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Iridium(III)-Catalyzed Tandem [3 + 2] Annulation: Synthesis of Spirocyclic Phosphoramide Derivatives

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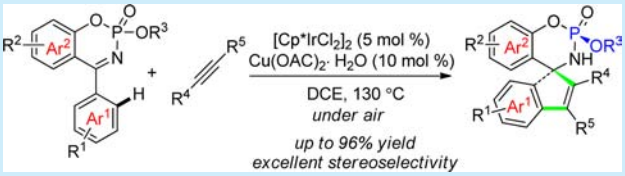
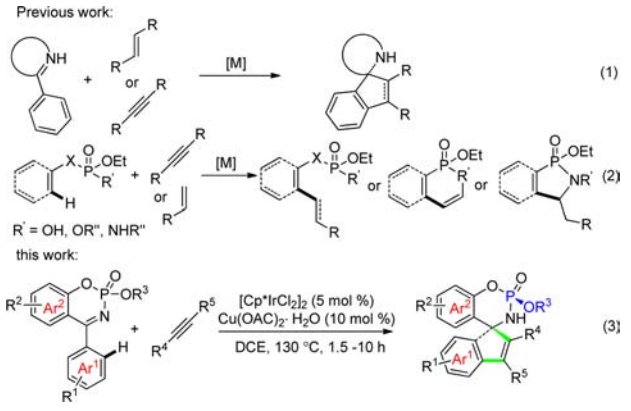
Supporting Information

ABSTRACT: A highly efficient iridium(III)-catalyzed C−H activation/tandem Grignard-type [3 + 2] annulation process was developed for the synthesis of novel spirocyclic phosphoramide derivatives. Compared with other transition-metal catalysts, $[Cp^*IrCl_2]_2$ exhibited favorite efficiency and best selectivity in this cascade reaction. The strategy could be applied to further construct more complex heterocyclic compounds.



The [3 + 2] cyclization reaction is a common strategy in the construction of C−C and C−heteroatom bonds to access complex structures.[1] Especially with the rapid development of the C−H activation reaction,[2] transition-metal-catalyzed [3 + 2] cyclization reaction has been widely explored in the past decade.[3] This approach is advantageous in that the amazing spirocyclic products,[4] which are otherwise difficult to synthesize, possess one of the most fascinating building structural motifs present in many natural products and biologically active molecules.[5] However, imines have found limited applications as directing groups for a metal-catalytic [3 + 2] tandem reaction sequence via direct C−H bond functionalization (Scheme 1, eq 1).[6]

Scheme 1. Transition-Metal-Catalyzed *Ortho* C−H Activation



Therefore, it is necessary to expand the scope of imines for Grignard-type [3 + 2] annulation.

Organophosphorus compounds not only exhibit unique biological and pharmacological activities[7] but also play key roles in organocatalysts.[8] Although several synthetic approaches for the construction of organophosphorus molecules using phosphamides or phosphates as directing groups have been described in recent years (Scheme 1, eq 2),[9] *N*-phosphoryl ketimines serving as both directing groups and electrophiles have been utilized to suffer from the Grignard-type [3 + 2] annulation, and formation of spirocyclic organophosphorus compounds has never been reported. Hence, we now disclose a novel synthesis of unique spirocyclic phosphoramide derivatives through an iridium(III)-catalyzed C−H activation/tandem Grignard-type [3 + 2] annulation process between cyclic *N*-phosphoryl ketimines and internal alkynes (Scheme 1, eq 3). This reaction proceeds with high efficiency and excellent stereoselectivity via an iridium(III) catalyst compared with ruthenium(II) and rhodium(III) catalysts.

At the outset of our study, we used cyclic *N*-phosphoryl ketimine **1a** and diphenylacetylene **2a** as model substrates to investigate the catalytic performance of different transition metals (Table 1). To our surprise, $[Cp^*RhCl_2]_2$ as a catalyst showed very high catalytic reactivity, generating the desired [3 + 2] cycloaddition product **3a** in 99% yield but albeit with very bad stereoselectivity (entry 1), while a single isomer **3a** was produced with moderate yields by using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst (entries 2 and 3). In contrast, $[Cp^*IrCl_2]_2$ showed most suitable reactivity, affording **3a** in good yield together with excellent stereoselectivity (entry 4). By careful analysis of the cascade reaction outcomes with these metal catalysts, $[Cp^*IrCl_2]_2$ was shown to exhibit favorite efficiency and best selectivity for this cascade [3 + 2] annulation, probably owing to the large ionic radius of iridium(III). This advantage intrigued us to perform further screening with $[Cp^*IrCl_2]_2$ as optimal catalyst. Increasing the reaction temperature and decreasing the loading of $Cu(OAc)_2{\cdot}H_2O$ was good for improving

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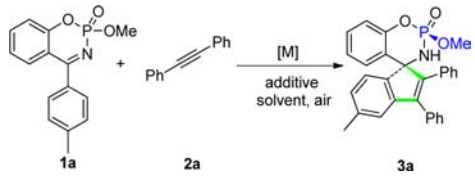
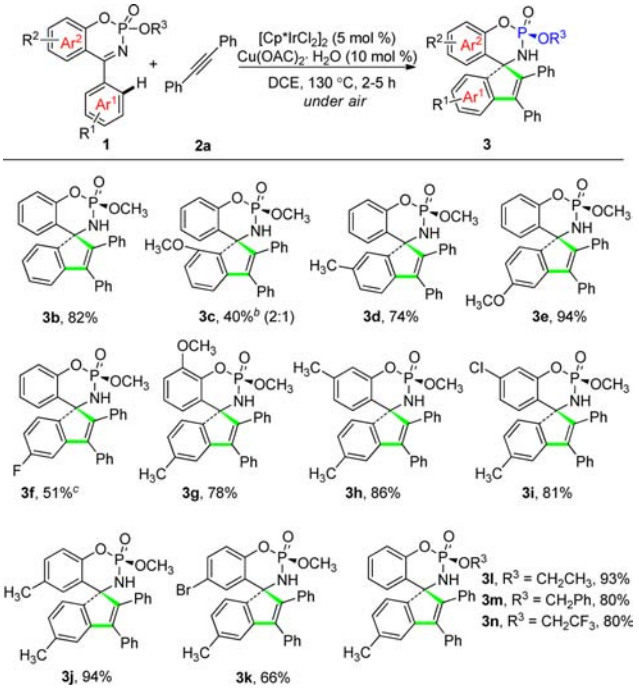
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive (equiv)	solvent	yield[b] (%)
1[c,d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	99 (1:1)
2[c]	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	32
3[c]	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.5)	DCE	40
4[c]	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.5)	DCE	76
5	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.5)	DCE	83
6	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	DCE	84
7	**$[Cp^*IrCl_2]_2$**	**$Cu(OAc)_2{\cdot}H_2O$ (0.1)**	**DCE**	**90**
8	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.05)	DCE	89
9[e]	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DCE	80
10[f]	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	DCE	84
11	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	toluene	NP
12	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	CH_3CN	58
13	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$ (0.1)	dioxane	NP
14	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$(0.1)	DMF	56
15	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$(0.1)	$CHCl_3$	40

[a]Reaction conditions unless otherwise specified: 0.05 mmol of **1a**, 1.2 equiv of **2a**, 5 mol % of catalyst, 0.5 mL of solvent, 130 °C, under air. [b]Isolated yield. [c]120 °C. [d]Stereoselectivity (1:1) has been detected, major isomer is shown. [e]2 mol % of $[Cp^*IrCl_2]_2$. [f]140 °C.

Scheme 2. Substrate Scope of the Cyclic *N*-Phosphoryl Ketimines[a]



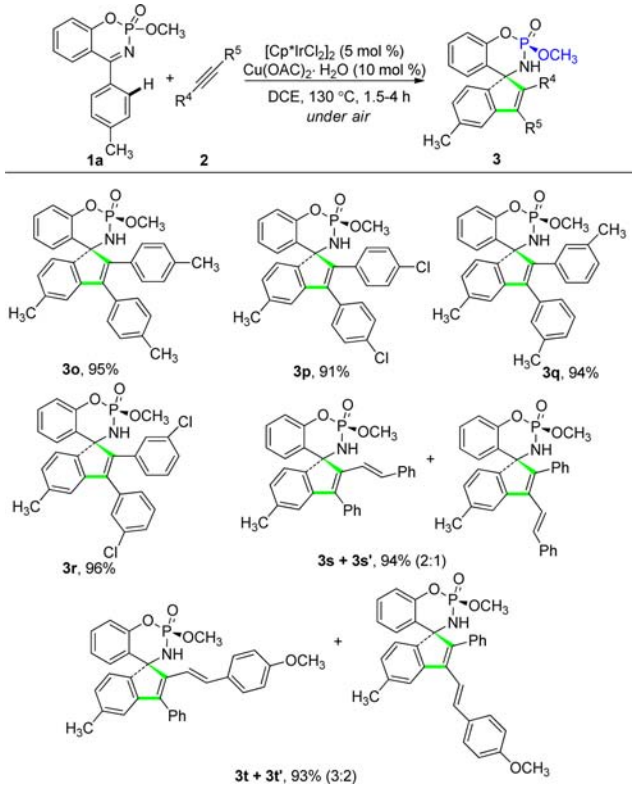
[a]Reaction conditions unless otherwise specified: 0.05 mmol of **1**, 1.2 equiv of **2a**, 5 mol % of $[Cp^*IrCl_2]_2$, 10 mol % of $Cu(OAc)_2{\cdot}H_2O$, 0.5 mL of DCE, 130 °C, under air, 1.5 h−10 h. Isolated yield, dr >99:1. [b]Stereoselectivity (2:1) has been detected; major isomer is shown. [c]5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 50 mol % of $Cu(OAc)_2{\cdot}H_2O$, 30 h.

the reaction efficiency (entries 5−7). However, further lowering the use of $Cu(OAc)_2{\cdot}H_2O$ to 0.05 equiv led to slightly lower yield (entry 8). Reducing the loading of $[Cp^*IrCl_2]_2$ or elevating the reaction temperature gave rise to a lower yield (entries 9 and 10). The subsequent solvent screening revealed that other solvents gave inferior results (entries 11−15).

Under the optimized reaction conditions, a variety of electronically and sterically diverse aryl-substituted *N*-phosphoryl ketimines **1** were examined using **2a** as a coupling partner to investigate the generality of the iridium(III)-catalyzed tandem [3 + 2] annulation (Scheme 2). Notably, *N*-phosphoryl ketimines **1** bearing substituents on the *ortho*, *meta*, and *para* positions of the Ar^1 ring were well tolerated in the reaction. The annulated product **3c** was only isolated in moderate yield albeit with poor stereoselectivity, probably due to the steric hindrance. As expected, the C−H activation process occurred at the less hindered position with the desired product **3d** obtained as the single product. Interestingly, the substrate **1f** with *p*-fluorine was invalid in the optimal conditions by using iridium(III) as catalyst, whereas the desired product **3f** could be constructed in 51% yield when ruthenium(II) was explored as catalyst. Delightfully, *N*-phosphoryl ketimines **1** carrying electron-donating or -withdrawing groups on the Ar^2 ring allowed the reaction to proceed smoothly, affording the corresponding products in good to excellent yields (**3g−k**). In addition, other phosphate esters such as ethyl, benzyl, and CH_2CF_3 esters (**1l−n**) also exhibited high reactivity in this catalytic system.

Subsequently, the scope of alkynes was investigated (Scheme 3). Remarkably, symmetrically substituted diarylacetylenes carrying

Scheme 3. Substrate Scope and Limitation of Alkynes[a]



[a]Reaction conditions unless otherwise specified: 0.05 mmol of **1a**, 1.2 equiv of **2**, 5 mol % of $[Cp^*IrCl_2]_2$, 10 mol % of $Cu(OAc)_2{\cdot}H_2O$, 0.5 mL of DCE, 130 °C, under air, 1.5 h −4 h. Isolated yield, dr >99:1.

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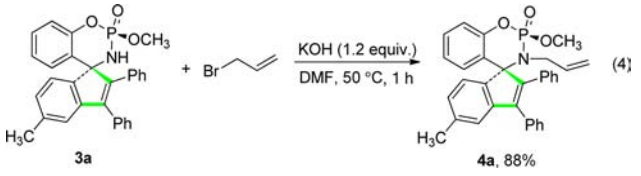
methyl or chlorine at the *para* and *meta* positions were good coupling partners, giving the spirocyclic products in excellent yields (**3o−r**). However, the alkyl-disubstituted alkynes and dimethyl acetylenedicarboxylate were completely incompatible with the standard conditions. To our delight, the unsymmetrical eneynes (**2s** and **2t**) were suitable for this transformation, delivering the corresponding products with extended conjugated dienes in high yields albeit with low regioselectivity.

The synthetic utility of spirocyclic phosphoramide derivatives was illustrated in Scheme 4 in which the versatile **3a** could be installed a useful allyl group (Scheme 4, eq 4).

Scheme 4. Synthetic Application of 3a



In summary, we have successfully achieved a novel synthesis of unique spirocyclic phosphoramide derivatives from cyclic *N*-phosphoryl ketimines and alkynes. Importantly, $[Cp^*IrCl_2]_2$ exhibited the high efficiency and excellent selectivity in this C−H activation/tandem Grignard-type [3 + 2] annulation process. Further transformation these spirocyclic molecules to other useful organophosphorus compounds is underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01895.

Experimental procedures, structural proofs, and NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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