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Synthesis of 5*H*-chromeno[3,4-*c*]pyridine derivatives through ruthenium-catalyzed [2+2+2] cycloaddition

William Parisot,^a Steve Huvelle,^a Mansour Haddad,^a Guillaume Lefèvre,^a Phannarath Phansavath,^a Virginie Ratovelomanana-Vidal^{a*}

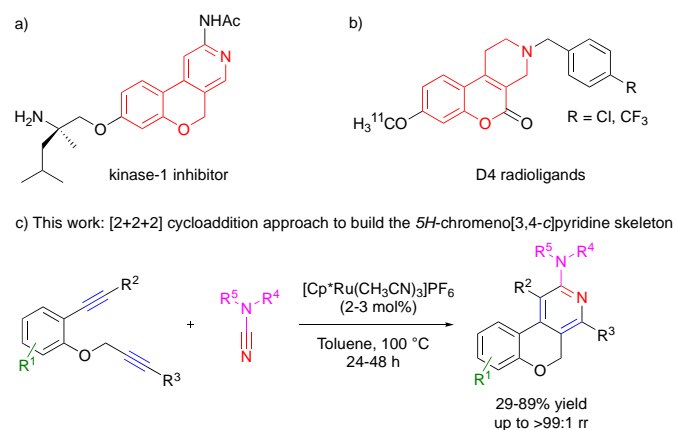
Valuable 5*H*-Chromeno[3,4-*c*]pyridines were conveniently prepared through ruthenium-catalyzed [2+2+2] cycloaddition of diversely substituted α,ω -diynes with various cyanamides. The reaction was highly regioselective and tolerated a wide range of 1-ethynyl-2-(prop-2-yn-1-yloxy)benzene derivatives and cyanamides providing 32 new tricyclic pyridines that can serve as building blocks for further functionalization and enable access to a biologically relevant intermediate.

Introduction

Chromenopyridines constitute an important class of structurally diverse molecules displaying a variety of biological and pharmaceutical properties, such as antibiotic, antiallergical, or antipsychotic activities.¹ In particular, chromeno[3,4-*c*]pyridines appear as promising candidates in medicinal chemistry. For example, a series of functionalized 5*H*-chromeno[3,4-*c*]pyridines recently proved to be an efficient dual ROCK1 and ROCK2 inhibitor (Scheme 1a).² In this case, the nature of the functional chain bound to the chromenopyridine unit plays a key role in the ROCK inhibition process. ¹³C-labeled radioligands involving chromeno[3,4-*c*]pyridin-5-one scaffolds were also used in *in vivo* PET studies for analysis of the dopamine D4 receptor subtype (Scheme 1b).³ It is of note that several 2,4-diaryl chromeno[3,4-*c*]pyridin-5-ones were also used as ruthenium(II) ligands to afford complexes with enhanced spectral absorption properties.⁴ From a synthetic standpoint, multicomponent one-pot procedures have been reported for the synthesis of chromeno[2,3-*b*]pyridines,⁵ relying on tandem Knoevenagel condensations followed by nucleophilic additions. Similarly, tetrahydro-5*H*-chromeno[2,3-*b*]pyridines can be obtained by reaction of benzaldehydes, malonitrile and cyclohexanediones.⁶ Recent protocols of synthesis of chromeno[4,3-*b*]pyridines involving cyclocondensations under high pressure conditions were also reported.⁷ However, the reported strategies for accessing the regioisomer skeleton 5*H*-chromeno[3,4-*c*]pyridine are more scarce. An example of functionalized 5*H*-chromeno[3,4-*c*]pyridine was synthesized from flavan-4-ones by a Vilsmeier-Haack / malonitrile addition sequence.⁸ Condensation of trinitriles with ammonium acetate was also used to access functionalized 5-oxo-5*H*-chromeno[3,4-*c*]pyridines.⁹ Other recent multicomponent methods

to access 5*H*-chromeno[3,4-*c*]pyridin-5-ones were also reported, using 4-chloro-3-(trifluoroacetyl) and heterocyclic amines in 2-step methods.¹⁰ Two reliable routes for the construction of the pyrane ring in 5*H*-chromeno[3,4-*c*]pyridines were also reported, involving

either S_NAr or Williamson etherification as key steps.^{2b} In addition to the aforementioned strategies relying on the multistep construction of *N*-containing ring in the 5*H*-chromeno[3,4-*c*]pyridine skeleton, the building of (hetero)aromatic rings by [2+2+2] cycloadditions is an extremely appealing tool since it allows the introduction of a high structural diversity in a single, atom-economic step.¹¹ Moreover, the cross-cyclization of 1,7-diynes with nitrile derivatives has already proved to be a powerful strategy for the obtention of functionalized aminopyridine substrates. As a continuation of our investigations on transition metal-catalyzed cycloaddition,¹² we hypothesized that novel 5*H*-chromeno[3,4-*c*]pyridines could be obtained through ruthenium-catalyzed [2+2+2] cycloaddition reactions. To the best of our knowledge, such an approach has not been reported so far (Scheme 1c).



Scheme 1 Examples of biologically active compounds containing the 5*H*-chromeno[3,4-*c*]pyridine (a, see ref. 2b) or the chromeno[3,4-*c*]pyridin-5-one (b, see ref. 3) scaffolds; (c) synthetic approach reported in this work: formation of 5*H*-chromeno[3,4-*c*]pyridines by [2+2+2] cycloaddition between 1,7-diynes and cyanamides.

A large scope of functionalized α,ω -diynes has been used, showing that a broad functional tolerance can be encompassed. Gram-scale and post-functionalization reactions on several cycloadducts are also described, making the process reported herein suitable for multistep high-scale syntheses.

Results and discussion

We started our study by investigating the [2+2+2] cycloaddition of 1-ethynyl-2-(prop-2-yn-1-yloxy)benzene **1a** and dimethylcyanamide **2a** using various transition metal complexes (Table 1). The reaction was first carried out in toluene at 100 °C with the ruthenium complex [Cp*RuCl]₄ (2 mol %). These conditions led to full conversion after 24 h with the formation of cycloadduct **3aa** as a single regioisomer albeit with a moderate isolated yield of 43% (Table 1, entry 1). However, under the same reaction conditions, the use of [Cp*Ru(CH₃CN)₃]PF₆ (5 mol %) provided the desired 5*H*-chromeno[3,4-*c*]pyridine **3aa** in 83% yield with a high regioisomeric ratio of 96:4 (Table 1, entry 2). [Cp*Ru(cod)Cl] was less efficient affording a yield of 37% for **3aa** (Table 1, entry 3) whereas RuCl₃·*n*H₂O only gave a conversion of 58% (Table 1, entry 4). Although the rhodium and iridium complexes [Rh(cod)Cl]₂ and [Ir(cod)Cl]₂ afforded a complete conversion, no formation of the expected cycloadduct was observed in these cases (Table 1, entries 5 and 6).

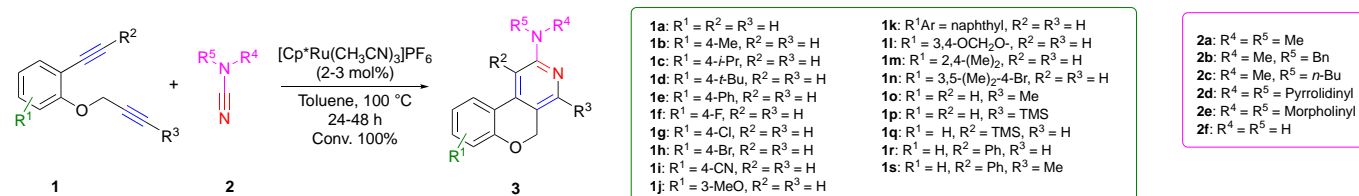
Table 1 Optimization of the reaction conditions for the metal-catalyzed [2+2+2] cycloaddition of diyne **1a** and cyanamide **2a**^a

Entry	Catalyst (mol %)	Solvent/T (°C)	Conv (%)	Yield (%)	3aa:3aa' ratio
1	[Cp*RuCl] ₄ (2)	toluene/100	100	43	>99:1
2	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (5)	toluene/100	100	83	96:4
3	[Cp*Ru(cod)Cl] (5)	toluene/100	92	37	>99:1
4	RuCl ₃ · <i>n</i> H ₂ O (5)	toluene/100	58	33	92:8
5	[Rh(cod)Cl] ₂ (5)	toluene/100	100	0	–
6	[Ir(cod)Cl] ₂ (5)	toluene/100	100	0	–
7	In(OTf) ₃ (5)	toluene/100	0	0	–
8	Fe(acac) ₃ (5)	toluene/100	0	0	–
9	FeSO ₄ (5)	toluene/100	0	0	–
10	[Cp ₂ Ni] (5), Xantphos (10), Cs ₂ CO ₃ (100)	toluene/100	0	0	–
11	CpCo(CO) ₂ (5)	toluene/100	26	21	76:24
12	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	toluene/100	100	84	96:4
13	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	DCE/80	54	40	97:3
14	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	DCM/50	43	26	97:3
15	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	EtOH/80	10	9	92:8
16	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	MeTHF/80	71	61	96:4
17	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (2)	toluene/90	95	77	96:4
18	[Cp*Ru(CH ₃ CN) ₃]PF ₆ (1)	toluene/100	62	61	96:4

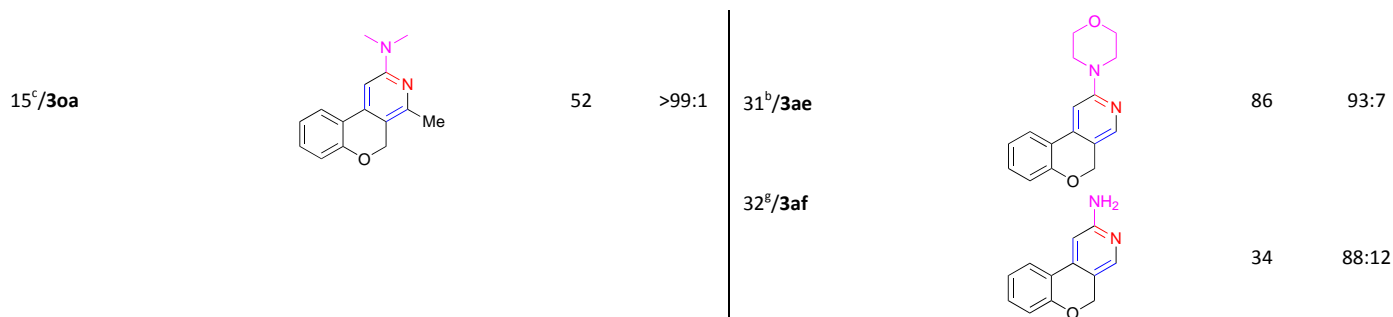
^a Reaction conditions: diyne **1a** (0.64 mmol, 100 mg), cyanamide **2a** (0.96 mmol, 1.5 equiv.), catalyst (1-5 mol %), solvent (0.3 M), 50-100 °C, 24 h.

On the other hand, the cycloaddition did not occur with In(OTf)₃, Fe(acac)₃, FeSO₄ or [Cp₂Ni]/Xantphos (Table 1, entries 7-10). The cobalt-catalyzed reaction using CpCo(CO)₂ not only led to a low yield

of 21% but the regioisomeric ratio **3aa:3aa'** was affected as well, dropping to 76:24 (Table 1, entry 11). We next decreased the catalyst loading of [Cp*Ru(CH₃CN)₃]PF₆ to 2 mol % and pleasingly, the reaction afforded results comparable to those observed with 5 mol % of the ruthenium complex (Table 1, entry 12 vs entry 2). A survey of solvents was then carried out and toluene proved to be the most suitable solvent for the cycloaddition since DCE, DCM, EtOH, and 2-MeTHF were less effective and led to conversions of only 10-71% (Table 1, entries 13-16). A decrease of the reaction temperature to 90 °C or of the catalyst loading to 1 mol % had a detrimental impact on the conversion and **3aa** was isolated 77% and 61% yields, respectively (Table 1, entries 17 and 18). Consequently, the optimized reaction conditions were established as follows: diyne **1a** (1 equiv.), cyanamide **2a** (1.5 equiv.), [Cp*Ru(CH₃CN)₃]PF₆ (2 mol %) as the catalyst, toluene (0.3 M) at 100 °C. Applying these conditions, we first evaluated the scope of the [2+2+2] cycloaddition by exploring the combination of a series of diversely substituted α,ω -diynes **1** with various cyanamides **2**, namely dimethylcyanamide **2a**, *N*-benzyl-*N*-methyl cyanamide **2b**, *N*-butyl-*N*-methyl cyanamide **2c**, pyrrolidine cyanamide **2d**, morpholine cyanamide **2e** and cyanamide **2f** (Table 2). The transformation proved to be very general and numerous functional groups were tolerated. The [2+2+2] cycloaddition was first investigated with dimethylcyanamide **2a** and a range of 1-ethynyl-2-(prop-2-yn-1-yloxy)benzene derivatives **1a-1i** bearing either no substituent, or electron-donating (Me, *i*-Pr, *t*-Bu) and withdrawing (Ph, F, Cl, Br, CN) substituents in the 4-position of the benzene ring. The corresponding cycloadducts **3aa-3ia** were produced in 69-89% yields with high regioselectivities observed in all cases, from 91:9 to 96:4 *rr* (Table 2, entries 1-9). It should be noted that the structure of the major regioisomer **3aa** was unambiguously assigned by X-ray crystallographic analysis. On the other hand, the ruthenium-catalyzed cycloaddition of 1-ethynyl-3-methoxy-2-(prop-2-yn-1-yloxy)benzene **1j**, 1-ethynyl-2-(prop-2-yn-1-yloxy)naphthalene **1k**, or 5-ethynyl-6-(prop-2-yn-1-yloxy)benzo[*d*][1,3]dioxole **1l** with **2a** regioselectively delivered the desired polycyclic pyridines **3ja**, **3ka**, **3la** in 57-74% yields and regioisomeric ratios of 89:11 to 98:2 (Table 2, entries 10-12). 1-Ethynyl-3,5-dimethyl-2-(prop-2-yn-1-yloxy)benzene **1m** carrying two methyl substituents on the benzene ring proved to be a suitable partner for this reaction since the corresponding 5*H*-chromeno[3,4-*c*]pyridine derivative **3ma** was obtained in 82% yield and 96:4 *rr* (Table 2, entry 13). Unsurprisingly and because cycloaddition is expected to be affected by the steric hindrance, the formation of **3na** incorporating a pentasubstituted benzene was more troublesome and the [2+2+2] cycloaddition proceeded in only 9% yield under the standard reaction conditions, and in 29% when using 5 mol% of the catalyst (Table 2, entry 14). To further evaluate the scope of the reaction, we examined internal diynes as coupling partners.

Table 2 Substrate scope of the ruthenium-catalyzed [2+2+2] cycloaddition of diene **1** and cyanamide **2**

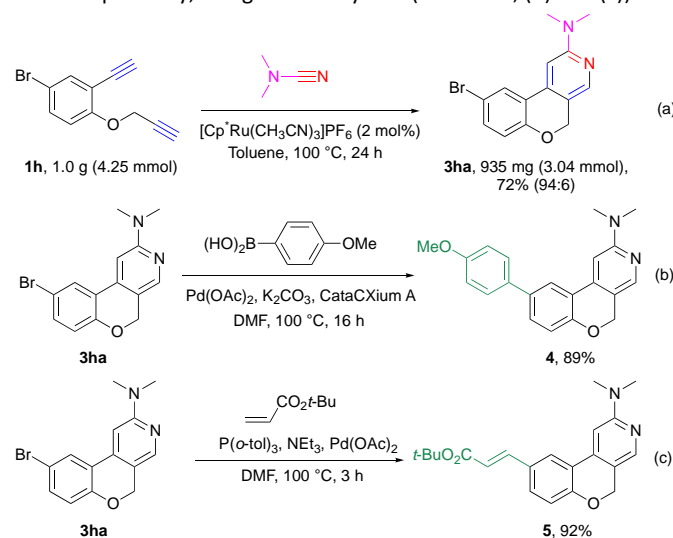
Entry	Compound	Yield (%) ^d	rr ^e	Entry	Compound	Yield (%) ^d	rr ^e
1 ^a / 3aa	R ¹ = H	84	96:4	16 ^a / 3ab	R ¹ = H	85	96:4
2 ^a / 3ba	R ¹ = 4-Me	87	96:4	17 ^a / 3cb	R ¹ = 4- <i>i</i> -Pr	43	92:8
3 ^a / 3ca	R ¹ = 4- <i>i</i> -Pr	81	95:5	18 ^a / 3gb	R ¹ = 4-Cl	74	93:7
4 ^a / 3da	R ¹ = 4- <i>t</i> -Bu	89	96:4	19 ^a / 3hb	R ¹ = 4-Br	81	94:6
5 ^a / 3ea	R ¹ = 4-Ph	88	94:6	20 ^a / 3lb		82	97:3
6 ^a / 3fa	R ¹ = 4-F	76	91:9	21 ^b / 3ac		65	95:5
7 ^a / 3ga	R ¹ = 4-Cl	69	91:9	22 ^a / 3ad	R ¹ = H	79	96:4
8 ^a / 3ha	R ¹ = 4-Br	78	94:6	23 ^a / 3bd	R ¹ = 4-Me	86	96:4
9 ^a / 3ia	R ¹ = 4-CN	78	91:9	24 ^b / 3dd	R ¹ = 4- <i>t</i> -Bu	77	94:6
10 ^a / 3ja		57	97:3	25 ^b / 3ed	R ¹ = 4-Ph	71	92:8
11 ^b / 3ka		67	89:11	26 ^a / 3fd	R ¹ = 4-F	83	94:6
12 ^a / 3la		74	98:2	27 ^b / 3id	R ¹ = 4-CN	77	93:7
13 ^a / 3ma		82	96:4	28 ^b / 3jd		68	97:3
14 ^f / 3na		29	59:41	29 ^b / 3kd		54	89:11
				30 ^b / 3md		78	96:4



^aConditions: diyne **1** (0.3–0.8 mmol), cyanamide **2** (1.5 equiv.), [Cp**Ru*(CH₃CN)₃]PF₆ (2 mol %), toluene (0.3 M), 100 °C, 24 h. ^b[Cp**Ru*(CH₃CN)₃]PF₆ (3 mol %), toluene, 100 °C, 48 h. ^c[Cp**Ru*(CH₃CN)₃]PF₆ (2 mol %), toluene, 100 °C, 120 h. ^dIsolated yield with complete conversion. ^eDetermined by ¹H NMR of the crude product after cycloaddition. ^f[Cp**Ru*(CH₃CN)₃]PF₆ (5 mol %), toluene, 100 °C, 64 h. ^g[Cp**Ru*(CH₃CN)₃]PF₆ (5 mol %), 2-MeTHF, 80 °C, 120 h.

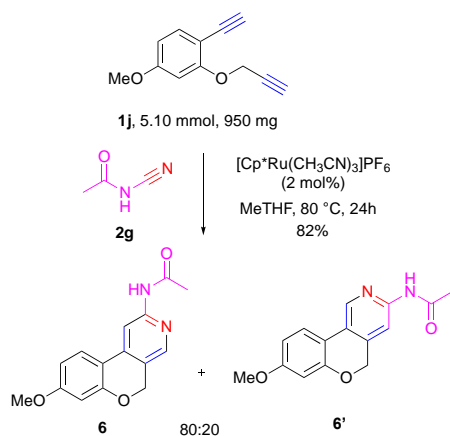
In this context, the cycloaddition was extended to an internal diyne bearing a methyl group at one end (**1o**, R² = H, R³ = Me) and provided the tetrasubstituted pyridine **30a** in 52% yield and an excellent regioselectivity of >99:1 (Table 2, entry 15). However, replacing the methyl substituent with the more sterically demanding trimethylsilyl group (**1p**, R¹, R² = H, R³ = TMS) had a detrimental impact and the expected product was isolated in only 8% yield (not shown). Positioning the trimethylsilyl group or a phenyl substituent on the other end of the diyne (**1q**, R¹ = H, R² = TMS, R³ = H and **1r**, R¹ = H, R² = Ph, R³ = H) did not allow the formation of the corresponding cycloadducts and the reaction of diyne **1s** (R¹ = H, R² = Ph, R³ = Me) bearing two internal alkynes also failed. The Ru-catalyzed cycloaddition was next examined by varying the substitution pattern on the cyanamide partner. Thus, reacting *N*-benzyl-*N*-methylcyanamide **2b** with variously substituted 1,7-diyne under the optimized conditions afforded the tricyclic pyridines in 43–85% yields with regioisomeric ratios ranging from 92:8 to 97:3 (Table 2, entries 16–20). The use of *N*-butyl-*N*-methylcyanamide **2c** in this reaction was less efficient than with its congeners **2a** or **2b** and the cycloadduct **3ac** was formed in a lower yield of 65% (Table 2, entry 21). On the other hand, pyrrolidine-1-carbonitrile **2d** proved to be an effective partner for the reaction that proceeded in 54–86% yields with *rr* values ranging from 89:11 to 97:3 (Table 2, entries 22–30). Finally, compound **3ae** bearing a morpholinyl substituent on the pyridine ring was successfully synthesized in 86% yield starting from morpholine cyanamide **2e** (Table 2, entry 31). Interestingly, the use of the non-protected cyanamide **2f** also allowed the formation of the corresponding tricyclic product although in a moderate yield of 34% and a *rr* value of 88:12 (Table 2, entry 32). Having established the scope of the reaction with respect to α,ω -diyne components, we turned our attention to post-functionalizations of the new valuable polycyclic products as well as to a scale-up of this transformation. The efficiency of the ruthenium-catalyzed [2+2+2] cycloaddition was indeed supported by a gram-scale experiment that was carried out with diyne **1h** and dimethylcyanamide **2a** under the optimized conditions. The reaction afforded the expected cycloadduct **3ha** in 72% yield and a regioisomeric ratio of 94:6, values comparable to those observed on smaller scale (Scheme 2, (a)). Moreover, the newly synthesized 5*H*-chromeno[3,4-*c*]pyridines can serve as useful

intermediates for further decoration on the benzene ring. For instance, **3ja** was subjected to Pd-catalyzed Suzuki-Miyaura and Heck cross-coupling reactions affording the targeted compounds **4** and **5** respectively, in high 89–92% yields (Scheme 2, (b) and (c)).



Scheme 2 Gram-scale and post-functionalization reactions

Finally, to further explore the synthetic methodology, the developed procedure was applied to the synthesis of the pharmaceutically relevant intermediate **6** of a potent inhibitor of AAK1 developed by Bristol Meyer Squibb.^{2b} Satisfyingly, the reaction provided **6** as a separable mixture of the 2 regioisomers **6** and **6'** in 82% yield and a regioisomeric ratio of 80:20 (Scheme 3).



Scheme 3 Application to the synthesis of the pharmaceutically relevant intermediate **6**

Conclusions

In summary, we have reported an efficient access to 5*H*-chromeno[3,4-*c*]pyridines that relies on the ruthenium-catalyzed [2+2+2] cycloaddition of 1-ethynyl-2-(prop-2-yn-1-yloxy)benzene derivatives with cyanamides. This atom-economical transformation was highly regioselective and produced the desired cycloadducts in yields up to 89% from a wide range of α,ω -diynes and cyanamides. Diversely functionalized 5*H*-chromeno[3,4-*c*]pyridines derivatives were readily prepared using this method that could be efficiently transposed to gram-scale. The process allowed the synthesis of 32 novel 5*H*-chromeno[3,4-*c*]pyridines. Moreover, the various tricyclic pyridines can serve as valuable building blocks for further post-functionalization reactions and enabled access to a biologically relevant intermediate.

Experimental

Typical procedure for the [2+2+2] cycloaddition: a sealed tube was charged with $[\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3]\text{PF}_6$ (6.5 mg, 1.28×10^{-2} mmol, 0.02 equiv.) and dimethylcyanamide **2a** (76 μL , 0.96 mmol, 1.5 equiv.) was added. Under argon a solution of diyne **1a** (100 mg, 640 μmol , 1.0 equiv.) in 1.8 mL of anhydrous toluene was added. The tube was sealed, and the reaction mixture was stirred vigorously at 100 °C for 24 h. When the reaction was complete, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , petroleum ether/EtOAc 80:20), then the excess of cyanamide was distilled off with a Kugelrohr distillation apparatus, affording **3aa** as a pale-brown oil (121 mg, 535 μmol , 84%).

Author Contributions

WP and SH contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

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