	94
6	 1g	**3gk**	reflux	24	0
7	 1h	**3hk**	rt	0.5	96
8	 1i	**3ik**	reflux	0.5	56

[a]Reaction condition: **1a** (1 mmol) and **2k** (1.2 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and (*R*)-BINAP (0.04 mmol) in 1,2-dichloropropane (5 mL). [b]Isolated yield.

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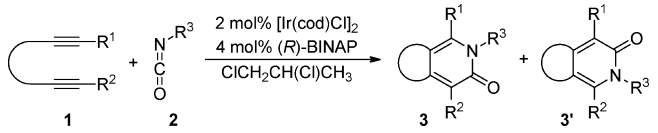
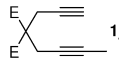
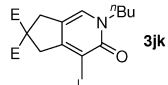
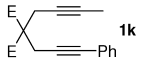
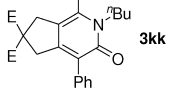
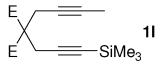
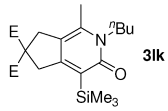
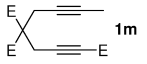
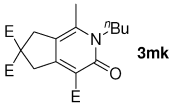
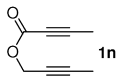
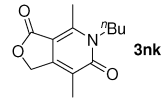
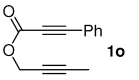
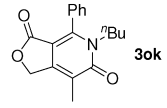
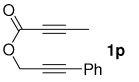
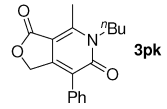
Table 4. Reaction of Unsymmetrical 1,6-Diynes (1) with Isocyanates 2[a]



1 2 3 3'

entry	1[b]	2	product	temperature	time (h)	yield (%)[c]	3/3'
1[d,e]	 1j	2k	 3jk	reflux	1	80	>99/1
2[e]	 1k	2k	 3kk	reflux	1	97	>99/1
3[e]	 1l	2k	 3lk	reflux	24	86	>99/1
4[f]	 1m	2k	 3mk	reflux	1	69	>99/1
5[f]	 1n	2k	 3nk	reflux	0.5	91	>99/1
6[e]	 1o	2k	 3ok	reflux	4	75	>99/1
7[e]	 1p	2k	 3pk	reflux	24	33	>99/1

[a]Reaction condition: **1** (1 mmol) and **2** (1.2 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and (*R*)-BINAP (0.04 mmol) in 1,2-dichloropropane (5 mL). [b]E = CO_2Me. [c]Isolated yield. [d]3equiv of **2** was used. [e]Structure of **3** was determined by 2D NMR. [f]Structures of **3mk** and **3nk** were unambiguously confirmed by X-ray analysis (Figures 1 and 2).

summarized in Table 4. All of the reactions were *regiospecific* to give the corresponding 2-pyridones as a single product. We first

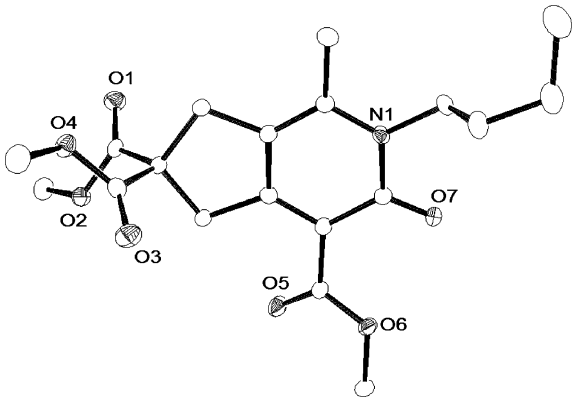


Figure 1. ORTEP drawing of **3mk**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

examined the reaction of malonate-derived diyne possessing a terminal alkyne moiety and a Me-substituted internal alkyne moiety (**1j**) with *n*-butyl isocyanate (**2k**). 2-Pyridone **3jk**, in which a methyl group was substituted at the α-position of the carbonyl group, was obtained in 80% yield as a single product (entry 1). Notably, the regioselectivity of the Ir-catalyzed

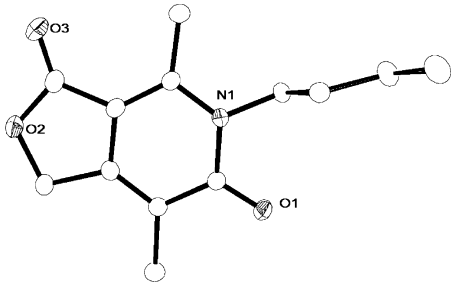


Figure 2. ORTEP drawing of **3nk**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

reaction was opposite that of the Ru-catalyzed reaction. The CpRu(cod)Cl-catalyzed reaction of **1j** with *n*-propyl isocyanate has been reported to give 2-pyridone in which a methyl group was substituted at the α-position relative to a nitrogen atom.[8a] An unsymmetrical diyne possessing two different internal alkyne moieties is a more challenging substrate for regioselective cycloaddition. We next examined the reactions of such diynes. Ph-substituted diyne **1k** underwent cycloaddition to give 2-pyridone **3kk** in which a phenyl group was substituted at the α-position relative to a carbonyl group in 97% yield as a single product (entry 2). Similarly, trimethylsilyl-substituted diyne **1l** smoothly reacted with **2k** to give 2-pyridone **3lk** in 86% yield as a single product (entry 3). These

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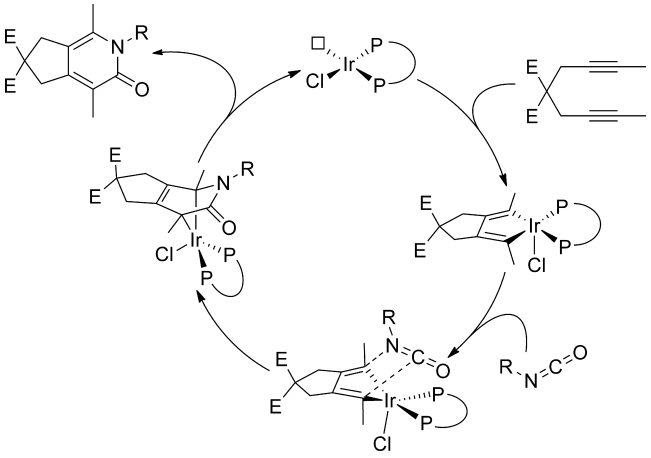
two reactions showed the same regioselectivity. A trimethylsilyl group is useful for introducing a functionality into the 2-pyridone ring. These diynes, **1j**, **1k**, **1l**, possessed sterically different alkyne moieties. We next examined the reactions of diynes possessing electronically different alkyne moieties. With diyne **1m**, the terminal ester group connected directly to an alkyne moiety. The reaction of **1m** with *n*-butyl isocyanate (**2k**) gave 2-pyridone **3mk** in 69% yield (entry 4). The α-carbon relative to the carbonyl group in **3mk** was substituted with an ester group. We examined the reaction of ester-tethered diyne **1n**. The reaction of **1n** with **2k** gave **3nk** in 91% yield (entry 5). The regioselective cycloaddition of an unsymmetrical diyne possessing two different internal alkyne moieties with isocyanates has been difficult. The CpRu(cod)Cl-catalyzed reaction of a similar amide-tethered diyne with *n*-propyl isocyanate has been reported to give a 83:17 mixture of regioisomeric 2-pyridones. Our Ir catalyst was able to overcome the regioselectivity problem. Ester-tethered diynes possessing Ph- and Me-substituted internal alkyne moieties **1o** and **1p** were examined. The reactions of **1o** and **1p** gave **3ok** and **3pk** in respective yields of 75% and 33% (entries 6 and 7). The regioselectivity of the reactions of **1o** and **1p** was the same as that of **1n**.

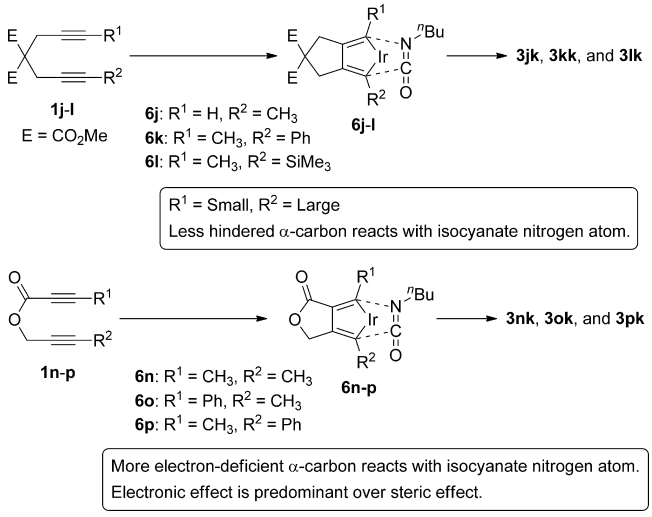
Regiochemical and Mechanistic Considerations. The regioselectivity observed here should be explained on the basis of mechanistic considerations. A plausible mechanism is as follows (Scheme 2). Diyne oxidatively adds to an iridium active

Scheme 2. Catalytic Cycle



species to give iridacyclopentadiene.[15] Isocyanate reacts with iridacyclopentadiene to give 2-pyridone. The regioselectivity is determined when iridacyclopentadiene reacts with isocyanate. 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. When the steric effect is predominant, the less-hindered α-carbon preferentially reacts with an isocyanate nitrogen atom. When the electronic effect is predominant, the more electron-deficient α-carbon in iridacyclopentadiene preferentially reacts with the more electron-rich isocyanate nitrogen atom (Scheme 3). We examined the reaction of malonate-derived diyne and ester-tethered diyne. When diynes **1j**–**l** possessing a sterically different alkyne terminus (Me vs H, Me vs Ph, and Me vs Me_3Si) were used, the less-hindered α-carbon of iridacyclopentadienes **6j**–**l** reacted with isocyanate nitrogen to decrease the steric repulsion with an alkyl group on nitrogen. Thus, 2-

Scheme 3. Plausible Reaction Pathway



pyridones **3jk**–**lk** were obtained. In the reaction of diyne **1m**, the α-substituents on iridacyclopentadiene **6m** are an EtO_2C group and a methyl group. Since steric congestion by the ester group is not much greater than that by a methyl group, it seems that the steric effect is not decisive in determining the regioselectivity. The regioselectivity of the reaction of **1m** was believed to be due to the fact that the more stable 1,3-dicarbonyl compound **3mk** was preferentially formed. Ester-tethered diyne **1n** is a good substrate for evaluating the electronic effect of a carbonyl group on regioselectivity, since, with regard to steric considerations, diyne **1n** possesses the same alkyne terminus, but an electronically different alkyne terminus. The steric hindrance at each α-carbon in iridacyclopentadiene **6n** is the same in this case. Consequently, the electronic effect plays a decisive role in determining the regioselectivity. With iridacyclopentadiene **6n**, 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. Isocyanate nitrogen reacts at the more electron-deficient α-carbon to give **3nk**. Ester-tethered diynes **1o** and **1p** possess sterically and electronically different alkyne termini. The electron-withdrawing property of the tethered-ester group plays a decisive role in determining the regioselectivity in both cases. The more electron-deficient α-carbon in iridacyclopentadienes **6o** and **6p** reacts with the isocyanate nitrogen to give **3ok** and **3pk**. Although the steric effect works in an opposite direction than the electronic effect in ester-tethered diyne **1o**, the regiochemical outcome shows that the electronic effect of the internal ester group is predominant over the steric effect of the terminal phenyl group. With ester-tethered diyne **1p**, the steric effect and electronic effect work in the same direction. Thus, we can conclude that the regioselectivity of the reaction of malonate-derived diyne **1j**–**l** is controlled by a steric effect, while that of ester-tethered diyne **1n**–**p** is controlled by an electronic effect.

The results presented in Table 2 clearly show that the electronic-properties of the substituent on isocyanate strongly affect the reaction. The reaction with an aliphatic isocyanate such as *n*-butyl isocyanate (**2k**) proceeded at room temperature, while that with an aromatic isocyanate such as phenyl isocyanate (**2a**) or *p*-methoxyphenyl isocyanate (**2b**) required heating to give the corresponding 2-pyridone in high yields. Moreover, the reaction with an electron-deficient aromatic

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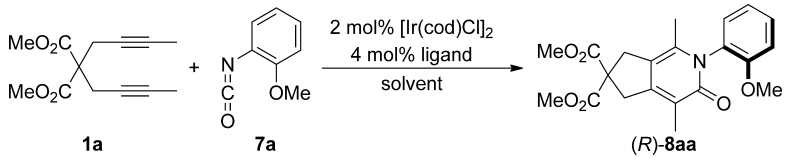
Table 5. Reaction of 1,6-Diynes (1a) with Isocyanate 7a[a]



entry	ligand	solvent	equiv of 7a	temperature	time (h)	yield (%)[b]	ee (%)[c]
1	(*R*)-BINAP	$ClCH_2CH(Cl)CH_3$	1.2	reflux	1	58	70
2	(*R*)-BINAP	$ClCH_2CH_2Cl$	1.2	reflux	24	60	71
3	(*R*)-BINAP	acetone	1.2	reflux	24	30	77
4	(*R*)-BINAP	THF	1.2	reflux	1	54	88
5	(*R*)-BINAP	1,4-dioxane	1.2	reflux	1	64	74
6	(*R*)-BINAP	$MeOCH_2CH_2OMe$	1.2	reflux	1	49	75
7	(*R*)-BINAP	toluene	1.2	reflux	1	57	79
8	(*R*)-BINAP	benzene	1.2	reflux	1	63	86
9	(*R*)-BINAP	benzene	1.2	60 °C	1	60	86
10	(*R*)-BINAP	benzene	1.2	40 °C	1	60	86
11	(*R*)-BINAP	benzene	1.2	rt	1	63	86
12	(*R*)-BINAP	benzene	1.2	0 °C	24	20	88
13	(*R*)-BINAP	benzene	3	rt	1	84	86
14	(*R*)-BINAP	benzene	5	rt	24	79	85
15	(*R*)-tol-BINAP	benzene	3	rt	24	45	85
16	(*R*)-SEGPHOS	benzene	3	rt	24	20	72
17	(*R*)-H_8–BINAP	benzene	3	rt	24	79	91
18	(*R*)-P-PHOS	benzene	3	rt	4	68	77
19	(*R*)-C_3-TUNEPHOS	benzene	3	rt	24	12	46
20	(*R*)-SYNPHOS	benzene	3	rt	24	39	69
21	(*R*)-MeO-BIPHEP	benzene	3	rt	24	59	72
22	(*R*,*S*)-JOSIPHOS	benzene	3	rt	24	0	–
23	(*S*,*S*)-DIPAMP	benzene	3	rt	24	0	–
24[d]	(*R*)-H_8-BINAP	benzene	3	reflux	1	78	94

[a]Reaction condition: **1a** (1 mmol) and **7a** in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol) and ligand (0.04 mmol) in solvent (5 mL). [b]Isolated yield. [c]Determined by HPLC. [d]Reaction condition: **1a** (0.5 mmol) and **7a** (1.5 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.01 mmol) and ligand (0.02 mmol) in solvent (2.5 mL).

isocyanate such as *p*-nitrophenyl isocyanate (**2j**) gave the product in low yield. These results show that the electron-density of isocyanate nitrogen has a profound effect on the reaction temperature and the yield. Although it is clear that the reaction of iridacyclopentadiene **6** with isocyanate **2** proceeds via a concerted mechanism, bond formation between the isocyanate nitrogen and the α-carbon in the transition state may be more advanced than that between the isocyanate carbon and another α-carbon. Consequently, the electron-density of the isocyanate nitrogen affects the reactivity. An electron-rich isocyanate is more reactive than an electron-deficient isocyanate.

Enantioselective Cycloaddition of Diyne 1a with Ortho Substituted Isocyanates 7a–g. C–N axially chiral compounds such as *N*-*o*-*tert*-butyl anilide have received much attention since the pioneering work by Curran.[16] A transition metal-catalyzed construction of C–N axial chirality has been developed. Kitagawa and Taguchi reported the Pd-catalyzed enantioselective N-arylation of *N*-*o*-*tert*-butyl anilides to give C–N axially chiral anilides in up to 95% ee.[17] The Rh-catalyzed enantioselective 1,4-addition of aryl boronic acid was successfully applied to the synthesis of axially chiral *N*-arylsuccinimides by Hayashi and Shintani.[18] In 2008, Tanaka reported a new approach to C–N axial chirality.[19] Malonate-derived 2,7-nonadiyne reacted with ortho-substituted aryl isocyanate to give axially chiral *N*-aryl-2-pyridone in the presence of cationic rhodium BINAP catalyst. However, the yield and enantioselectivity needed to be improved. For example, the reaction of **1a** with *o*-methyl phenyl isocyanate (**7b**) has been reported to give a product in 83% yield with 30% ee. The reaction of **1a** with *o*-bromophenyl isocyanate (**7f**) has been reported to give a product in 27% yield with 87% ee. None of the examples showed both high yield and high enantioselectivity. We tried to improve both the yield and enantioselectivity. The reaction conditions and chiral ligand were optimized in the reaction of **1a** with *o*-methoxyphenyl isocyanate (**7a**). The results are summarized in Table 5. The effect of the solvent on the reaction was examined (entries 1–8). Benzene gave a good yield (63%) with high enantioselectivity (86% ee) (entry 8). Thus, we next examined the effect of temperature using benzene as solvent. The reaction temperature did not appear to influence the enantioselectivity (entries 8–11). The reaction at 0 °C gave a slightly increased enantioselectivity (88% ee) with a considerable decrease in yield (20%) (entry 12). An increase in the amount of isocyanate **7a** from 1.2 equiv to 3 equiv increased the yield from 63% to 84% (entries 11 and 13), but a further increase in the amount of **7a** to 5 equiv resulted in a slight decrease in yield (entry 14). We examined the effect of a chiral ligand using the reaction at room temperature in benzene with 3 equiv of isocyanate **7a**. (*R*)-Tol-BINAP gave almost the same enantioselectivity as (*R*)-BINAP, but the yield was lower than that with (*R*)-BINAP (entry 15). (*R*)-SEGPHOS gave a lower yield and enantioselectivity than (*R*)-BINAP (entry 16). (*R*)-

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H_8-BINAP gave 91% enantioselectivity with 79% yield (entry 17). Other chiral diphosphines were less efficient than (*R*)-BINAP (entries 18−23). The reaction using (*R*)-H_8−BINAP under refluxing conditions increased the enantioselectivity to 94% (entry 24). The reaction of **1a** with **7a** in the presence of $[Rh(cod)_2]BF_4$/(*R*)-BINAP has been reported to give **8aa** in 92% yield with 58% ee. Our Ir catalyst improved the enantioselectivity to 94% ee. The absolute configuration of **8aa** was determined to be *R* by the anomalous dispersion method (Figure 3).

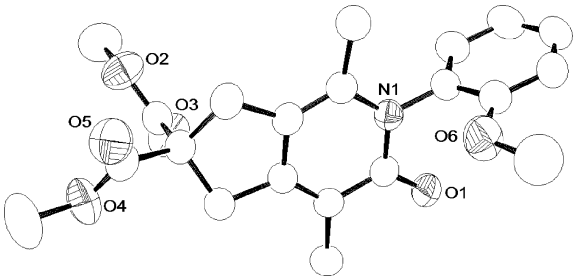


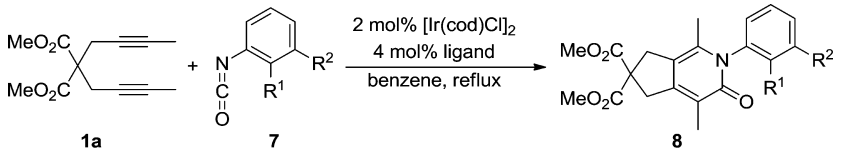
Figure 3. ORTEP drawing of (*R*)-**8aa**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

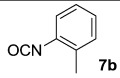
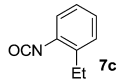
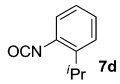
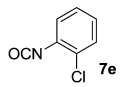
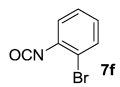
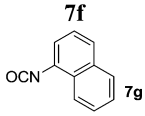
We subjected *o*-substituted isocyanates to the reaction under the optimized conditions described above. (*R*)-BINAP and (*R*)-H_8-BINAP were examined as ligands for each isocyanate. The results are summarized in Table 6. The reaction of *o*-tolyl isocyanate (**7b**) gave **8ab** in 61% yield with 78% ee (entry 2). A change in the substituent at the ortho position from a methyl group to an ethyl group or isopropyl group decreased the yield (entries 3−6), but the enantioselectivity of the reaction with **7d** reached 90% ee (entry 6). *o*-Halophenyl isocyanates underwent cycloaddition to give **8ae** and **8af** in high yields with good enantioselectivities. The reaction was tolerant of the aromatic carbon-halogen bond. The reaction with *o*-chlorophenyl isocyanate (**7e**) gave **8ae** in 83% yield with 87% ee (entry 8). The reaction with *o*-bromophenyl isocyanate (**7f**) gave a slightly lower yield and enantioselectivity than those with *o*-chlorophenyl isocyanate (**7e**) (entries 9 and 10). 1-Naphthyl isocyanate (**7g**) underwent cycloaddition to give **8ag** in 64% yield with 73% ee (entry 11). The enantioselectivities of the reaction with **7a−e** and the yield of **8af** were improved compared to the results with Rh.[19] These results suggest that an Ir catalyst was more enantioselective for constructing C−N axial chirality than a Rh catalyst.

CONCLUSION

In summary, we have developed a new catalyst for the [2+2+2] cycloaddition of α,ω-diynes with isocyanates. The $[Ir(cod)Cl]_2$/BINAP catalyst has a wide range of both diyne and isocyanate substrates. The reaction proceeded under mild conditions to give the corresponding 2-pyridones in high yields.

Table 6. Reaction of 1,6-Diynes (1a) with Isocyanates 7[a]



entry	7	product	ligand	time (h)	yield (%)[b]	ee (%)[c]	lit.[d] yield (%)	lit.[d] ee (%)
1	 **7b**	**8ab**	(*R*)-BINAP	12	70	73	83	30
2	**7b**	**8ab**	(*R*)-H_8-BINAP	24	61	78	–	–
3	 **7c**	**8ac**	(*R*)-BINAP	3	58	76	47	39
4	**7c**	**8ac**	(*R*)-H_8-BINAP	3	45	38	–	–
5	 **7d**	**8ad**	(*R*)-BINAP	1	51	83	41	67
6	**7d**	**8ad**	(*R*)-H_8-BINAP	1	51	90	–	–
7	 **7e**	**8ae**	(*R*)-BINAP	5	82	79	78	56
8	**7e**	**8ae**	(*R*)-H_8-BINAP	3	83	87	–	–
9	 **7f**	**8af**	(*R*)-BINAP	3	73	69	27	87
10	**7f**	**8af**	(*R*)-H_8-BINAP	9	68	77	–	–
11	 **7g**	**8ag**	(*R*)-BINAP	24	64	73	–	–
12	**7g**	**8ag**	(*R*)-H_8-BINAP	24	53	66	–	–

[a]Reaction condition: **1a** (0.5 mmol) and **7** (1.5 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.01 mmol) and ligand (0.02 mmol) in solvent (2.5 mL). [b]Isolated yield. [c]Determined by HPLC. [d]lit. Ref 19a.

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The results described here should lead to new opportunities for the application of organoiridium chemistry in cycloaddition.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were measured at 500 and 125 MHz using TMS as an internal standard. Samples were dissolved in $CDCl_3$. GC analyses were performed using 3.2 mm × 2 m glass columns packed with 5% OV-17 on 60/80 mesh Chromosorb WAW-DMCS. High-resolution mass spectra were obtained by FAB.

Materials. All reagents and solvents were dried and purified before use by the usual procedures. $[Ir(cod)Cl]_2$ was prepared as described previously.[20] Diynes **1a**,[12b] **1b**,[21] **1c**,[22] **1e**,[23] **1f**,[22] **1h**,[21] **1j**,[12b] **1l**,[24] and **1n**[25] were prepared as described in the literature. Diyne **1d** was prepared by reaction of the sodium salt of dimedone with 1-bromo-2-butyne. Diyne **1g** was purchased. Diyne **1i** was prepared by reaction of the sodium salt of dimethyl malonate with propargyl bromide. Diyne **1k** was prepared by Sonogashira reaction of **1j** with iodobenzene. Diyne **1m** was prepared by reaction of **1j** with methyl chloroformate. Diynes **1o** and **1p** were prepared by condensation reaction similar to that for the preparation of **1n**. Isocyanates **2** and **7** were purchased.

Representative Procedure for the Cycloaddition of Diyne (1) with Isocyanate (2). A flask was charged with $[Ir(cod)Cl]_2$ (14.0 mg, 0.02 mmol) and (*R*)-BINAP (24.9 mg, 0.04 mmol). The flask was evacuated and filled with argon. To the flask were added 1,2-dichloropropane (5 mL) and phenyl isocyanate (**2a**) (164 mg, 1.4 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 **3aa** (*n*-hexane/AcOEt = 30/70, 344 mg, 0.97 mmol, 97% yield).

Representative Procedure for the Enantioselective Cycloaddition of Diyne (1a) with Isocyanate (7). A flask was charged with $[Ir(cod)Cl]_2$ (14.0 mg, 0.02 mmol) and (*R*)-H_8-BINAP (24.9 mg, 0.04 mmol). The flask was evacuated and filled with argon. To the flask were added benzene (2.5 mL) and 2-methoxyphenyl isocyanate (**7a**) (164 mg, 1.4 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 **8aa** (*n*-hexane/AcOEt = 30/70, 344 mg, 0.97 mmol, 97% yield).

Spectroscopic data of **3**, **5**, and **8** are as follows.

*Dimethyl 1,4-dimethyl-3-oxo-2-phenyl-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3aa**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.07 (s, 3H), 3.40 (s, 2H), 3.48 (s, 2H), 3.80 (s, 6H), 7.15 (d, J = 7.3 Hz, 2H), 7.42 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 18.2, 37.6, 39.3, 53.2, 59.2, 116.4, 120.7, 128.0, 128.3, 129.5, 136.1, 139.5, 150.0, 164.0, 171.5. HRMS (FAB): calcd for $C_{20}H_{22}NO_5$ ([M + H]$^+$), 356.1498. Found: m/z 356.1500. IR (KBr): 1736, 1666 cm^{-1}.

*Dimethyl 2-(4-methoxyphenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]-pyridine-6,6-dicarboxylate (**3ab**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (s, 3H), 2.06 (s, 3H), 3.39 (s, 2H), 3.47 (s, 2H), 3.79 (s, 6H), 3.84 (s, 3H), 6.99 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 18.2, 37.6, 39.3, 53.1, 55.4, 59.2, 114.8, 116.3, 120.6, 128.9, 132.1, 136.6, 149.9, 159.2, 164.2, 171.5. HRMS (FAB): calcd for $C_{21}H_{24}NO_6$ ([M + H]$^+$), 386.1604. Found: m/z 386.1605. IR (KBr): 1729, 1664 cm^{-1}.

*Dimethyl 1,4-dimethyl-2-(4-methylphenyl)-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ac**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.06 (s, 3H), 2.40 (s, 3H), 3.39 (s, 2H), 3.47 (s, 2H), 3.79 (s, 6H), 7.02 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.2, 21.1, 37.6, 39.3, 53.1, 59.2, 116.3, 120.6, 127.7, 130.2, 136.3, 136.8, 138.2, 149.9, 164.1, 171.5. HRMS (FAB): calcd for $C_{21}H_{24}NO_5$ ([M + H]$^+$), 370.1654. Found: m/z 370.1664. IR (KBr): 1748, 1667 cm^{-1}.

*Dimethyl 2-(4-chlorophenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ae**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.06 (s, 3H), 3.39 (s, 2H), 3.47 (s, 2H), 3.79 (s, 6H), 7.10 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.2, 37.5, 39.3, 53.2, 59.2, 116.7, 120.8, 129.5, 129.8, 134.3, 135.7, 137.9, 150.3, 163.8, 171.4. HRMS (FAB): calcd for $C_{20}H_{21}{}^{35}ClNO_5$ ([M + H]$^+$), 390.1108. Found: m/z 390.1117. IR (KBr): 1745, 1670 cm^{-1}.

*Dimethyl 2-(4-bromophenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3af**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.06 (s, 3H), 3.39 (s, 2H), 3.47 (s, 2H), 3.79 (s, 6H), 7.04 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.2, 37.5, 39.3, 53.2, 59.2, 116.8, 120.8, 122.4, 129.9, 132.8, 135.7, 138.5, 150.3, 163.8, 171.4. HRMS (FAB): calcd for $C_{20}H_{21}{}^{79}BrNO_5$ ([M + H]$^+$), 434.0603. Found: m/z 434.0610. IR (KBr): 1742, 1670 cm^{-1}.

*Dimethyl 1,4-dimethyl-3-oxo-2-(4-trifluoromethylphenyl)-5H-2,3,6,7-tetrahydrocyclopenta[c]-pyridine-6,6-dicarboxylate (**3ag**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.07 (s, 3H), 3.40 (s, 2H), 3.48 (s, 2H), 3.80 (s, 6H), 7.31 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 18.0, 37.4, 39.2, 53.0, 59.1, 116.9, 120.8, 123.6 (q, J_{CF} = 272.5 Hz), 126.6 (q, J_{CF} = 3.8 Hz), 128.8, 130.5 (q, J_{CF} = 32.6 Hz), 135.2, 142.6 (q, J_{CF} = 1.4 Hz), 150.5, 163.6, 171.3. HRMS (FAB): calcd for $C_{21}H_{21}F_3NO_5$ ([M + H]$^+$), 424.1372. Found: m/z 424.1361. IR (KBr): 1740, 1671 cm^{-1}.

*Dimethyl 2-(4-acetylphenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ah**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H), 2.07 (s, 3H), 2.64 (s, 3H), 3.40 (s, 2H), 3.48 (s, 2H), 3.80 (s, 6H), 7.28 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.1, 26.7, 37.5, 39.3, 53.2, 59.2, 116.9, 120.9, 128.6, 129.6, 135.3, 136.9, 143.7, 150.4, 163.7, 171.4, 197.1. HRMS (FAB): calcd for $C_{22}H_{23}NO_6$ ([M]$^+$), 397.1525. Found: m/z 397.1532. IR (KBr): 1735, 1664 cm^{-1}.

*Dimethyl 2-(4-cyanophenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ai**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.06 (s, 3H), 3.40 (s, 2H), 3.48 (s, 2H), 3.80 (s, 6H), 7.32 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.2, 37.4, 39.3, 53.2, 59.1, 112.6, 117.3, 118.0, 121.1, 129.5, 133.5, 134.9, 143.6, 150.8, 163.5, 171.3. HRMS (FAB): calcd for $C_{21}H_{21}N_2O_5$ ([M + H]$^+$), 381.1450. Found: m/z 381.1451. IR (KBr): 1733, 1668 cm^{-1}.

*Dimethyl 1,4-dimethyl-2-(4-nitrophenyl)-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3aj**):* yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (s, 3H), 2.07 (s, 3H), 3.40 (s, 2H), 3.49 (s, 2H), 3.81 (s, 6H), 7.38 (d, J = 9.0 Hz, 2H), 8.37 (d, J = 9.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 18.2, 37.5, 39.3, 53.2, 59.2, 117.4, 121.2, 124.9, 129.7, 134.8, 145.2, 147.6, 150.9, 163.5, 171.3. HRMS (FAB): calcd for $C_{20}H_{20}N_2O_7$ ([M]$^+$), 400.1271. Found: m/z 400.1271. IR (KBr): 1740, 1668 cm^{-1}.

*Dimethyl 2-(n-butyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ak**):* brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.8 Hz, 3H), 1.42 (sextet, J = 7.8 Hz, 2H), 1.63 (quintet, J = 7.8 Hz, 2H), 2.05 (s, 3H), 2.28 (s, 3H), 3.37 (s, 2H), 3.41 (s, 2H), 3.77 (s, 6H), 3.97 (t, J = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 13.7, 16.9, 20.3, 30.6, 37.9, 39.2, 44.7, 53.1, 59.1, 116.6, 120.0, 135.7, 148.8, 163.3, 171.5. HRMS (FAB): calcd for $C_{18}H_{26}NO_5$ ([M + H]$^+$), 336.1811. Found: m/z 336.1817. IR (NaCl, neat): 1735, 1661 cm^{-1}.

*Dimethyl 2-(n-heptyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3al**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.25−1.41 (m, 8H), 1.64 (quintet, J = 7.8 Hz, 2H), 2.05 (s, 3H), 2.28 (s, 3H), 3.37 (s, 2H), 3.41 (s, 2H), 3.77 (s, 6H), 3.96 (t, J = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.0, 16.9, 22.5, 27.0, 28.6, 28.9, 31.7, 37.9, 39.2, 44.9, 53.1, 59.1, 116.6, 120.0, 135.7, 148.8, 163.3, 171.5. HRMS (FAB): calcd for $C_{21}H_{32}NO_5$ ([M + H]$^+$), 378.2280. Found: m/z 378.2276. IR (KBr): 1735, 1663 cm^{-1}.

*Dimethyl 1,4-dimethyl-3-oxo-2-phenylmethyl-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3am**):* white

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solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.18 (s, 3H), 3.36 (s, 2H), 3.45 (s, 2H), 3.77 (s, 6H), 5.32 (s, 2H), 7.14 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.29 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.2, 37.8, 39.3, 47.6, 53.1, 59.1, 116.9, 120.1, 126.5, 127.1, 128.6, 136.4, 137.0, 149.5, 163.8, 171.5. HRMS (FAB): calcd for $C_{21}H_{24}NO_5$ ([M + H]$^+$), 370.1654. Found: m/z 370.1660. IR (KBr): 1735, 1663 cm^{-1}.

*Dimethyl 1,4-dimethyl-3-oxo-2-(2-phenylethyl)-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3an**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.15 (s, 3H), 2.96 (t, J = 7.8 Hz, 2H), 3.34 (s, 2H), 3.43 (s, 2H), 3.77 (s, 6H), 4.17 (t, J = 7.8 Hz, 2H), 7.21–7.25 (m, 3H), 7.28–7.31 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 16.8, 34.6, 37.9, 39.2, 46.7, 53.1, 59.1, 116.7, 120.1, 126.5, 128.5, 128.8, 135.8, 138.6, 149.1, 163.3, 171.5. HRMS (FAB): calcd for $C_{22}H_{26}NO_5$ ([M + H]$^+$), 384.1811. Found: m/z 384.1815. IR (KBr): 1735, 1663 cm^{-1}.

*Dimethyl 2-(2-furyl)methyl-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ao**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.41 (s, 3H), 3.38 (s, 2H), 3.41 (s, 2H), 3.76 (s, 6H), 5.20 (s, 2H), 6.30 (dd, J = 1.8 and 3.2 Hz, 1H), 6.36 (d, J = 3.2 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 17.2, 37.8, 39.2, 40.9, 53.1, 59.1, 109.0, 110.5, 116.8, 120.1, 136.1, 141.8, 149.5, 150.2, 163.3, 171.5. HRMS (FAB): calcd for $C_{19}H_{21}NO_6$ ([M]$^+$), 359.1369. Found: m/z 359.1365. IR (KBr): 1738, 1662 cm^{-1}.

*Dimethyl 1,4-dimethyl-3-oxo-2-(2-propenyl)-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3ap**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.26 (s, 3H), 3.37 (s, 2H), 3.43 (s, 2H), 3.77 (s, 6H), 4.68 (brd, J = 5.0 Hz, 2H), 5.00 (dd, J = 1.4 and 17.4 Hz, 1H), 5.16 (dd, J = 1.4 and 10.5 Hz, 1H), 5.92 (ddt, J = 10.5, 17.4, and 5.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 16.7, 37.8, 39.2, 46.6, 53.1, 59.1, 116.3, 116.7, 120.0, 132.6, 136.1, 149.2, 163.2, 171.5. HRMS (FAB): calcd for $C_{17}H_{22}NO_5$ ([M + H]$^+$), 320.1498. Found: m/z 320.1504. IR (KBr): 1742, 1661 cm^{-1}.

*Dimethyl 2-ethoxycarbonylmethyl-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]- pyridine-6,6-dicarboxylate (**3aq**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 2.06 (s, 3H), 2.20 (s, 3H), 3.39 (s, 2H), 3.43 (s, 2H), 3.77 (s, 6H), 4.23 (q, J = 6.9 Hz, 2H), 4.76 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 14.1, 17.1, 37.7, 39.3, 45.8, 53.1, 59.1, 61.6, 117.0, 120.0, 135.6, 150.0, 163.4, 168.4, 171.4. HRMS (FAB): calcd for $C_{18}H_{23}NO_7$ ([M]$^+$), 365.1475. Found: m/z 365.1469. IR (KBr): 1757, 1735, 1663 cm^{-1}.

*Dimethyl 2-isopropyl-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6- dicarboxylate (**3as**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59 (br, 6H), 2.01 (s, 3H), 2.28 (br, 3H), 3.36 (s, 2H), 3.39 (s, 2H), 3.77 (s, 6H), 4.40 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7 (br), 17.4, 19.1 (br), 37.9, 38.8, 50.8 (br), 52.7, 58.7, 116.6 (br), 120.9 (br), 135.5 (br), 148.1, 163.8, 171.2. HRMS (FAB): calcd for $C_{17}H_{24}NO_5$ ([M + H]$^+$), 322.1654. Found: m/z 322.1648. IR (KBr): 1740, 1663 cm^{-1}.

*Dimethyl 2-cyclohexyl-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6- dicarboxylate (**3at**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.32 (m, 3H), 1.57–1.66 (m, 3H), 1.85–1.87 (m, 2H), 2.00 (s, 3H), 2.26 (br, 3H), 2.85–2.92 (m, 2H), 3.36 (s, 2H), 3.39 (s, 2H), 3.77 (s, 6H), 3.90 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 17.6, 25.0, 26.3, 27.9, 38.1, 39.0, 52.9, 58.9, 60.1, 116.8, 121.3, 135.5, 148.2, 164.0, 171.3. HRMS (FAB): calcd for $C_{20}H_{28}NO_5$ ([M + H]$^+$), 362.1967. Found: m/z 362.1975. IR (KBr): 1738, 1666 cm^{-1}.

*6,6-Diacetyl-2-(n-butyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine (**3bk**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.41 (sextet, J = 7.3 Hz, 2H), 1.62 (quintet, J = 7.3 Hz, 2H), 2.06 (s, 3H), 2.18 (s, 6H), 2.30 (s, 3H), 3.28 (s, 2H), 3.32 (s, 2H), 3.97 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 13.7, 16.9, 20.3, 26.4, 30.6, 34.9, 36.2, 44.7, 73.7, 116.3, 120.1, 136.0, 148.6, 163.2, 203.9. HRMS (FAB): calcd for $C_{18}H_{26}NO_3$ ([M + H]$^+$), 304.1913. Found: m/z 304.1918.

*Methyl 2-(n-butyl)-1,4-dimethyl-3-oxo-6-phenyl-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6- carboxylate (**3ck**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.8 Hz, 3H), 1.42 (sextet, J = 7.8 Hz, 2H), 1.64 (quintet, J = 7.8 Hz, 2H), 2.11 (s, 3H), 2.32 (s, 3H), 3.08 (d, J = 14.9 Hz, 1H), 3.14 (d, J = 16.8 Hz, 1H), 3.63 (s, 3H), 3.79 (d, J = 14.9 Hz, 1H), 3.80 (d, J = 16.8 Hz, 1H), 3.98 (t, J = 7.8 Hz, 2H), 7.28 (t, J = 6.9 Hz, 1H), 7.32–7.37 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 13.7, 16.8, 20.3, 30.7, 40.3, 41.1, 44.7, 52.8, 58.0, 117.6, 120.0, 126.4, 127.3, 128.6, 135.6, 142.0, 149.8, 163.4, 175.3. HRMS (FAB): calcd for $C_{22}H_{28}NO_3$ ([M + H]$^+$), 354.2069. Found: m/z 354.2063.

*2-(n-Butyl)-1,4,5′,5′-tetramethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6-spiro-2′- cyclohexan-1′,3′-dione (**3dk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.41 (sextet, J = 7.3 Hz, 2H), 1.61 (quintet, J = 7.3 Hz, 2H), 2.04 (s, 3H), 2.26 (s, 3H), 2.69 (d, J = 14.2 Hz, 2H), 2.73 (d, J = 14.2 Hz, 2H), 3.21 (s, 2H), 3.26 (s, 2H), 3.96 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 13.7, 16.9, 20.3, 28.0, 28.5, 30.57, 30.61, 36.6, 36.8, 44.6, 51.3, 69.8, 116.3, 119.7, 135.6, 149.0, 163.3, 206.2. HRMS (FAB): calcd for $C_{21}H_{30}NO_3$ ([M + H]$^+$), 344.2226. Found: m/z 344.2224.

*2-(n-Butyl)-1,2′,2′,4-tetramethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6-spiro-5′-(1′,3′-dioxan-4′,6′-dione) (**3ek**):* yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.43 (sextet, J = 7.3 Hz, 2H), 1.64 (quintet, J = 7.3 Hz, 2H), 1.82 (s, 6H), 2.04 (s, 3H), 2.27 (s, 3H), 3.47 (s, 2H), 3.50 (s, 2H), 3.99 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 13.7, 17.1, 20.3, 28.9, 29.0, 30.6, 43.1, 43.6, 44.8, 51.7, 105.3, 115.8, 119.9, 135.7, 148.1, 163.3, 170.2. HRMS (FAB): calcd for $C_{19}H_{26}NO_5$ ([M + H]$^+$), 348.1811. Found: m/z 348.1813.

*Tetraethyl 2-(n-butyl)-1,4-dimethyl-3-oxo-5,6,7,8-tetrahydroisoquinoline-6,6,7,7-tetracarboxylate (**3fk**):* yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.43 (sextet, J = 7.3 Hz, 2H), 1.65 (quintet, J = 7.3 Hz, 2H), 2.10 (s, 3H), 2.31 (s, 3H), 3.21 (s, 2H), 3.30 (s, 2H), 4.07 (brt, J = 7.3 Hz, 2H), 4.18–4.26 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.2, 13.66, 13.68, 14.1, 15.5, 20.3, 30.5, 31.7, 33.0, 45.1, 56.8, 57.0, 60.3, 61.90, 61.94, 109.6, 121.9, 138.3, 141.6, 161.9, 169.5, 169.6. HRMS (FAB): calcd for $C_{27}H_{40}NO_9$ ([M + H]$^+$), 522.2703. Found: m/z 522.2697.

*5-(n-Butyl)-4,7-dimethyl-6-oxo-2-tosyl-1,3,5,6-tetrahydropyrrolo-[3,4-c]pyridine (**3hk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.8 Hz, 3H), 1.39 (sextet, J = 7.8 Hz, 2H), 1.58 (quintet, J = 7.8 Hz, 2H), 1.97 (s, 3H), 2.22 (s, 3H), 2.43 (s, 3H), 3.95 (t, J = 7.8 Hz, 2H), 4.37 (s, 4H), 7.35 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 13.6, 17.0, 20.2, 21.5, 30.5, 44.6, 51.4, 52.2, 113.3, 119.0, 127.5, 129.9, 133.2, 135.6, 143.9, 144.8, 163.0. HRMS (FAB): calcd for $C_{20}H_{27}N_2O_3S$ ([M + H]$^+$), 375.1742. Found: m/z 375.1733.

*Dimethyl 2-(n-butyl)-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]-pyridine-6,6-dicarboxylate (**3ik**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.36 (sextet, J = 7.3 Hz, 2H), 1.70 (quintet, J = 7.3 Hz, 2H), 3.34 (s, 2H), 3.42 (s, 2H), 3.76 (s, 6H), 3.86 (t, J = 7.3 Hz, 2H), 6.40 (s, 1H), 7.11 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 19.8, 31.4, 36.5, 39.7, 49.6, 53.1, 60.6, 114.6, 118.8, 131.2, 154.7, 162.3, 171.0. HRMS (FAB): calcd for $C_{16}H_{22}NO_5$ ([M + H]$^+$), 308.1498. Found: m/z 308.1504.

*Dimethyl 2-(n-butyl)-4-methyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3jk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.36 (sextet, J = 7.3 Hz, 2H), 1.70 (quintet, J = 7.3 Hz, 2H), 2.07 (s, 3H), 3.36 (s, 2H), 3.40 (s, 2H), 3.77 (s, 6H), 3.87 (t, J = 7.3 Hz, 2H), 7.00 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 13.7, 19.9, 31.4, 37.0, 39.0, 50.1, 53.1, 60.3, 118.1, 123.3, 128.1, 150.0, 162.4, 171.3. HRMS (FAB): calcd for $C_{17}H_{24}NO_5$ ([M + H]$^+$), 322.1654. Found: m/z 322.1657.

*Dimethyl 2-(n-butyl)-1-methyl-3-oxo-4-phenyl-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3kk**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.8 Hz, 3H), 1.42 (sextet, J = 7.8 Hz, 2H), 1.68 (quintet, J = 7.8 Hz, 2H), 2.35 (s, 3H), 3.41 (s, 2H), 3.42 (s, 2H), 3.73 (s, 6H), 4.01 (t, J = 7.8 Hz, 2H), 7.27–7.30 (m, 1H), 7.37–7.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

13.7, 17.2, 20.3, 30.5, 37.8, 40.2, 45.0, 53.1, 59.3, 116.9, 124.0, 127.1, 127.9, 129.6, 135.6, 138.2, 149.6, 162.1, 171.3. HRMS (FAB): calcd for $C_{23}H_{27}NO_5$ ([M]$^+$), 397.1889. Found: *m*/*z* 397.1885.

*Dimethyl 2-(n-butyl)-1-methyl-3-oxo-4-trimethylsilyl-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**3lk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.30 (s, 9H), 0.95 (t, *J* = 7.8 Hz, 3H), 1.40 (sextet, *J* = 7.8 Hz, 2H), 1.61 (quintet, *J* = 7.8 Hz, 2H), 2.28 (s, 3H), 3.29 (s, 2H), 3.46 (s, 2H), 3.76 (s, 6H), 3.91 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.4, 13.8, 17.1, 20.3, 30.7, 37.0, 41.5, 44.3, 53.1, 59.1, 117.2, 120.9, 140.0, 159.0, 165.8, 171.6. HRMS (FAB): calcd for $C_{20}H_{32}NO_5Si$ ([M + H]$^+$), 394.2050. Found: *m*/*z* 394.2051.

*Trimethyl 2-(n-butyl)-1-methyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-4,6,6-tricarboxylate (**3mk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.8 Hz, 3H), 1.42 (sextet, *J* = 7.8 Hz, 2H), 1.65 (quintet, *J* = 7.8 Hz, 2H), 2.37 (s, 3H), 3.37 (s, 2H), 3.77 (s, 6H), 3.79 (s, 2H), 3.89 (s, 3H), 3.99 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 17.8, 20.3, 30.2, 37.4, 41.8, 45.1, 51.9, 53.2, 58.7, 113.3, 117.2, 144.2, 157.7, 160.2, 166.4, 171.3. HRMS (FAB): calcd for $C_{19}H_{26}NO_7$ ([M+H]$^+$), 380.1709. Found: *m*/*z* 380.1708.

*5-(n-Butyl)-4,7-dimethyl-6-oxo-5,6-dihydrofuro[3,4-c]pyridin-3(1H)-one (**3nk**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.8 Hz, 3H), 1.46 (sextet, *J* = 7.8 Hz, 2H), 1.66 (quintet, *J* = 7.8 Hz, 2H), 2.04 (s, 3H), 2.81 (s, 3H), 4.10 (t, *J* = 7.8 Hz, 2H), 5.07 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.1, 13.6, 14.2, 20.2, 30.2, 44.7, 66.7, 102.8, 116.9, 149.1, 150.1, 162.8, 169.6. HRMS (FAB): calcd for $C_{13}H_{18}NO_3$ ([M + H]$^+$), 236.1287. Found: *m*/*z* 236.1294.

*5-(n-Butyl)-7-methyl-6-oxo-4-phenyl-5,6-dihydrofuro[3,4-c]-pyridin-3(1H)-one (**3ok**):* white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (t, *J* = 7.8 Hz, 3H), 1.15 (sextet, *J* = 7.8 Hz, 2H), 1.54 (quintet, *J* = 7.8 Hz, 2H), 2.12 (s, 3H), 3.86 (t, *J* = 7.8 Hz, 2H), 5.11 (s, 2H), 7.29−7.31 (m, 2H), 7.51−7.57 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 13.3, 19.9, 30.7, 46.2, 66.6, 103.5, 119.1, 128.2, 128.6, 130.09, 130.11, 149.1, 151.1, 162.7, 167.7. HRMS (FAB): calcd for $C_{18}H_{20}NO_3$ ([M + H]$^+$), 298.1443. Found: *m*/*z* 298.1440.

*5-Butyl-4-methyl-6-oxo-7-phenyl-5,6-dihydrofuro[3,4-c]pyridin-3(1H)-one (**3pk**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.8 Hz, 3H), 1.47 (sextet, *J* = 7.8 Hz, 2H), 1.72 (quintet, *J* = 7.8 Hz, 2H), 2.89 (s, 3H), 4.15 (t, *J* = 7.8 Hz, 2H), 5.11 (s, 2H), 7.33−7.37 (m, 1H), 7.39−7.44 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.6, 20.3, 30.2, 45.2, 67.2, 103.3, 120.7, 128.2, 128.5, 128.7, 133.0, 150.1, 151.9, 161.5, 169.3. HRMS (FAB): calcd for $C_{18}H_{20}NO_3$ ([M + H]$^+$), 298.1443. Found: *m*/*z* 298.1440.

*Tetramethyl 1,1′,4,4′-tetramethyl-3,3′-dioxo-2,2′-hexamethylenebis(5H-2,3,6,7- tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate) (**5**):* brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42−1.48 (m, 4H), 1.62−1.68 (m, 4H), 2.04 (s, 6H), 2.27 (s, 6H), 3.37 (s, 4H), 3.40 (s, 4H), 3.77 (s, 12H), 3.96 (t, *J* = 7.8 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 16.9, 26.6, 28.4, 37.9, 39.2, 44.7, 53.1, 59.1, 116.7, 120.0, 135.7, 148.9, 163.3, 171.5. HRMS (FAB): calcd for $C_{34}H_{45}N_2O_{10}$ ([M + H]$^+$), 641.3074. Found: *m*/*z* 641.3062.

*Dimethyl 2-(2-Methoxyphenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]- pyridine-6,6-dicarboxylate (**8aa**).* A white solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 6.44 min (*S*) and 12.01 (*R*)). $[\alpha]^{30}_D$ −19.7 (*c* 0.50, $CHCl_3$) (94% ee (*R*)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.07 (s, 3H), 3.41 (s, 2H), 3.46 (d, *J* = 17.7 Hz, 1H), 3.51 (d, *J* = 17.7 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 7.02−7.10 (m, 3H), 7.37−7.41 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 17.4, 37.6, 39.4, 53.10, 53.13, 55.7, 59.2, 112.0, 116.1, 120.3, 121.1, 128.0, 129.4, 129.9, 136.7, 150.1, 154.6, 163.6, 171.5, 171.7. HRMS (FAB): calcd for $C_{21}H_{24}NO_6$ ([M + H]$^+$), 386.1604. Found: *m*/*z* 386.1605.

*Dimethyl 1,4-Dimethyl-2-(2-methylphenyl)-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**8ab**).* A white solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 6.28 min (minor) and 7.26 (major)). $[\alpha]^{28}_D$ −52.0 (*c* 1.12, $CHCl_3$) (79% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 3.41 (s, 2H), 3.47 (d, *J* = 17.7 Hz, 1H), 3.52 (d, *J* = 17.7 Hz, 1H), 3.795 (s, 3H), 3.797 (s, 3H), 7.03−7.05 (m, 1H), 7.27−7.34 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 17.3, 17.6, 37.6, 39.3, 53.1, 53.2, 59.2, 116.6, 120.7, 127.2, 127.8, 128.6, 131.1, 135.2, 135.9, 138.6, 150.2, 163.3, 171.5, 171.6. HRMS (FAB): calcd for $C_{21}H_{24}NO_5$ ([M + H]$^+$), 370.1654. Found: *m*/*z* 370.1648.

*Dimethyl 2-(2-Ethylphenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**8ac**).* A yellow solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 5.37 min (minor) and 7.28 (major)). $[\alpha]^{29}_D$ −62.2 (*c* 0.75, $CHCl_3$) (75% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.8 Hz, 3H), 1.80 (s, 3H), 2.08 (s, 3H), 2.29 (dq, *J* = 15.1 and 7.8 Hz, 1H), 2.38 (dq, *J* = 15.1 and 7.8 Hz, 1H), 3.41 (s, 2H), 3.48 (d, *J* = 17.4 Hz, 1H), 3.52 (d, *J* = 17.4 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 7.02 (d, *J* = 7.3 Hz, 1H), 7.27−7.32 (m, 1H), 7.36−7.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 13.3, 17.8, 23.4, 37.6, 39.4, 53.1, 53.2, 59.2, 116.6, 120.7, 127.0, 127.9, 128.8, 128.9, 136.1, 138.0, 140.6, 150.1, 163.5, 171.5, 171.6. HRMS (FAB): calcd for $C_{22}H_{26}NO_5$ ([M + H]$^+$), 384.1811. Found: *m*/*z* 384.1820.

*Dimethyl 2-(2-Isopropylphenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]- pyridine-6,6-dicarboxylate (**8ad**).* A yellow solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 4.80 min (minor) and 6.97 (major)). $[\alpha]^{28}_D$ −71.6 (*c* 0.75, $CHCl_3$) (90% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.80 (s, 3H), 2.07 (s, 3H), 2.56 (septet, *J* = 6.9 Hz, 1H), 3.41 (s, 2H), 3.47 (d, *J* = 17.9 Hz, 1H), 3.52 (d, *J* = 17.9 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 6.99 (d, *J* = 7.3 Hz, 1H), 7.28 (ddd, *J* = 7.8, 7.3, and 1.4 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 7.8 and 1.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 18.0, 23.1, 24.0, 27.9, 37.7, 39.4, 53.1, 53.2, 59.2, 116.4, 120.6, 126.8, 126.9, 127.9, 129.0, 136.3, 137.1, 145.6, 150.0, 163.7, 171.58, 171.63. HRMS (FAB): calcd for $C_{23}H_{28}NO_5$ ([M + H]$^+$), 398.1967. Found: *m*/*z* 398.1967.

*Dimethyl 2-(2-Chlorophenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**8ae**).* A white solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 6.60 min (minor) and 8.28 (major)). $[\alpha]^{29}_D$ −45.5 (*c* 0.90, $CHCl_3$) (87% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.08 (s, 3H), 3.42 (s, 2H), 3.49 (s, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 7.20−7.25 (m, 1H), 7.37−7.42 (m, 2H), 7.52−7.57. (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 17.4, 37.5, 39.3, 53.15, 53.18, 59.2, 116.7, 120.8, 128.0, 129.888, 129.892, 130.4, 132.5, 135.7, 137.2, 150.6, 163.2, 171.3, 171.6. HRMS (FAB): calcd for $C_{20}H_{21}{}^{35}ClNO_5$ ([M + H]$^+$), 390.1108. Found: *m*/*z* 390.1114.

*Dimethyl 2-(2-Bromophenyl)-1,4-dimethyl-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**8af**).* A white solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 6.76 min (minor) and 8.85 (major)). $[\alpha]^{28}_D$ −48.0 (*c* 0.75, $CHCl_3$) (77% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 3H), 2.08 (s, 3H), 3.42 (s, 2H), 3.50 (s, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 7.23 (dd, *J* = 1.4 and 7.8 Hz, 1H), 7.31 (dt, *J* = 1.4 and 7.8 Hz, 1H), 7.45 (dt, *J* = 1.4 and 7.8 Hz, 1H), 7.72 (dd, *J* = 1.4 and 7.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 17.5, 37.5, 39.4, 53.15, 53.18, 59.2, 116.7, 120.9, 122.8, 128.7, 129.9, 130.0, 133.6, 135.6, 138.9, 150.6, 163.1, 171.4, 171.6. HRMS (FAB): calcd for $C_{20}H_{20}{}^{79}BrNO_5$ ([M]$^+$), 433.0525. Found: *m*/*z* 433.0520.

*Dimethyl 1,4-Dimethyl-2-(1-naphthyl)-3-oxo-5H-2,3,6,7-tetrahydrocyclopenta[c]pyridine-6,6-dicarboxylate (**8ag**).* A white solid. The ee value was determined by HPLC analysis with a Chiralpak AY-H column (eluent: *n*-hexane/2-propanol = 50/50, flow rate: 1.0 mL/min, column temperature: 35 °C, retention time: 7.62 min (minor) and 10.79 (major)). $[\alpha]^{29}_D$ −108.4 (*c* 0.34, $CHCl_3$) (73% ee).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (s, 3H), 2.11 (s, 3H), 3.45 (s, 2H), 3.56 (s, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 7.32−7.36 (m, 2H), 7.44−7.51 (m, 2H), 7.55−7.58 (m, 1H), 7.90−7.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 17.5, 37.6, 39.4, 53.185, 53.192, 59.2, 116.7, 120.8, 122.0, 125.6, 125.9, 126.4, 127.4, 128.4, 129.0, 129.9, 134.4, 136.2, 136.8, 150.4, 164.0, 171.55, 171.60. HRMS (FAB): calcd for $C_{24}H_{24}NO_5$ ([M + H]$^+$), 406.1654. Found: m/z 406.1654.

X-ray Crystallographic Studies of 3lk. Colorless crystals of **3lk** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2/*n*-hexane. A single crystal was mounted using liquid paraffin on a 0.4−0.5 mm CryoLoop (Hampton Research) and used for data collection. All measurements were made on a Bruker APEX II CCD area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software.[26] An ORTEP drawing is shown in Figure 1. The details of crystal and data collection parameters are summarized in Supporting Information. The analysis was carried out using Yadokari-XG.[27] The program ORTEP3[28] was used to generate the X-ray structural diagrams.

X-ray Crystallographic Studies of 3mk. Yellow crystals of **3mk** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2/*n*-hexane. A single crystal was mounted using liquid paraffin on a 0.4−0.5 mm CryoLoop (Hampton Research) and used for data collection. All measurements were made on a Bruker APEX II CCD area detector with graphite monochromated Mo-Ka radiation. The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least-squares against F^2 using SHELXL-97 software.[26] An ORTEP drawing is shown in Figure 2. The details of crystal and data collection parameters are summarized in Supporting Information. The analysis was carried out using Yadokari-XG.[27] The program ORTEP3[28] was used to generate the X-ray structural diagrams.

X-ray Crystallographic Studies of 8aa. Colorless crystals of **8aa** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2/*n*-hexane. A single crystal was mounted using Paratone-N (Hampton Research) on a 200 μm MicroMount (MiTeGen) and used for data collection. All measurements were made on a Rigaku R-AXIS RAPID II with a VariMax Cu diffractometer using graphite monochromated Cu Kα radiation. The structure was solved by direct methods with SIR2008[29] and refined by full-matrix least-squares against F^2 using SHELXL-97[26] software. The absolute structure was deduced on the basis of the Flack parameter.[30] An ORTEP drawing is shown in Figure 3. The details of crystal and data collection parameters are summarized in Supporting Information. All calculations were performed using the CrystalStructure[31] crystallographic software package except for refinement, which was performed using SHELXL-97.[26] The program ORTEP3[28] was used to generate the X-ray structural diagrams.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of **3aa**−**at**, **3bk**−**ek**, **3fk**−**ik**, **3jk**−**pk**, **5**, **8aa**−**ag** and single-crystal X-ray diffraction data of compounds **3mk**, **3nk** and **8aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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