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ARTICLE

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Aldiyar Shakenov, Krishna Prasad Gnyawali and Chae S. Yi*

The Ru–H complex $(PCy_3)_2(CO)RuHCl$ (**1**) was found to be a highly effective catalyst for the three-component deaminative coupling reaction of anilines with aldehydes and allylamines to form 2,3-disubstituted quinoline products. The analogous coupling reaction of anilines with aldehydes and cyclic enamines led to the selective formation of the tricyclic quinoline derivatives. The reaction profile study showed that the imine is initially formed from the dehydrative coupling of aniline and aldehyde, and it undergoes the deaminative coupling and annulation reaction with amine substrate to form the quinoline product. The catalytic coupling method provides a step-efficient synthesis of 2,3-disubstituted quinoline derivatives without employing any reactive reagents or forming wasteful byproducts.

Introduction

Catalytic deaminative coupling methods using simple amines and amino group containing compounds as reagents have attracted considerable attention in recent years in part because these amino substrates are readily obtained from biomass-derived feedstocks and the coupling methods would be driven by the formation of ammonia and amine byproducts.[1] Most notably, Katritzky salts, which are readily prepared from the condensation reaction of pyrylium salts with simple amines, have been found to be versatile electrophilic reagents for a variety of deaminative C–C cross coupling reactions under both thermal and photocatalytic conditions.[2] Suzuki-Miyaura type of deaminative cross coupling methods of arylamines via direct arene $C(sp^2)$–N bond cleavage have also been successfully employed for the synthesis of a variety of elaborated arene products.[3] Garg[4] and Szostak[5] groups independently developed Ni-catalyzed coupling methods via amide C–N bond cleavage to synthesize a variety of amides and related nitrogen containing products. Martin group also reported site-selective Ni-catalyzed deaminative alkylation of unactivated olefins by using pyridinium salts,[6] and the group subsequently devised a highly enantioselective version of the alkylation reaction of unactivated olefins.[7] Recently, a number of photocatalytic deaminative methods have been successfully developed for chemoselective alkylation and arylation reactions from using amines and amides.[8] Despite such remarkable advances, however, catalytic deaminative coupling methods using simple amines have been seldomly employed in synthesis of complex organic molecules.

The Povarov reaction, which is a multicomponent coupling reaction of aniline, benzaldehyde and an electron-rich alkene, has been found to be a particularly efficient synthetic method for quinoline products.[9] In recent years, a variety of Povarov-type of coupling methods of imines with olefins and their surrogate substrates have been developed by using Lewis acid and transition metal catalysts as well as photocatalysts for the synthesis of substituted quinoline derivatives.[10] A number of asymmetric version of the Povarov reaction have been developed for enantioselective synthesis of tetrahydroquinoline and related chiral nitrogen heterocyclic products.[11] A one-pot Povarov-type of coupling reaction has also been successfully employed to synthesize quinoline-linked covalent organic framework materials.[12]

We recently discovered that the cationic Ru-H complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ with a redox active catechol/benzoquinone ligand is an effective catalyst system for a number of deaminative coupling reactions of simple amines to form oxygen and nitrogen heterocyclic products.[13] We also used the same catalytic system to promote the deaminative coupling reactions of 2-aminophenyl ketones and 2-aminobenzamides with amines to form flavanone and quinazolinone derivatives, respectively.[14] As part of on-going efforts to extend synthetic applicability of the deaminative coupling methods, we have been exploring the feasibility of multi-component deaminative coupling reactions of arenes and carbonyl compounds with simple amines. Herein, we report a Ru-catalyzed three-component deaminative coupling method of anilines and aldehydes with allylamines, which leads to an efficient formation of substituted quinoline derivatives without employing any reactive reagents or forming toxic byproducts.

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233 United States. chae.yi@marquette.edu

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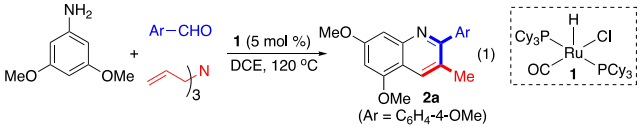
Results and discussion

We initially discovered that both the cationic and neutral Ru–H complexes $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ and $(PCy_3)_2(CO)RuHCl$ (**1**) are effective catalysts for the three-component coupling reaction of 3,5-dimethoxyaniline, 4-methoxybenzaldehyde and triallylamine to form the 2,3-disubstituted quinoline product **2a** (eq 1). The subsequent catalyst screening and optimization efforts established that the neutral Ru–H complex **1** exhibited the highest activity among screened Ru catalysts in yielding the quinoline product **2a** (Table 1). The screening of a variety of acid, base or benzoquinone additives did not significantly improve the product yields (entries 2-4), and the cationic Ru–H complexes generally exhibited lower catalytic activity than the neutral ones (entries 5-9).



We surveyed substrate scope for the three-component coupling reaction by using the standard conditions as established in Table 1. In general, electron-rich anilines were found to be suitable substrates for the coupling reaction with aryl-substituted aldehydes and triallylamine in yielding the 2,3-disubstituted quinoline products **2a**-**j**. In contrast, no quinoline product was formed with electron-deficient anilines, even though the formation of imine was detected in the reaction mixture (*vide infra*). In most cases, aryl-substituted aldehydes were found to give the quinoline products from the coupling reaction with 3,5-dimethoxyaniline and triethylamine, but the coupling reaction with cyclohexanecarbaldehyde also gave the quinoline product **2f** in a modest yield. *Para*-substituted benzaldehydes with both electron-donating and electron-withdrawing group were found to be suitable substrates for the coupling reaction with 3,5-dimethoxyaniline and triallylamine to form the quinoline products **2a**-**e**. A scale-up reaction of 3,5-dimethoxyaniline (3.0 mmol), 4-(trifluoromethyl)benzaldehyde (3.0 mmol) and triallylamine (3.0 mmol) led to the isolation of the product **2e** in 56% yield (0.58 g). It should also be emphasized that the analogous reaction with either allylic alcohol or allyl acetate instead of allylamine did not give any quinoline products under otherwise similar conditions.

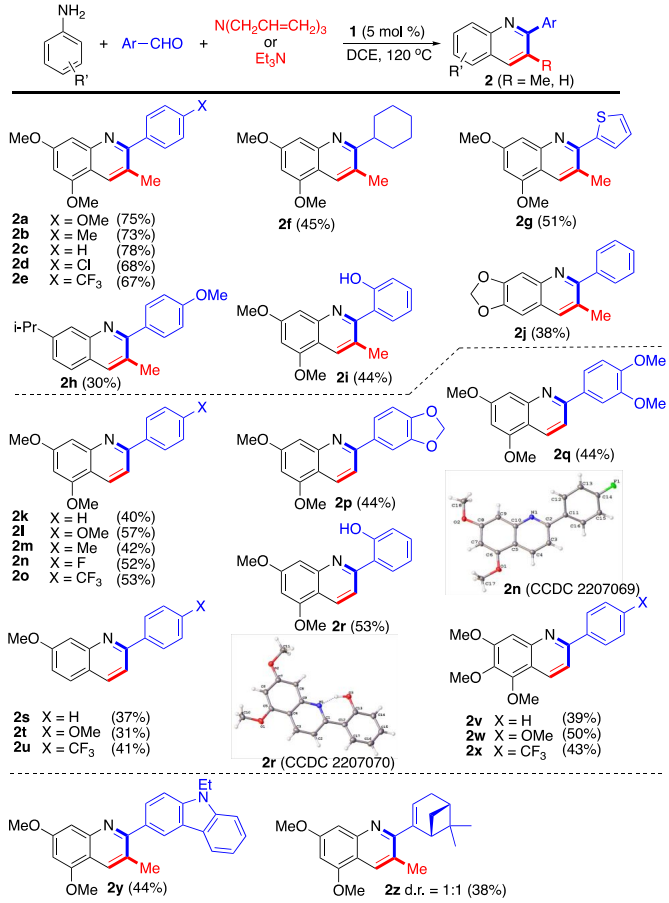
Table 1. Catalyst Screening for the Coupling Reaction of 3,5-Dimethoxyaniline, 4-Methoxybenzaldehyde and Triallylamine.[a]

entry	catalyst	additive (mol %)	**2a** (%)[b]
1	**1**		78
2	**1**	BQ (10 mol %)[c]	20
3	**1**	$HBF_4{\cdot}OEt_2$ (10 mol %)	<5
4	**1**	AgOAc (30 mol %)	<5
5	$[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$		33
6	$[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$		30
7	$[(PCy_3)(CO)RuH]_4(O)(OH)_2$		26
8	$[(p\text{-cymene})RuCl_2]_2$		40
9	$(PPh_3)_3RuCl_2$		43
10	$Ru_3(CO)_{12}$		27
11	$[(COD)RuCl_2]_x$		0
12	$(PPh_3)_3(CO)RuH_2$		0
13	$AlCl_3$		0
14	PCy_3		<5

[a] Reaction conditions: 3,5-dimethoxyaniline (0.3 mmol), catalyst (5 mol %), 4-methoxybenzaldehyde (0.3 mmol), triallylamine (0.3 mmol) 1,2-dichloroethane (1.5 mL), 120 °C, 20 h. [b] The product yield was determined by GC-MS using hexamethylbenzene as an internal standard. [c] BQ = 3,4,5,6-tetrachloro-1,2-benzoquinone.

In an effort to extend the amine substrate scope, we explored the reactivity of both saturated and unsaturated amines and found that triethylamine is a suitable substate for the deaminative coupling reaction. Thus, the coupling reaction of electron-rich anilines such as 3,5-dimethoxyaniline and 3,4,5-trimethoxyaniline with benzaldehydes and triethylamine under the standard conditions led to the selective formation of 2-substituted quinoline products **2k-x**. Unfortunately, the analogous reaction with tertiary amines bearing a longer aliphatic group such as tri(*n*-propyl)amine and tri(*n*-hexyl)amine gave a low quinoline product yield (<10%), which suggests that the generation of enamine intermediate might be less favored for these tertiary amines. We believe that triethylamine first undergoes dehydrogenation and isomerization to form an enamine, which is the actual substrate for coupling reaction. In support of this notion, Szostak and co-workers recently reported the formation of similar enamine (imine) in deaminative coupling reactions of triethylamine.[15]

Table 2. Three-Component Deaminative Coupling Reaction of Anilines, Aldehydes and Amines.[a]

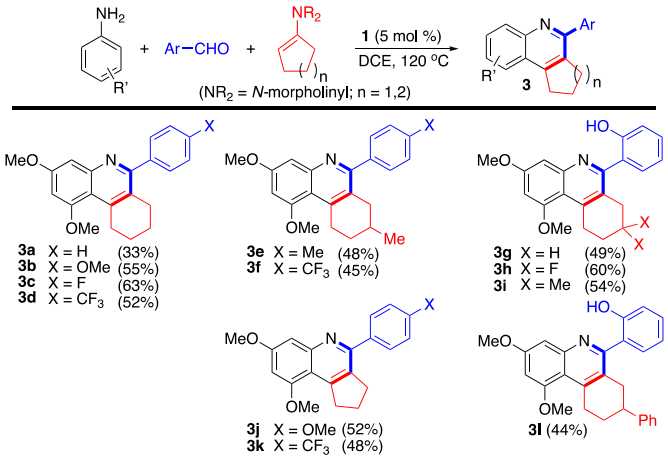


[a] Reaction conditions: aniline (0.3 mmol), aldehyde (0.3 mmol), amine (0.3 mmol), **1** (5 mol %), 1,2-dichloroethane (1.5 mL), 120 °C, 20 h.

The quinoline products are readily isolated by silica gel column chromatography and their structures were completely established by spectroscopic method. The solid-state structure of **2n** and **2r** was also determined by X-ray crystallography, and the molecular structure of **2r** showed a strong hydrogen bonding interaction between the quinoline nitrogen and phenolic hydrogen atoms. The reaction of highly functionalized aldehydes 9-ethyl-9*H*-carbazole-3-carbaldehyde and myrtenal with 3,5-dimethoxyaniline and triallylamine predictively formed the corresponding quinoline products **2y** and **2z**, respectively, which further illustrates synthetic utility of the coupling method.

The fact that both triallylamine and triethylamine are suitable reagents for the deaminative coupling reaction suggested that the reaction might proceed via the formation of enamines. We next explored the deaminative coupling reaction by using pre-synthesized enamines to further extend the amine substrate scope. Thus, the coupling reaction of 3,5-dimethoxyaniline with aryl-substituted aldehydes and 4-(cyclohex-1-en-1-yl)morpholine afforded the tricyclic quinoline derivatives **3a**-**i**, **l** (Table 3). The analogous coupling reaction with 4-(cyclopent-1-en-1-yl)morpholine formed the 5-membered tricyclic quinoline products **3j**, **k**. Enamine substrates are readily synthesized from the reaction of cyclic ketone and morpholine by following the literature procedure,[16] and the structure of these quinoline products was completely established by using spectroscopic methods.

Table 3. Three-Component Coupling Reaction of Anilines with Aldehydes and Cyclic Enamines.[a]



[a] Reaction conditions: aniline (0.3 mmol), aldehyde (0.3 mmol), enamine (0.3 mmol), **1** (5 mol %), 1,2-dichloroethane (1.5 mL), 120 °C, 20 h.

To gain mechanistic insights, we monitored the coupling reaction of 3,5-dimethoxyaniline, 4-methoxybenzaldehyde and triallylamine by using NMR spectroscopic method. The reaction mixture containing complex **1** (0.10 mmol), 3,5-dimethoxyaniline (0.10 mmol), 4-methoxybenzaldehyde (0.1 mmol) and triallylamine (0.10 mmol) in CD_2Cl_2 (0.5 mL) in an NMR tube was heated in an oil bath set at 120 °C. The tube was taken out of the oil bath at 20 min intervals and was analyzed by ^{1}H NMR. As shown in Fig. 1, 3,5-dimethoxy-*N*-(4-methoxybenzylidene)aniline (**4a**) was rapidly formed within 20 min of the reaction time, which was gradually consumed as the product **2a** was formed in 3 h of the reaction time.

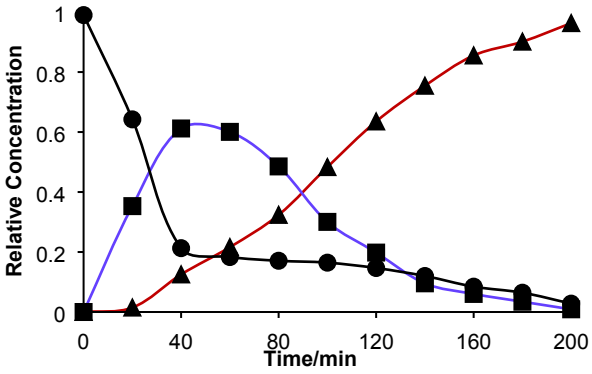
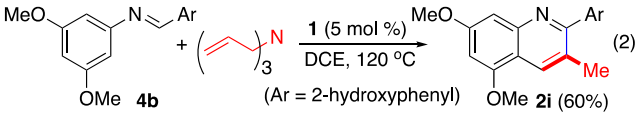
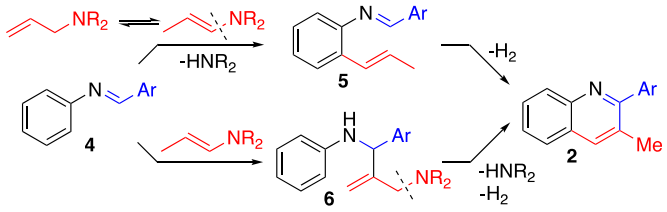


Fig. 1. Reaction Profile of 3,5-Dimethoxyaniline with *p*-OMe-C_6H_4CHO and Triallylamine. *p*-OMe-C_6H_4CHO (●), **2a** (▲), **4a** (■).



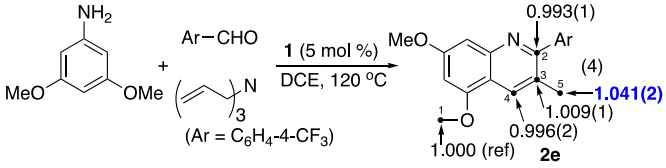
In a separate experiment, the reaction of 2-(((3,5-dimethoxyphenyl)imino)methyl)phenol (**4b**) (0.3 mmol), which was independently synthesized from the reaction of 3,5-dimethoxyaniline and salicylaldehyde, with triallylamine (0.3 mmol) under the standard conditions formed the quinoline derivative **2i** in 60% yield (eq 2). These results clearly showed that the initially formed imine **4** is the actual substrate for the deaminative coupling reaction in forming the quinoline product **2**.



Scheme 1. Two Possible Mechanistic Sequence for the Coupling Reaction of Imine with Allylamine.

We considered two possible reaction sequences between the imine **4** and triallylamine in forming the quinoline product **2** (Scheme 1). One possibility is that the imine **4** could first undergo *ortho*-arene deaminative allylation reaction with triallylamine (or an enamine) to form the 2-vinylated imine **5**, which would subsequently undergo the annulation to form the quioline product **2**. Alternatively, the imine moiety of **4** could directly couple with triallylamine (or an enamine) to form an elaborated allylaniline **6**, from which the deaminative annulation would proceed to form the product **2**. To distinguish between these two possible reaction pathways, we independently synthesized both *N*-(4-methoxybenzylidene)-2-((*E*)-prop-1-en-1-yl)aniline (**5a**) and 3-(dimethylamino)-1-

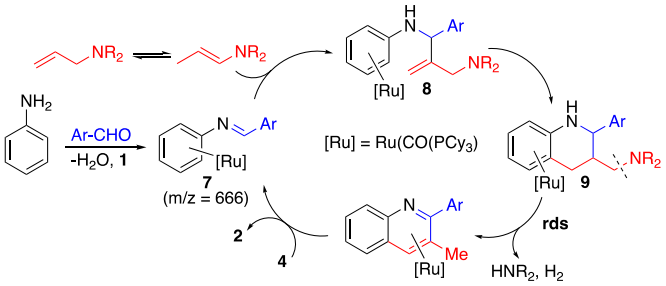
phenylpropylidene)-3,5-dimethoxyaniline (**6a**) by following reported procedures.[16,17] When both **5a** and **6a** were separately subjected to the catalytic conditions, only the reaction from **6a** led to the the quinoline product **2k** in 50% yield, while 77% of unreacted **5a** was recovered from the reaction mixture (eq 3). These results are consistent with the reaction pathway, which involves the direct coupling of imine and enamine via the formation of **6**.



To discern rate-limiting step of the coupling reaction, we measured the carbon kinetic isotope effect (KIE) of the coupling reaction by using Singleton's high precision NMR method.[18] The high conversion sample of **2e** was obtained from three separate reaction mixture of 3,5-dimethoxyaniline (1.0 mmol), 4-(trifluoromethyl)benzaldehyde (1.0 mmol) and triallylamine (1.0 mmol) under the standard reaction conditions after 20 h of the reaction time (avg. 88% conversion) (eq 4). The low conversion sample of **2e** was similarly obtained from three separate reactions of 3,5-dimethoxyaniline (1.0 mmol), 4-(trifluoromethyl)benzaldehyde (1.0 mmol) and triallylamine (1.0 mmol) in 1,2-dichloroethane (1.5 mL) after 2.5 h of the reaction time under the standard reaction conditions (avg. 16% conversion). The most significant carbon KIE was observed on the methyl carbon of the product **2e** when the ^{13}C ratio of the product from a high conversion was compared with the sample obtained from a low conversion (^{13}C(avg. 88% conversion)/^{13}C(avg. 16% conversion) at C(5) = 1.041(2); average of two runs) (Table S2, SI). The observation of a significant carbon KIE on the methyl carbon indicates the C–N bond cleavage as the turnover-limiting step for the deaminative coupling reaction.

To probe electronic influence of the benzaldehyde substrate on the coupling reaction, we constructed a Hammett plot from comparing the rates of *para*-substituted benzaldehyde substrates. Thus, the treatment of 3,5-dimethoxyaniline (0.10 mmol), *p*-X-C_6H_5CHO (X = OMe, Me, H, Cl, CF_3) (0.10 mmol), triallylamine (0.10 mmol) and complex **1** (5 mol %) in 1,2-dichloroethane-d_4 (0.3 mL) in a J-Young NMR tube was immersed in an oil bath at 120 °C, and the reaction progress was periodically analyzed by ^1H NMR. The k_{obs} of each reaction was determined from the first-order plot of -*ln*[(3,5-dimethoxyaniline)$_t$/(3,5-dimethoxyaniline)$_0$] vs time. The Hammett plot constructed from plotting log(k_X/k_H) vs σ_p exhibited virtually no electronic effects on the rate from these para-substitutedbenzaldehyde substrates (ρ = +0.04 ± 0.2) (Figure S2, SI). The results indicate that the aldehyde-to-allylamine C–C bond formation is not likely the turnover-limiting step for the coupling reaction.

In an effort to detect catalytically relevant species, we monitored the reaction mixture of **1** (0.1 mmol) with the imine substrate **4a** (0.2 mmol) in CD_2Cl_2 (0.5 mL) by NMR. Upon heating the reaction mixture at 120 °C for 2 min, the formation of a new set of the phosphorous peaks at δ 57.9 (s) and 38.9 (s) ppm was observed by $^{31}P\{^1H\}$ NMR, at the expense of the peak due to **1**. The singlet peak at δ 57.9 ppm indicates that the Ru complex contains only one PCy_3, and the peak at δ 38.9 ppm was assigned to Cy_3PHCl. When the reaction mixture was analyzed by LC-MS, a prominent absorption peak with m/z of 666.10 was observed (Fig. S3, SI), whose mass-ion corresponds to imine substrate **4a** complexed to the Ru(CO)(PCy_3) moiety.



Scheme 2. Plausible Mechanistic Sequence for Three-Component Coupling Reaction of Aniline, Arylaldehyde and Allylamine.

We present a plausible mechanistic sequence for the coupling reaction on the basis of these experimental results (Scheme 2). As revealed in the reaction profile study, the imine substrate **4**, which is initially formed from the dehydrative coupling of aniline and an aryl-substituted aldehyde, would coordinate to the Ru catalyst to form the Ru-arene complex **7**. We propose that the Ru catalyst promotes the nucleophilic coupling reaction of imine with an enamine substrate to form the elaborated aniline intermediate **8**. Allylamine-enamine isomerization reaction has been known to be quite facile,[19] and we previously reported that the complex **1** is a highly efficient catalyst for olefin isomerization reactions.[20] The spectroscopic detection of imine-bound Ru complex provides direct evidence for the Ru-mediated catalytic coupling process. The subsequent *ortho*-arene C–H insertion and annulation steps would form the hydroquinoline species **9**. In support of this notion, ruthenium catalysts have been well-established to mediate *ortho*-arene C–H alkylation and vinylation reactions.[21] The subsequent deamination and dehydrogenation/aromatization steps from **9** should form the quinoline product **2**. The carbon KIE results indicate the deamination (C–N bond cleavage) as the turnover-limiting step, while an apparent lack of electronic effects from *para*-substituted benzaldehydes suggests that the C–C bond formation is not likely involved in the rate-limiting step of the coupling reaction. While the proposed pathway shares similar mechanistic features with the recently published Povarov-type

of coupling reactions,[22] the proposed pathway illustrates new mechanistic insights on the catalytically relevant intermediate species as well as the role of Ru catalyst on mediating the deaminative coupling reaction.

Conclusions

In summary, we have successfully devised a new three-component deaminative coupling method to synthesize substituted quinolines. The catalytic method efficiently assembles biologically important quinoline core structures from combining readily available aniline, benzaldehyde and amine substrates. The preliminary experimental data suggest that the reaction proceeds sequentially via the initial formation of imine followed by the deaminative coupling and annulation steps. We are currently focusing our efforts to examine the detailed mechanism as well as to extend synthetic utility of the deaminative coupling methods.

Experimental section

General Procedure for the Coupling Reaction of an Aniline with an Aldehyde and an Amine. In a glove box, complex **1** (11 mg, 5 mol %), an aniline (0.3 mmol), an aldehyde (0.3 mmol) and an amine (0.3 mmol) were dissolved in 1,2-dichloroethane (1.5 mL) in a 25 mL Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar. The tube was brought out of the glove box and was stirred in an oil bath set at 120 °C for 20 h. The reaction tube was taken out of the oil bath and was cooled to room temperature. After the tube was open to air, the solution was filtered through a short silica gel column by eluting with CH_2Cl_2 (1 mL), and the filtrate was analyzed by GC-MS. The analytically pure product **2** was isolated by column chromatography on silica gel (40-63 μm particle size, hexanes/EtOAc = 100:1 to 95:5). The product was analyzed by NMR and GC-MS spectroscopic methods.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 Recent reviews: (*a*) K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev*., 2015, **115**, 12045-12090; (*b*) Q. Wang, Y. Su, L. Li, H. Huang, *Chem. Soc. Rev*., 2016, **45**, 1257-1272; (*c*) K. J. Berger, M. D. Levin, *Org. Biomol. Chem*., 2021, **19**, 11-36; (*d*) Y.-N. Li, F. Xiao, Y. Guo, Y.-F. Zeng, *Eur. J. Org. Chem*., 2021, **2021**, 1215-1228.

2 (*a*) F.-S. He, S. Ye, J. Wu, *ACS Catal*., 2019, **9**, 8943-8960; (*b*) S. Ni, C.-X. Li, Y. Mao, J. Han, Y. Wang, H. Yan, Y. Pan, *Sci. Adv.,* 2019, **5**, eaaw9516; (*c*) S. Plunkett, C. H. Basch, S. O. Santana, M. P. Watson, *J. Am. Chem. Soc*., 2019, **141**, 2257-2262; (*d*) J. T. M. Correia, V. A. Fernandes, B. T. Matsuo, J. A. C. Delgado, W. C. de Souza, M. W. Paixão, 2020, **56**, 503-514; (*e*) J. Xu, O. P. Bercher, M. R. Talley, M. P. Watson, *ACS Catal*., 2021, **11**, 1604-1612; (*f*) X. Zhang, D. Qi, C. Jiao, X. Liu, G. Zhang, *Nat. Commun*., 2021, **12**, 1-9; (*g*) C.-S. Zhang, L. Bao, K.-Q. Chen, Z.-X. Wang, X.-Y. Chen, *Org. Lett*., 2021, **23**, 1577-1581.

3 (*a*) S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc*., 2003, **125**, 6046-6047; (*b*) S. Ueno, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc*., 2007, **129**, 6098-6099; (*c*) T. Koreeda, T. Kochi, F. Kakiuchi, *J. Am. Chem. Soc*., 2009, **131**, 7238-7239; (*d*) T. Koreeda, T. Kochi, F. Kakiuchi, *Organometallics,* 2013, **32**, 682-690; (*e*) M. Tobisu, K. Nakamura, N. Chatani, *J. Am. Chem. Soc*., 2014, **136**, 5587-5590; (*f*) M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu, T. P. Loh, *J. Am. Chem. Soc*., 2015, **137**, 1341-1347; (*g*) Z. Luo, L. Xiong, T. Liu, Y. Zhang, S. Lu, Y. Chen, W. Guo, Y. Zhu, Z. Zeng, *J. Org. Chem*., 2019, **84**, 10559-10568; (*h*) Q. Zhao, J. Zhang, M. Szostak, *ACS Catal*., 2019, **9**, 8171-8177.

4 (*a*) N. A. Weires, E. L. Baker, N. K. Garg, *Nat. Chem*. 2016, **8**, 75-79; (*b*) J. E. Dander, N. K. Garg, *ACS Catal*., 2017, **7**, 1413-1423.

5 S. Shi, S. P. Nolan, M. Szostak, *Acc. Chem. Res*., 2018, **51**, 2589-2599.

6 (*a*) S.-Z. Sun, C. Romano, R. Martin, *J. Am. Chem. Soc*., 2019, **141**, 16197-16201; (*b*) R. Martin-Montero, V. R. Yatham, H. Yin, J. Davies, R. Martin, *Org. Lett*., 2019, **21**, 2947-2951.

7 S.-Z. Sun, Y. M. Cai, D. L. Zhang, J. B. Wang, H. Q. Yao, X. Y. Rui, R. Martin, M. Shang, *J. Am. Chem. Soc*., 2022, **144**, 1130-1137.

8 (*a*) F. J. R. Klauck, M. J. James, F. Glorius, *Angew. Chem., Int. Ed*., 2017, **56**, 12336-12339; (*b*) J. Yi, S. O. Badir, L. M. Kammer, M. Ribagorda, G. A. Molander, *Org. Lett*., 2019, **21**, 3346-3351; (*c*) X. Jiang, M.-M. Zhang, W. Xiong, L.-Q. Lu, W.-J. Xiao, *Angew. Chem., Int. Ed*., 2019, **58**, 2402-2406; (*d*) M. A. Ashley, T. Rovis, *J. Am. Chem. Soc*., 2020, **142**, 18310-18316; (*e*) T. Yang, Y. Wei, M. J. Koh, *ACS Catal*., 2021, **11**, 6519-6525; (*f*) N. Neerathilingam, M. B. Reddy, R. Anandhan, *J. Org. Chem*., 2021, **86**, 15117-15127.

9 (*a*) V. V. Kouznetsov, *Tetrahedron,* 2009, **65**, 2721-2750; (*b*) D. Bello, R. Ramon, R. Lavilla, *Curr. Org. Chem*., 2010, **14**, 332-356.

10 (*a*) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev*., 2008, **77**, 137-159; (*b*) Q. Gao, S. Liu, X. Wu, A. Wu, *Org. Lett*., 2014, **17**, 4582-4585; (*c*) A. M. Jadhav, V. V. Pagar, R.-S. Liu, *Angew. Chem., Int. Ed*., 2012, **51**, 11809-11813.

11 (*a*) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, *J. Am. Chem. Soc*., 2009, **131**, 4598-4599; (*b*) H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* 2010, **327**, 986-990; (*c*) C. Min, N. Mittal, D. X. Sun, D. Seidel, *Angew. Chem., Int. Ed*., 2013, **52**, 4084-14088; (*d*) F. Shi, G.-J. Xing, R.-Y. Zhu, W. Tan, S. Tu, *Org. Lett*., 2013, **15**, 128-131; (*e*) W. Dai, X.-L. Jiang, J.-Y. Tao, F. Shi, *J. Org. Chem*., 2016, **81**, 185-192; (*f*) L.-L. Su, Y.-W. Zheng, W.-G. Wang, B. Chen, X.-Z. Wei, L.-Z. Wu, C.-H. Tung, *Org. Lett*., 2022, **24**, 1180-1185; (*g*) D. Barik, R.-S. Liu, *J. Org. Chem*., 2022, **87**, 7097-7105.

12 (*a*) X.-T. Li, J. Zou, T.-H. Wang, H.-C. Ma, G.-J. Chen, Y.-B. Dong, *J. Am. Chem. Soc*., 2020, **142**, 6521-6526; (*b*) X.-R. Ren, B. Bai, Q. Zhang, Q. Hao, Y. Guo, L.-J. Wan, D. Wang, *J. Am. Chem. Soc*., 2022, **144**, 2488-2494.

13 (*a*) P. T. K. Arachchige, H. Lee, C. S. Yi, *J. Org. Chem*., 2018, **83**, 4932-4947; (*b*) P. T. K. Arachchige, S. Handunneththige, M. R. Talipov, N. Kalutharage, C. S. Yi, *ACS Catal*., 2021, **11**, 13962-13972; (*c*) P. T. K. Arachchige, C. S. Yi, *Org. Lett*., 2019, **21**, 3337-3341.

14 K. Gnyawali, P. T. K. Arachchige, C. S. Yi, *Org. Lett*., 2022, **24**, 218-222.

15 S. Liu, J. Liang, P. Zhang, Z. Li, L.-Y. Jiao, W. Jia, Y. Ma, M. Szostak, *Org. Chem. Front*., 2023, **10**, 22-29.

16 (*a*) M. Smith, J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th Ed., Wiley-Interscience, New York, 2007; (*b*) C. Gilbert, *Enamines: Synthesis: Structure, and Reactions*, 2nd Ed., Marcel Dekker, New York, 1988.
17 F.-U. Rahman, A. Ali, R. Guo, W.-K. Wang, H. Wang, Z.-T. Li, Y. Lin, D.-W. Zhang, *Dalton Trans*., 2015, **44**, 9872-9880.
18 (*a*) D. A. Singleton, A. A. Thomas, *J. Am. Chem. Soc.,* 1995, **117**, 9357-9358; (*b*) D. T. Nowlan III, T. M. Gregg, H. M. L. Davies, D. A. Singleton, *J. Am. Chem. Soc*., 2003, **125**, 15902-15911; (*c*) D. T. Nowlan III, D. A. Singleton, *J. Am. Chem. Soc*., 2005, **127**, 6190-6191.
19 (*a*) W. R. Ashcroft, N. R. Carrington, M. J. Field, I. H. Hillier, J. A. Joule, S. A. Pope, C. I. F. Watt, *J. Chem. Soc. Perkin Trans II*, 1985, 1187-1190; (*b*) S.-i. Inoue, H. Takaya, K. Tani, S. Otsuka, T. Sato, R. Noyori, *J. Am. Chem. Soc*. 1990, **112**, 4897-4905; (*c*) B. M. Novak, J. T. Cafmeyer, J*. Am. Chem. Soc*. 2001, **123**, 11083-11084.
20 D. W. Lee, C. S. Yi, *Organometallics* 2010, **29**, 3413-3417.
21 Recent reviews: (*a*) P. Arockiam, C. Bruneau, P. Dixneuf, *Chem. Rev.* 2012, **112**, 5879-5918; (b) N. K. Mishra, S. Sharma, J. Park, S. Han, I. S. Kim, *ACS Catal*., 2017, **7**, 2821-2847; (*c*) S. Dutta, T. Bhattacharya, B. Werz, D. Maiti, *Chem,* 2021, **7**, 555-605
22 (*a*) L. R. Domingo, M. J. Aurell, J. A. Saez, S. M. Mekellechec, *RSC Adv*. 2014, **4**, 25268-25278; (*b*) J. Clerigué, M. T. Ramos, J. C. Menéndez, *Org. Biomol. Chem*., 2022, **20**, 1550-1581; (*c*) C. Li, J. K. Bera, H. S. Soo, *ACS Catal*., 2022, **12**, 15168-15180; (*d*) Q. Gao, Y. Guo, Z. Sun, X. He, Y. Gao, G. Fan, P. Cao, L. Fang, S. Bai, Y. Jia, *Org. Lett*. 2023, **25**, 109-114.

