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Generation of Rhodium(I) Carbenes from Ynamides and Their Reactions with Alkynes and Alkenes

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Abstract

Rh(I) carbenes were conveniently generated from readily available ynamides. These metal carbene intermediates could undergo metathesis with electron-rich or neutral alkynes to afford 2-oxo-pyrrolidines or be trapped by tethered alkenes to yield 3-azabicyclo[3.1.0]hexanes, a common skeleton in numerous bioactive pharmaceuticals. Although the scope of the former is limited, the latter reaction tolerates various substituted alkenes.

Metal carbene is one of the most important intermediates in organic synthesis and it is involved in numerous reactions such as cyclopropanation, C-H insertion, dipolar cycloaddition, and metathesis reactions.[1] The most frequently used method for the preparation of metal carbenes is the decomposition of diazo compounds or related derivatives. Considering the hazardous and potential explosive nature of diazo compounds, other alternative carbene precursors are highly desirable. Recently, readily available ynamides[2,3] have emerged as a versatile carbene precursor, and in particular, oxidation of ynamide **1** by dimethyl dioxirane (DMDO)[4] or other oxidants[5] was shown to afford the push-pull α-oxo carbene **3** through the oxirene intermediate **2** (Scheme 1). Interestingly, a complementary α-oxo gold carbene **5** (M = Au) was formed *via* intermediate **4**, in the presence of gold catalysts and mild external oxidants (e.g. pyridine *N*-oxide).[6,7]

We envision that the choice of metal catalysts and ligands may have significant impact on the reactivity of carbene **5**. We herein report that α-oxo Rh(I)-carbene **5** (M = Rh) can be generated from ynamides **6** or **7** and these Rh(I) carbenes then react with the tethered alkyne or alkene to afford heterocycles **8** or **9**, respectively (eq 1). In contrast, keto-imide **10** was often the predominant product observed by us and others in the presence of gold(I) catalysts.[6]

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Supporting Information

Detailed experimental procedures, characterization and spectra data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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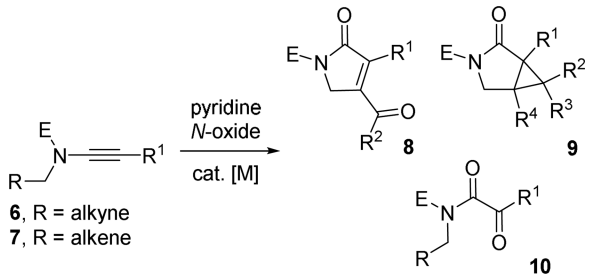
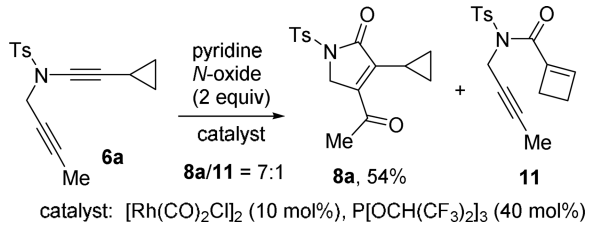


(1)

Our interest in the chemistry of cyclopropyl metal carbenes[8] and π-acidic Rh(I) complexes[9] prompted us to investigate the possibility of generating Rh(I) carbenes[10] from ynamide **6a** for cycloisomerization reactions. We prepared ynamide **6a** and treated it with pyridine *N*-oxide and a complex of $[Rh(CO)_2Cl]_2$/$P[OCH(CF_3)_2]_3$ (eq 2), which was shown to successfully promote acyloxy migration of propargylic esters,[11] a process that was typically catalyzed by π-acidic transition metals.[9,12] Compound **8a** was isolated as the major product and cyclobutene **11** was also observed as the minor product. A metal carbene similar to intermediate **5** was presumably generated from ynamide **6a** through the mechanism shown in Scheme 1. Ring expansion of this metal carbene intermediate would produce cyclobutene **11**.[8]



(2)

When the cyclopropyl group was replaced by other substituents, the formation of cyclobutene can be avoided and a 62% yield of cycloisomerization product **8b** was obtained from diyne **6b** under conditions employed for diyne **6a** (entry 1, Table 1). The structure of product **8b** was unambiguously assigned by X-ray analysis.[13] The oxidative cycloisomerization of diyne **6b** was then optimized under different conditions. Keto-imide **12b** appeared when the phosphite ligand was removed (entry 2).[14] Other ligands produced worse results (entries 3 and 4). No reaction occurred using $Rh_2(OAc)_4$ as the catalyst (entry 5). Interestingly, only keto-imide **12b** was observed when gold catalyst was employed (entry 6). $PtCl_2$ catalyst provided a complex mixture (entry 7). We then examined different substituted pyridine *N*-oxides, such as *p*-methoxy-, *p*-nitro-, 2,6-dichloro-, and 3,5-dichloropyridine *N*-oxides. Among them, 3,5-dichloropyridine *N*-oxide provided the best result (entry 8). Among all solvents that we screened, dioxane afforded the highest yield (entry 9). No desired product was obtained when other rhodium complexes, such as $[Rh(COD)Cl]_2$, Wilkinson's catalyst, and $[Rh(COD)BF_4]$ were employed.

With the optimized condition in hand, the scope of oxidative cycloisomerization of diyne **6** was investigated (Table 2). The yield of product **8c** became slightly lower than that of **8b** when R^2 was a phenyl group. Both R^1 and R^2 could tolerate aryl groups with an *ortho*

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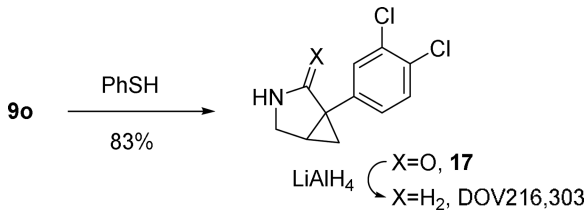
substituent (substrates **6d** and **6e**). When R^2 was an electron-deficient aryl group (e.g. *p*-ClC_6H_4, *p*-$NO_2C_6H_4$), a complex mixture was obtained. When R^2 was a methyl group in substrate **6f**, diene **13** was isolated in 10% yield. When R^1 was hydrogen in substrate **6g**, the carbene became more reactive and the reaction could be carried out at even room temperature. When R^1 was an alkyl group in substrate **6h**, 1,2-hydrogen migration product **14** was observed. For substrates **6i** and **6j** with a more functionalized R^1 or R^2 substituent, complex mixtures were observed.

We then examined the reactivity of α-oxo Rh(I) carbenes towards alkenes (Table 3). Under previously optimized conditions for oxidative cycloisomerization of diynes, cyclopropanation product **9a** was obtained in a 78% yield from enyne **7a**. No improvement was observed after screening different Rh(I) complexes, ligands, or other substituted pyridine *N*-oxides. When $Au(PPh_3)Cl$ /AgOTf was employed as the catalyst, keto-imide **15a** was isolated as the major product together with small amount of cyclopropane **9a**. No reaction occurred when $Rh_2(OAc)_4$ was used as the catalyst.

The scope of oxidative cycloisomerization of enyne **7** was then investigated. For terminal ynamides **7b–7e**, the reaction could be conducted at room temperature. Among them, terminal alkene **7b** produced the best yield. A 70% yield was obtained for cyclopropanation of non-substituted styrene **7c**. For diyne **6**, R^2 needs to be an electron-neutral or -rich aryl group to allow the oxidative cycloisomerization to proceed. On the other hand, it has been shown that α-oxo Rh(I) carbene derived from 1,2-acyloxy migration of propargylic esters only reacts with electron-deficient alkynes or alkenes.[15] To our delight, both electron-rich and electron-poor styrenes underwent cyclopropanation to form bicyclic products **9d** and **9e**, respectively. It is worth to point out that a nitro group, which has been used as external oxidant in gold catalysis,[7r] can be tolerated.

Alkene and ether functionalities can be tolerated for the R^1 substituent in substrate **7f**. When R^1 in substrate **7g** was an alkyl group, surprisingly, hydrolysis product **16** was obtained. A complex mixture was observed when an olefin functional group was introduced to substrate **7h**. Alkenes with a *gem*-dimethyl substituent or a methyl group on the internal position participated in the cyclopropanation and yielded products **9i** and **9j**, respectively. A six-atom tether could also be tolerated and bicyclic product **9k** was prepared in a 78% yield.



(3)

Nosyl group is generally easier to be removed than tosyl group.[16] We were pleased to find that yields for products **9l** and **9m** were comparable to their tosyl counterparts **9a** and **9b**. The nosyl group in products **9o** was removed smoothly under mild conditions to yield compound **17** (eq 3),[16] which is the precursor for triple reuptake inhibitor DOV216,303.[17,18] The 3-azabicyclo[3.1.0]hexane skeleton[19] is also present in numerous other pharmaceuticals with broad biological activities, such as analgesic, antibacterial, and inhibition of aromatase.[17,20]

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The mechanism for the oxidative cycloisomerization of diynes and enynes is proposed in Scheme 2. Metal carbenes **18** and **21** can be generated from ynamides **6** or **7b**, respectively, following the mechanism shown in Scheme 1. Metathesis of metal carbene **18** with the tethered alkyne through metallacyclobutene **19** may afford a new carbene **20**,[21] which can be oxidized by pyridine *N*-oxide to yield product **8**. When R^1 or R^2 was an alkyl group, 1,2-hydrogen migration produced small amount of byproducts **14** or **13**, respectively. DFT calculations indicate that the barrier for the conversion of **18** to **20** is 20.7 kcal/mol and this process can take place at room temperature.[13] Rh(I) carbene **21** may react with the tethered alkene to form product **9b** in two pathways: I) a concerted cyclopropanation; II) a metathesis followed by reductive elimination through intermediate **22**. DFT calculations suggest that pathway I is preferred since the reductive elimination of intermediate **22** in pathway II is relatively difficult.[13]

In summary, we have developed an efficient method for the generation of α-oxo Rh(I) carbenes from ynamides.[10] We demonstrated that $[Rh(CO)_2Cl]_2/P[OCH(CF_3)_2]_3$ complex was acidic enough to mediate the addition of external oxidant to ynamides under mild conditions. The Rh(I) carbenes produced from this process can then react with electron-rich or neutral alkynes or various substituted alkenes to afford heterocycles 2-oxo-pyrrolidines and 3-azabicyclo[3.1.0]-hexanes, respectively. Further studies on the novel reactivity of Rh(I) carbenes are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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13. See Supporting Information for details.

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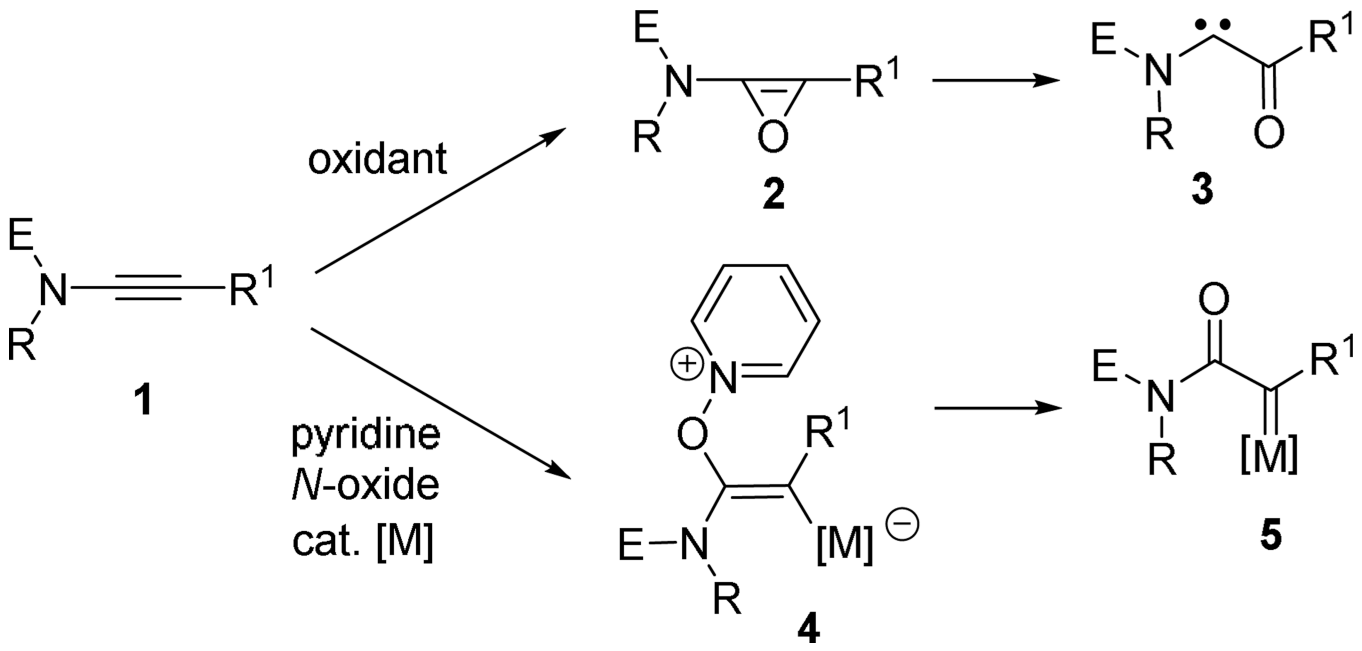

Scheme 1.
Complementary Carbenes from Ynamides

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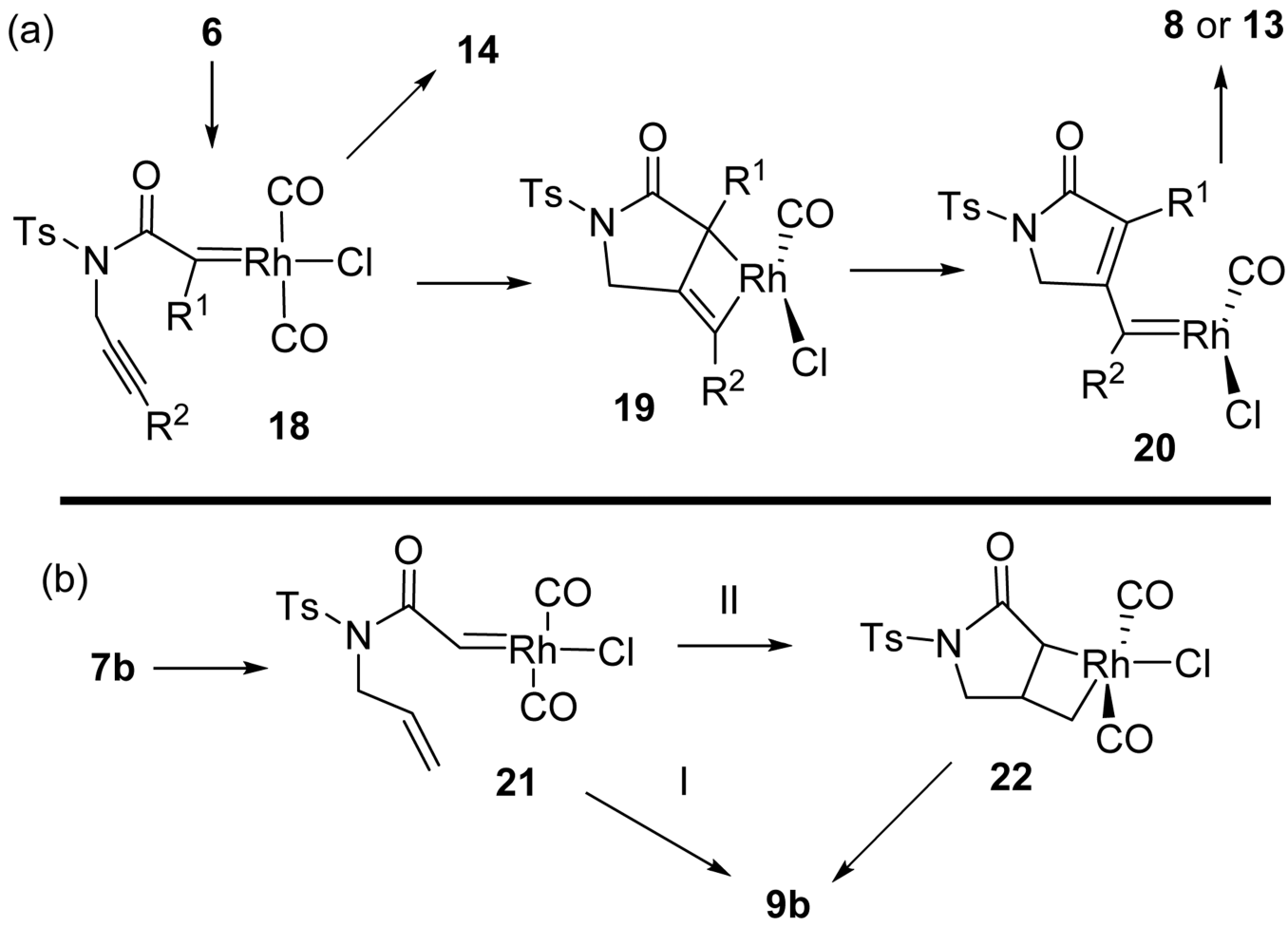

Scheme 2.
Proposed Mechanism for Oxidative Cycloisomerization of Diynes (a) and Enynes (b)

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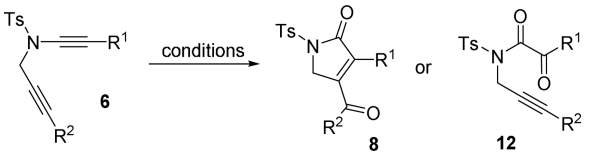
Table 1

Screening of Conditions for the Oxidative Cycloisomerization of Diyne 6[a]



6b, **8b**, and **12b**: R^1 = Ph, R^2 = *p*-$MeOC_6H_4$

Entry	Conditions	8b / 12b[b]	Yield[c]
1	$[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%)	1 : 0	62%
2	$[Rh(CO)_2Cl]_2$ (5 mol%)	5 : 1	-
3	$[Rh(CO)_2Cl]_2$ (5 mol%), $P(OPh)_3$ (20 mol%)	no reaction	
4	$[Rh(CO)_2Cl]_2$ (5 mol%), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (20 mol%)	5 : 1	-
5	$Rh_2(OAc)_4$ (5 mol%)	no reaction	
6	$Au(PPh_3)Cl$ (10 mol%), AgOTf (10 mol%)	0 : 1	-
7	$PtCl_2$ (5 mol%)	complex mixture	
8[d]	See entry 1 for catalyst	1 : 0	70%
9[d,e]	See entry 1 for catalyst	1 : 0	78%

[a] Conditions: pyridine *N*-oxide (3 equiv), $ClCH_2CH_2Cl$, 80 °C, 4h, unless noted otherwise.

[b] The ratio was determined by ^1H NMR of crude product.

[c] Isolated yield of **8b**.

[d] 3,5-dichloropyridine *N*-oxide (3 equiv) was used as the oxidant.

[e] Dioxane was used as the solvent.

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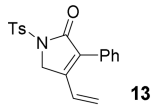
Table 2

Oxidative Cycloisomerization of Diynes[a]

Substrate 6	Product	Yield[b]
6c, R^1 = Ph, R^2 = Ph	8c,	67%
6d, R^1 = Ph, R^2 = *o*-$MeOC_6H_4$	8d,	76%
6e, R^1 = *o*-FC_6H_4, R^2 = *p*-$MeOC_6H_4$	8e,	75%
6f, R^1 = Ph, R^2 = Me	8f + 13	56% (10%)[c]
6g,[d] R^1 = H, R^2 = *p*-$MeOC_6H_4$	8g,	80%
6h, R^1 = $PhCH_2CH_2CH_2$, R^2 = *p*-$MeOC_6H_4$	8h + 14	67% (11%)[e]
6i, R^1 = H, R^2 = $CH_2OCH_2CH{=}CH_2$	complex mixture	
6j, R^1 = $CH{=}CHCH_2OCH_2CH{=}CH_2$, R^2 = *p*-$MeOC_6H_4$	complex mixture	

byproducts:



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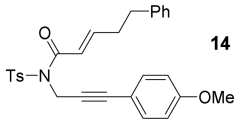

14

[a] Conditions: $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%), 3,5-dichloropyridine *N*-oxide (3 equiv), dioxane, 80 °C, 4h.

[b] Isolated yields.

[c] Yield of byproduct **13**.

[d] rt, 3h.

[e] Yield of byproduct **14**.

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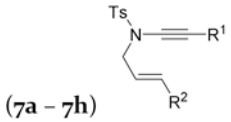
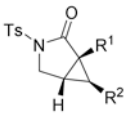
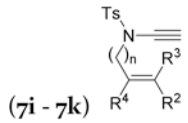
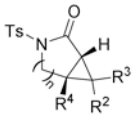
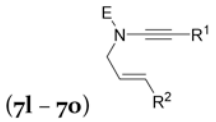
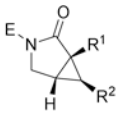
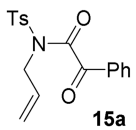
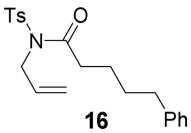
Table 3

Oxidative Cycloisomerization of Enynes[a]

Substrate 7	Product	Yield[b]
 (7a – 7h)	 (9a – 9h)	
7a,[c] R^1 = Ph, R^2 = H	9a,	78%
7b, R^1 = H, R^2 = H	9b,	88%
7c, R^1 = H, R^2 = Ph	9c,	70%
7d, R^1 = H, R^2 = *p*-$MeOC_6H_4$	9d,	62%
7e, R^1 = H, R^2 = *p*-$NO_2C_6H_4$	9e,	63%
7f,[c] R^1 = $CH=CHCH_2OBn$, R^2 = H	**9f**,	78%
7g,[c] R^1 = $(CH_2)_3Ph$, R^2 = H	**16**,	68%
7h, R^1 = H, R^2 = $CH_2OCH_2CH=CH_2$	complex mixture	
 (7i - 7k)	 (9i - 9k)	
7i, R^2 = R^3 = CH_3, R^4 = H, n=1	9i,	87%
7j, R^2 = R^3 = H, R^4 = CH_3, n=1	9j,	72%
7k, R^2 = R^3 = R^4 = H, n=2	9k,	78%
 (7l – 7o)	 (9l – 9o)	
7l, E = *p*-Ns, R^1 = H, R^2 = H	9l,	80%
7m [c] E = *p*-Ns, R^1 = Ph, R^2 = H	9m,	76%
7n,[c] E = *p*-Ns, R^1 = *p*-$CH_3C_6H_4$, R^2 = H	9n,	60%
7o,[c] E = *o*-Ns, R^1 = 3,4-$Cl_2C_6H_3$, R^2 = H	9o,	81%
byproducts:  **15a**	 **16**	

[a] Conditions: $[Rh(CO)_2Cl]_2$ (5 mol%), $P[OCH(CF_3)_2]_3$ (20 mol%), 3,5-dichloropyridine *N*-oxide (1.0 equiv), dioxane, rt., 2h.

[b] Isolated yields.

[c] 80 °C, 4–8 h.