博士論文

論文題目　Development of Organocatalytic Functionalizations of C-H Bonds
（有機分子触媒を用いたC-H結合官能基化反応の開発）

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Development of Organocatalytic Functionalizations of C-H Bonds

（有機分子触媒を用いた C-H 結合官能基化反応の開発）

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Contents

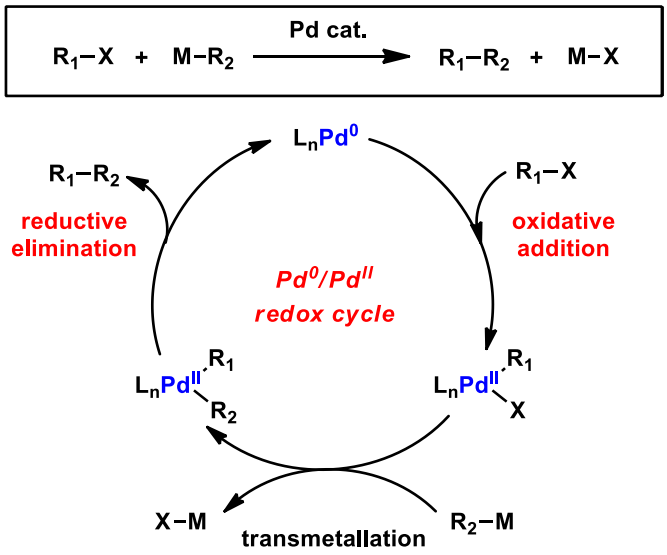
Abbreviations

Ac	acetyl
aq.	aqueous
bpy	2,2'-bipyridyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
cat.	catalytic
COX	cyclooxygenase
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DIBAL	diisobutylaluminium hydride
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
eq.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EY	Eosin Y
FT/IR	Fourier transform infrared spectroscopy
GPC	gel permeation chromatography
h	hour(s)
Hantzsch ester	diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate
LED	light emitting diode
M	molar
Me	methyl
Mes	2,4,6-trimethylphenyl
min	minute(s)
MW	microwave
n	normal
naph	naphthyl
NMR	nuclear magnetic resonance
Ph	phenyl
phd	1,10-phenanthroline-5,6-dione
Piv	pivaloyl
ppb	parts per billion
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
^{i}Pr	2-propyl
quant.	quantitative

rt	room temperature
rpm	rotation per minute
SM	starting material
salophen	N,N'-bis(salicylidene)-1,2-phenylenediamine
T	temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
WSCI	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide

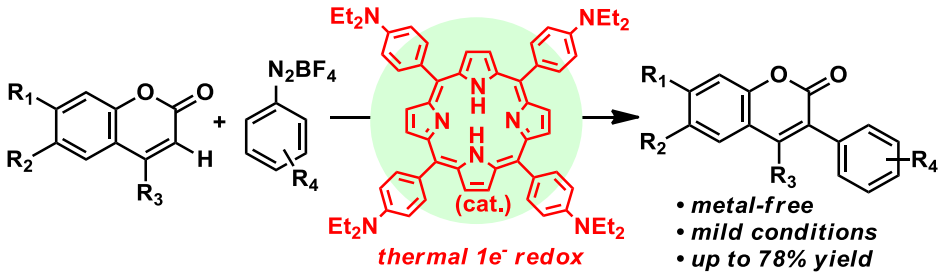
1. Introduction

20th century has witnessed a substantial development of organometallic chemistry, not only in its basic understandings but also in its synthetic applications. As is evident from an example of Pd-catalyzed cross coupling reactions, redox behavior of transition metals is often indispensable for their catalytic activity (Scheme 1). However, due to the rapid expansion of demands for metal resources along with industrialization and economic growth in the developing world, supply of transition metals is expected to be at risk. According to a survey by National Institute for Materials Science (NIMS), it is predicted that transition metals such as Mn, Fe, Co, Ni, Cu, Mo, Pd, Ag, W, Pt and Au are expected to be run out by 2050 (http://www.nims.go.jp/research/elements/rare-metal/probrem/dryness.html Accessed on January 2, 2017). Thus, in order to achieve sustainable development in the 21st century, a novel alternative to the transition metal catalysts is in high demand. In my Ph.D. course, I focused on two transition-metal-catalyzed C-H bond functionalization reactions, and developed two related organocatalytic transformations by utilizing organic compounds which facilitate redox processes. I believe that these **redox organocatalysis** would provide new prospects for the sustainable development of synthetic organic chemistry.



Scheme 1. Palladium as a redox mediator in cross coupling reactions

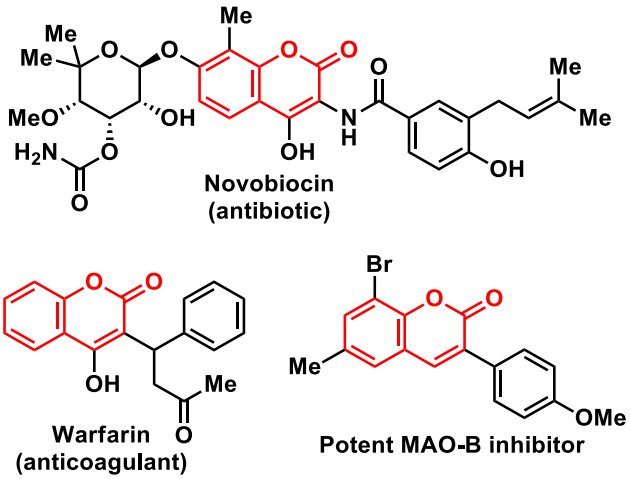
2. Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin



2-1. Research background

2-1-1. Coumarins in chemical science

Coumarins represent a desirable structural motif in pharmaceutical science, chemical biology or materials chemistry.[1-3] For example, marketed drugs such as novobiocin or warfarin contains coumarin motif in its central skeleton. Recently, 3-arylcoumarins were identified as a selective monoamine oxidase-B (MAO-B) inhibitor and are recognized as new lead compounds for the treatment of Alzheimer's or Parkinson's disease (Scheme 2).[1] Moreover, controllable fluorescent property of coumarin derivatives is intensively utilized in chemical biology.[2] In addition, coumarin-based dyes are frequently employed in light-harvesting materials as efficient dopants in light-emitting diodes.[3] Due to the wide range of application studies, facile functionalization of coumarin skeleton which enables rapid access to its new derivatives would contribute to various fields of chemical science.

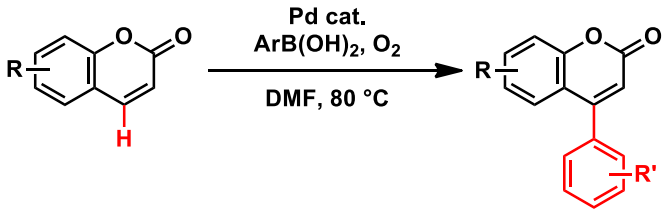


Scheme 2. Representative coumarin derivatives in pharmaceutical science

2-1-2. C-H arylation of coumarins

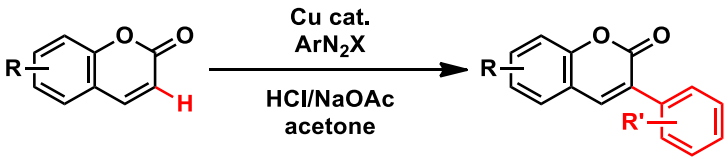
As one of the most well-developed derivatization methods for coumarins, I focused on site selective C-H arylation reactions. Palladium catalysis is versatile in many types of C-H arylation reactions, and has also been employed for the C(3)-H or C(4)-H arylation of coumarin derivatives.[4] For example, Duan reported a palladium-catalyzed, Heck-type C(4)-H arylation of coumarins with arylboronic acids and molecular oxygen (Scheme 3).[4d] This Heck-type transformation is beneficial because no prefunctionalization of

coumarin skeleton is necessary. However, functional group tolerance of this transformation had a room for improvement. Although alkyl, chloro, nitro, or hydroxy groups were tolerated in this transformation, bromo-substituted arylboronic acid produced complex mixture of the product because Suzuki-Miyaura coupling occurred simultaneously. Considering that bromo group is useful for subsequent transformations, this observation could be a typical drawback of palladium-catalyzed C-H arylation methods. In addition, high cost and toxicity of palladium are disadvantageous for the potential application to the preparation of pharmaceutical agents.



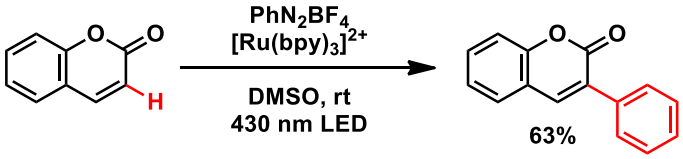
Scheme 3. Palladium-catalyzed C(4)-H arylation of coumarin[4d]

For another example of C-H arylation of coumarins, Meerwein arylation is known as a classical method (Scheme 4).[5] In a typical Meerwein arylation, transition metal catalysts produce aryl radicals by one electron reduction of aryldiazonium salts. Then, aryl radicals attack 3 position of coumarins, affording the C(3)-H arylated product. However, there remain several challenges in this classical approach. In the case of Meerwein-type C-H arylation, substrate generality is yet limited because of the side reactions of aryldiazonium salts. Also, aqueous solvents are required, making the expansion of substrate scope difficult. Moreover, yields of the product are often low to moderate (typically < 50%) for the copper catalyzed reaction.[6]



Scheme 4. Classical Meerwein arylation for C(3)-H arylation of coumarin[6]

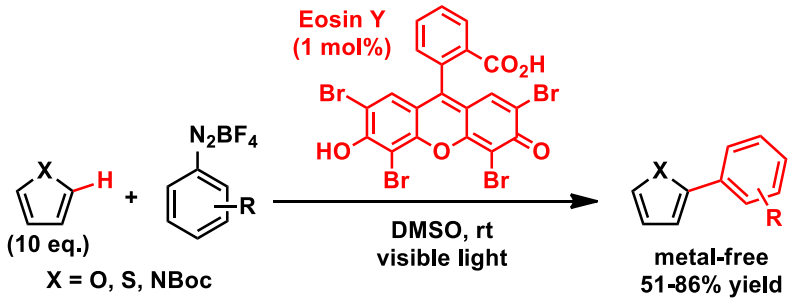
Recently, König reported a visible light driven C(3)-H arylation of coumarin by $[Ru(bpy)_3]^{2+}$ photoredox catalyst (Scheme 5).[7] However, substrate scope was not extensively investigated and requirement of precious ruthenium based catalyst is a drawback of the transformation.



Scheme 5. Meerwein arylation by $[Ru(bpy)_3]^{2+}$ photoredox catalysis[7]

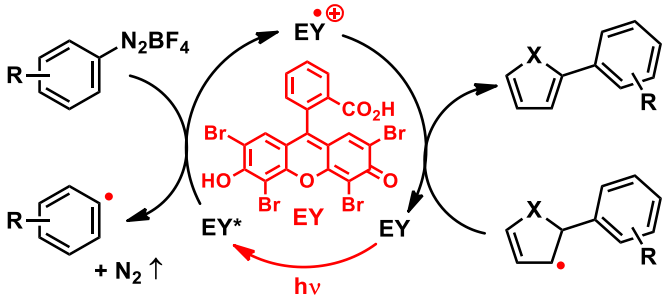
2-1-3. Metal-free C-H functionalization of (hetero)arenes

In order to overcome the drawbacks of transition-metal-mediated Meerwein arylation, metal-free Meerwein-type arylation has been intensively investigated.[8-14] As a representative example, in 2012, König reported a metal-free, visible light mediated C-H arylation of heteroarenes using Eosin Y as an organocatalyst (Scheme 6).[8a]



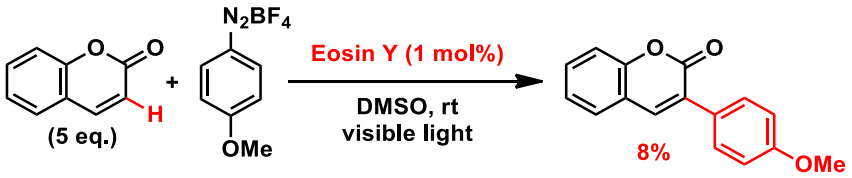
Scheme 6. Eosin Y catalyzed C-H arylation of heterocycles[8a]

It is proposed that the reaction proceeds via the one electron reduction of aryldiazonium salts by the excited photocatalyst, addition of aryl radical to the unsaturated bond of heteroarenes, and one electron oxidation of the radical intermediate by the oxidized form of the photocatalyst (Scheme 7). Due to the mild reaction conditions (room temperature, visible light), high yield and excellent functional group tolerance are achieved.



Scheme 7. Plausible reaction mechanisms for the Eosin Y catalyzed C-H arylation

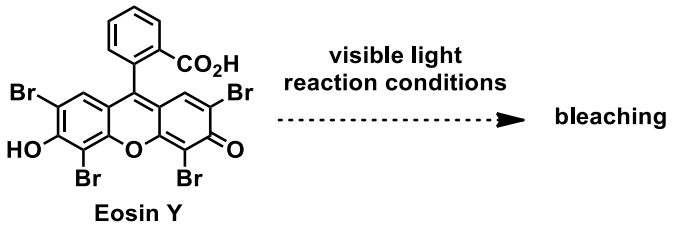
However, the scope of heteroarenes of this organocatalytic C-H arylation is limited to reactive 5-membered heterocycles (furans, thiophenes, and pyrrole derivatives). Following this method, I tried the C-H arylation of coumarins, but the desired product was obtained in only 8% yield (Scheme 8). This result suggests that the present organocatalytic C-H arylation is not applicable to coumarins.



Scheme 8. Eosin Y catalyzed C(3)-H arylation of coumarin

2-2. Reaction design

In the course of the evaluation of Eosin Y catalyzed functionalization of coumarins, bleaching of the photocatalyst was observed after long reaction time under deaerated conditions (Scheme 9).

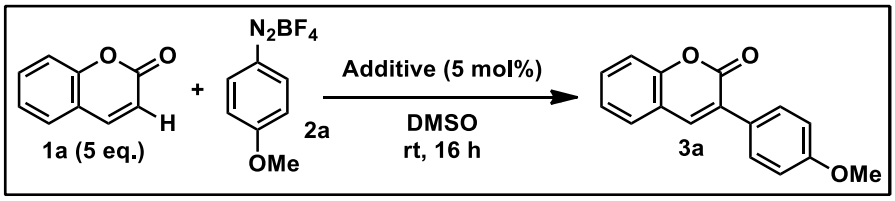


Scheme 9. Bleaching of Eosin Y during the arylation of coumarin

I suspected that decomposition of Eosin Y could be one reason for the low reactivity. Therefore, I hypothesized that high stability of the catalyst during the reaction could be important for high catalytic efficiency. In that context, I planned to employ **metal-free porphyrin** as a new organocatalyst for the C-H arylation. Metal-free porphyrin is known to possess a reversible one electron redox activity, and is widely utilized as one electron redox mediator in the field of artificial photosynthesis.[15] Using metal-free porphyrin as an organocatalyst, more efficient C-H arylation of coumarins should be achieved under environmentally benign and mild reaction conditions.[16]

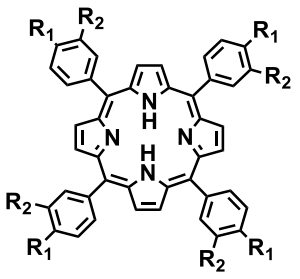
2-3. Reaction development

In order to evaluate the validity of my hypothesis, I started the initial reaction development as is shown in Scheme 10. In the presence of catalytic amounts of porphyrin derivatives **4a-4f**, C(3)-H arylation of coumarin **1a** was attempted using 4-methoxybenzenediazonium tetrafluoroborate **2a**. Although porphyrins with phenyl (**4a**) or 4-methoxyphenyl (**4b**) substituents did not afford the desired product (Scheme 10, entries 1-2), the coupling product was obtained in 17% yield in the presence of the porphyrin with 4-aminophenyl group **4c** (entry 3). Evaluation of other porphyrins with different nitrogen substituent (**4d**, **4e**, **4f**) revealed that 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin **4e** possessed the highest reactivity for the Meerwein-type arylation (entries 4-6). The low reactivity of **4d** could be derived from its low solubility in DMSO solvent.[17]



Entry	Additive	Yield [%][a]
1	4a	0
2	4b	0
3	4c	17
4	4d	0
5	4e	24
6	4f	20

[a] ^{1}H NMR yield.



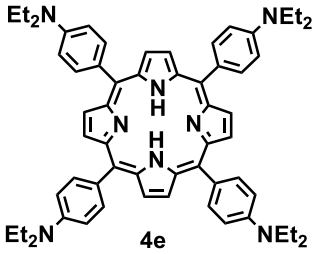
Additive:
4a: $R_1 = R_2 = H$
4b: $R_1 = OMe$, $R_2 = H$
4c: $R_1 = NH_2$, $R_2 = H$
4d: $R_1 = NMe_2$, $R_2 = H$
4e: $R_1 = NEt_2$, $R_2 = H$
4f: $R_1 = NH_2$, $R_2 = OMe$

Scheme 10. Evaluation of porphyrin derivatives for C-H arylation of coumarin

Encouraged by the result, optimization of the reaction conditions was performed (Scheme 11). When the reaction was run under dark conditions, the yield of the product did not change significantly, suggesting the thermal reaction pathway (Scheme 11, entry 2). The optimal amount of the porphyrin additive was determined to be 10 mol% (entries 1, 3-4) and the highest yield of the product was observed when the reaction temperature was raised to 40 °C, affording the desired product in 63% isolated yield (entry 5). As for control experiments, reactions without **4e** or with catalytic amounts of N,N-diethylaniline (partial structure of **4e**) was performed (entries 6-7). In either case,

no product formation was observed. These results imply that porphyrin skeleton is indispensable for the Meerwein-type arylation.

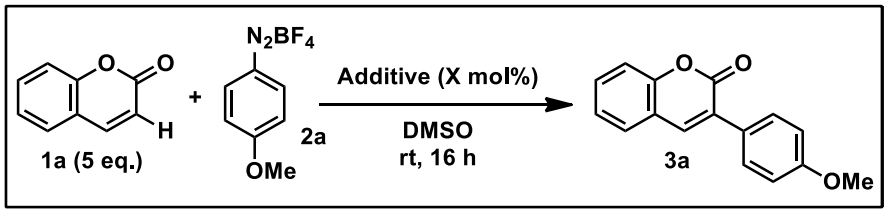
Entry	X	T [°C]	Yield [%][a]
1	5	rt	24
2[b]	5	rt	26
3	10	rt	31
4	20	rt	29
5	10	40	68 (63)[c]
6	0	40	0
7[d]	0	rt	0



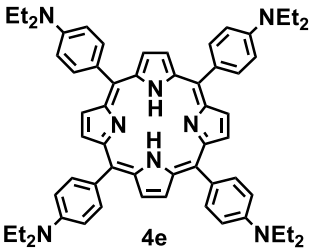
[a] ^{1}H NMR yield. [b] In the dark. [c] Isolated yield.
[d] 10 mol% of $PhNEt_2$ was added.

Scheme 11. Optimization of the porphyrin-mediated C(3)-H arylation of coumarin

In order to evaluate the efficiency of C-H arylation by **4e**, C(3)-H arylation of coumarin was investigated using reported metal-free Meerwein-type arylation methods (Scheme 12). As a result, catalytic amounts of **4e** produced the desired product in higher yield compared to all the investigated methods (Scheme 12, entries 1-5). These results support that **4e** is the most effective organic promoter for the C(3)-H arylation of coumarins.[18]



Entry	Additive (X mol%)	Yield [%][a]
1	4e (10)	31
2[b]	Eosin Y (1)	8
3	Ascorbic acid (10)	0
4	KI (10)	15
5	Benzoyl peroxide (2)	0



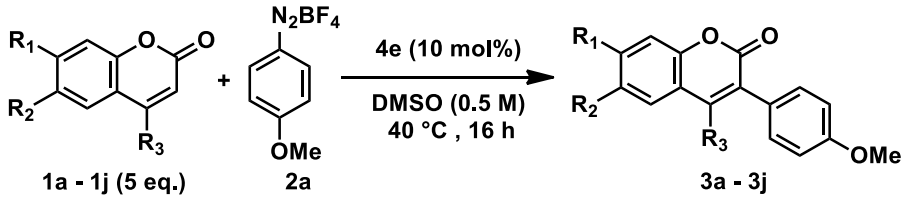
[a] ^{1}H NMR yield. [b] Exposed to visible light irradiation.

Scheme 12. Evaluation of other metal-free C-H arylation methods

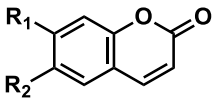
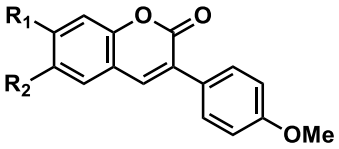
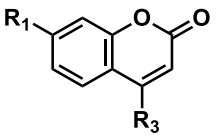
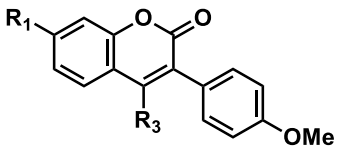
2-4. Substrate scope study

2-4-1. Scope of coumarins

With the optimized reaction conditions, substrate scope of the Meerwein-type arylation in terms of coumarins was evaluated (Scheme 13). Unsubstituted and 6-methyl coumarins were arylated in good yield (Scheme 13, entries 1-2). 6-Alkoxy substituted coumarins afforded the desired products in the highest yield (entries 3-4). Unprotected hydroxy group and diethylamino group were tolerated in the reaction conditions (entries 5-6). However, electron withdrawing nitro group on 6 position of the coumarin suppressed the C-C bond formation (entry 7). Amide substituted coumarin was arylated in good yield in spite of the relatively low amount (2.5 eq.) of the coumarin coupling partner (entry 8). 4-Substituted coumarins were arylated in good yield in spite of the steric demands (entries 9-10). These results suggest that the present metal-free arylation method is generally applicable to a series of coumarin derivatives.



1a - 1j (5 eq.) 2a 3a - 3j

Entry	Coumarin (2)	Product (3): Yield
		
1	**1a**: R_1 = H, R_2 = H	**3a**: 63%
2	**1b**: R_1 = H, R_2 = Me	**3b**: 61%
3	**1c**: R_1 = OMe, R_2 = H	**3c**: 73%
4	**1d**: R_1 = OEt, R_2 = H	**3d**: 78%
5	**1e**: R_1 = OH, R_2 = H	**3e**: 66%
6	**1f**: R_1 = NEt_2, R_2 = H	**3f**: 70%
7	**1g:** R_1 = H, R_2 = NO_2	**3g**: 36%
8[a]	**1h:** R_1 = H, R_2 = NHPiv	**3h**: 60%
		
9	**1i**: R_1 = NEt_2, R_3 = Me	**3i**: 63%
10	**1j**: R_1 = H, R_3 = OH	**3j**: 71%

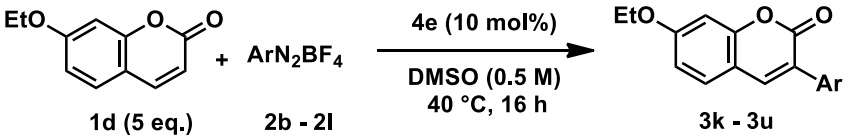
[a] 2.5 eq. of **1h** were used.

Scheme 13. Scope of coumarin derivatives

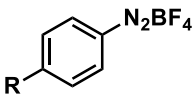
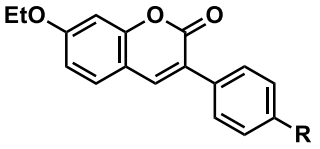
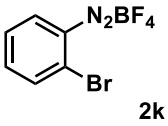
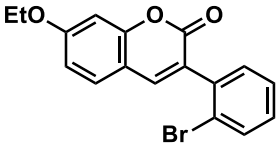
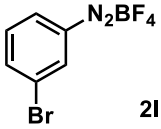
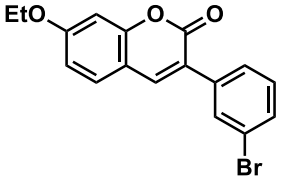
2-4-2. Scope of aryldiazonium salts

Substrate scope in terms of aryldiazonium tetrafluoroborate was also investigated (Scheme 14). Unsubstituted (Scheme 14, etnry 1), methyl (entry 2), or halogen-substituted (entries 3-6) aryldizonium salts produced the product in moderate to good yield. It is noteworthy that the 4-bromo and 4-iodo substituted aryldiaznonium salts were applicable to the C-H arylation because these aryl groups cannot be readily installed by palladium-catalyzed C-H arylation. Electron withdrawing functionalities such as ethyl ester (entry 7), trifluoromethyl (entry 8) made minor differences in reactivity. 4-Nitrobenzenediazonium tetrafluoroborate (entry 9) afforded the product in lower yield, possibly because reoxidation of the benzyl radical intermediate could be hampered by its strong electron withdrawing effect (vide infra). *Ortho-* and *meta-* substituted diazonium salts can be employed in the reaction (entries 10-11), although

the products were obtained in slightly lower yield. Together with the results of the substrate scope on coumarins, these results support that porphyrin-mediated sp^2 C-H arylation method is highly versatile for the preparation of C(3)-substituted coumarins.



1d (5 eq.) 2b - 2l 3k - 3u

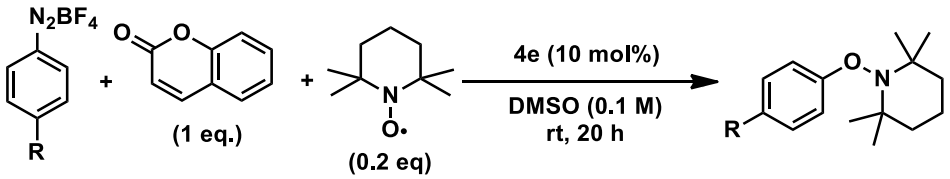
Entry	Aryl diazonium tetrafluoroborate (1)	Product (3): Yield
		
1	**2b**: R = H	**3k**: 70%
2	**2c**: R = Me	**3l**: 72%
3	**2d**: R = F	**3m**: 67%
4	**2e**: R = Cl	**3n**: 65%
5	**2f**: R = Br	**3o**: 71%
6	**2g**: R = I	**3p**: 56%
7	**2h:** R = CO_2Et	**3q**: 60%
8	**2i:** R = CF_3	**3r**: 67%
9	**2j:** R = NO_2	**3s**: 45%
10	 **2k**	 **3t**: 53%
11	 **2l**	 **3u**: 59%

Scheme 14. Scope of aryldiazonium tetrafluoroborates

2-5. Mechanistic discussions

2-5-1. Detection of aryl radical by TEMPO trapping experiments

It is widely accepted that transition metal catalyzed Meerwein arylation of coumarins proceeds via aryl radical. In order to confirm the presence of aryl radical in the present reaction, TEMPO trapping experiment was performed (Scheme 15). In the presence of 10 mol% of **4e**, aryldiazonium tetrafluoroborate (1 eq.), coumarin (1eq.), and TEMPO (2 eq.) was mixed. After 20 hours, no C-C bond formation was observed in all the cases. Instead, TEMPO trapped products were obtained from 4-nitrobenzenediazonium, 4-ethoxycarbonylbenzenediazonium or phenyldiazonium salts. These results support that aryl radical is generated in the present reaction conditions. Isolation of the TEMPO trapped product from 4-methoxybenzenediazonium tetrafluoroborate was not successful by several purification procedures possibly because of the instability of the electron rich aromatic product. Nevertheless, generation of aryl radical from 4-methoxybenzenediazonium tetrafluoroborate was indirectly confirmed by the radical clock experiment (vide infra).



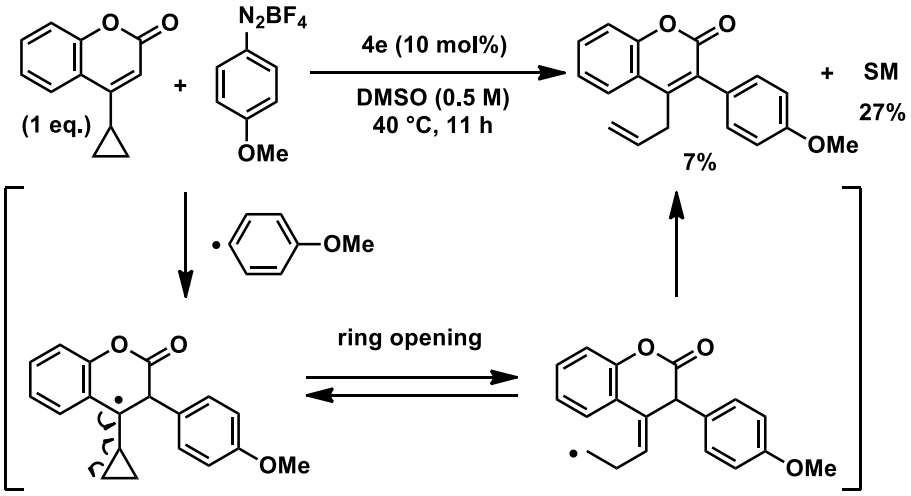
R	Yield (based on ArN_2BF_4)
NO_2	16%
CO_2Et	14%
H	12%
OMe	decomposed

Scheme 15. Detection of aryl radical by the TEMPO trapping experiment

2-5-2. Detection of benzyl radical by radical clock experiment

Following the confirmation of aryl radical intermediate, radical clock experiment was performed in order to confirm the presence of benzyl radical intermediate (Scheme 16). Using 4-cyclopropylcoumarin, C(3)-H arylation was attempted using 10 mol% of **4e** and 4-methoxybenzenediazonium tetrafluoroborate. After 11 hours, consumption of 3-cyclopropylcoumarin and complexation of the reaction was observed. However,

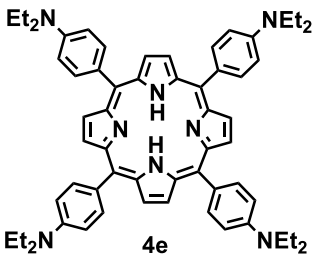
3-aryl-4-allylcoumarin was isolated from the crude mixture in 7% yield. The ring opening of the cyclopropane indicated the presence of benzyl radical intermediate, which was produced by the addition of 4-methoxyphenyl radical to the C(3) position of the coumarin.



Scheme 16. Detection of benzyl radical intermediate by the radical clock experiment

2-5-3. Inductively coupled plasma (ICP) analysis

In order to evaluate the metal contamination in the porphyrin **4e**, inductively coupled plasma (ICP) analysis was performed. Using ICP analysis, quantification of elements in the sample is possible. After the ICP analysis, it was revealed that amount of iron, copper, titanium (a potential catalyst for Meerwein arylation) and palladium (a potential catalyst for Heck-type arylation) were all below the detection limit (Scheme 17). These results support that the present reaction is not catalyzed by transition metal impurities.

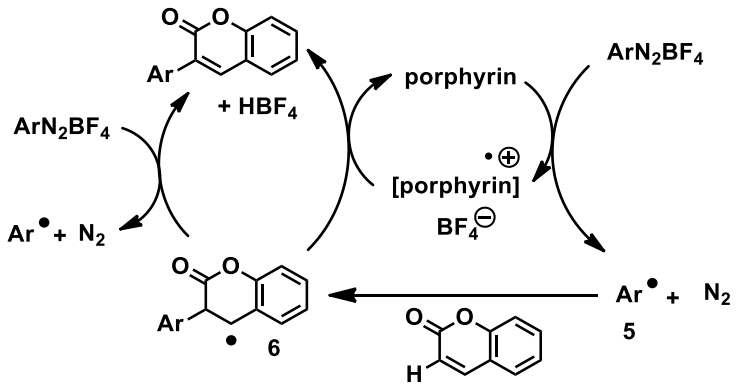


Entry	Metal	Amount [ppb]
1	Fe	< 3.5
2	Cu	< 1.2
3	Ti	< 2.6
4	Pd	< 4.5

Scheme 17. Quantification of metal contamination in **4e** by ICP analysis

2-5-4. Plausible reaction mechanisms

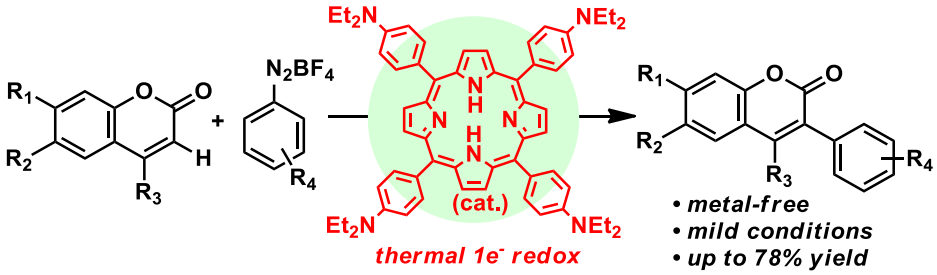
Based on the experimental findings, a plausible reaction mechanism for the porphyrin-mediated C-H arylation of coumarins is shown in Scheme 18. One electron reduction of aryldiazonium tetrafluoroborate by the porphyrin produces aryl radical **5** and nitrogen gas. The addition of aryl radical to the 3 position of coumarin affords benzyl radical intermediate **6**. The benzyl radical intermediate is then oxidized by porphyrin radical cation, leading to the formation of C(3)-arylated coumarin and regeneration of the porphyrin catalyst. This reoxidation of **6** could be difficult when electron withdrawing functional groups are present either on coumarin or on aryldiazonium salt, resulting in the lower yield of nitro group containing products (Scheme 13, entry 7 and Scheme 14, entry 9). Oxidation of **6** could be also possible with another molecule of aryldiazonium tetrafluoroborate.



Scheme 18. Plausible reaction mechanisms

2-6. Conclusions

In the first part of my Ph.D. study, I have disclosed that metal-free porphyrin, especially 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin **4e**, works as a novel redox active organocatalyst for the selective *sp*^{2} C-H arylation of coumarins. The porphyrin catalysis provides superior method for the Meerwein-type C-H arylation compared to conventional transition-metal-mediated or metal-free approaches, affording a variety of 3-arylcoumarins in synthetically useful yields.[19]. It is expected that the present reaction contributes not only to the discovery of new coumarin analogues in chemical sciences but also to the development of a new class of organocatalytic C-H functionalization reactions.[20] Investigations toward more precise understanding of reaction mechanisms and application of this catalytic reaction to substrates other than coumarin[21] are in progress.



Scheme 19. Metal-free C(3)-H arylation of coumarins promoted by 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin[19]

2-7. References

1. a) S. Sandhu, Y. Bansal, O. Silakari, G. Bansal, *Bioorg. Med. Chem.* **2014**, *22*, 3806; b) P. O. Patil, S. B. Bari, S. D. Firke, P. K. Deshmukh, S. T. Donda, D. A. Patil, *Bioorg. Med. Chem.* **2013**, *21*, 2434; c) S. Carradori, D. Secci, A. Bolasco, P. Chimenti, M. D'Ascenzio, *Expert. Opin. Ther. Pat.* **2012**, *22*, 759.
2. a) X. Zhou, Y. Kwon, G. Kim, J. H. Ryu, J. Yoon, *Biosens. Bioelectron.* **2015**, *64*, 285; b) K. B. Zheng, W. Y. Lin, L. Tan, H. Chen, H. J. Cui, *Chem. Sci.* **2014**, *5*, 3439; c) J. Liu, Y. Q. Sun, H. X. Zhang, Y. Y. Huo, Y. W. Shi, H. P. Shi, W. Guo, *RSC Adv.* **2014**, *4*, 64542; d) G. P. Li, D. J. Zhu, Q. Liu, L. Xue, H. Jiang, *Org. Lett.* **2013**, *15*, 2002; e) Q. J. Zhang, Z. C. Zhu, Y. L. Zheng, J. G. Cheng, N. Zhang, Y. T. Long, J. Zheng, X. H. Qian, Y. J. Yang, *J. Am. Chem. Soc.* **2012**, *134*, 18479.
3. a) X. G. Liu, Z. C. Xu, J. M. Cole, *J. Phys. Chem. C* **2013**, *117*, 16584; b) C. H. Chang, H. C. Cheng, Y. J. Lu, K. C. Tien, H. W. Lin, C. L. Lin, C. J. Yang, C. C. Wu, *Org. Electron.* **2010**, *11*, 247; c) M. T. Lee, C. K. Yen, W. P. Yang, H. H. Chen, C. H. Liao, C. H. Tsai, C. H. Chen, *Org. Lett.* **2004**, *6*, 1241; d) S. A. Swanson, G. M. Wallraff, J. P. Chen, W. J. Zhang, L. D. Bozano, K. R. Carter, J. R. Salem, R. Villa, J. C. Scott, *Chem. Mater.* **2003**, *15*, 2305; e) A. Adronov, S. L. Gilat, J. M. J. Frechet, K. Ohta, F. V. R. Neuwahl, G. R. Fleming, *J. Am. Chem. Soc.* **2000**, *122*, 1175.
4. a) F. Jafarpour, M. B. A. Olia, H. Hazrati, *Adv. Synth. Catal.* **2013**, *355*, 3407; b) F. Jafarpour, H. Hazrati, N. Mohasselyazdi, M. Khoobi, A. Shafiee, *Chem. Commun.* **2013**, *49*, 10935; c) M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour, A. Shafiee, *Chem. Commun.* **2012**, *48*, 2985; d) Y. M. Li, Z. S. Qi, H. F. Wang, X. M. Fu, C. Y. Duan, *J. Org. Chem.* **2012**, *77*, 2053; e) M. Min, S. Hong, *Chem. Commun.* **2012**, *48*, 9613.
5. For reviews on the Meerwein arylation, see: a) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734; b) F. Y. Mo, G. B. Dong, Y. Zhang, J. B. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582; c) M. R. Heinrich, *Chem. – Eur. J.* **2009**, *15*, 821; d) C. S. Rondestvedt, *Org. React.* **1976**, *24*, 225.
6. H. Meerwein, E. Buchner, K. van Emster, *J. Prakt. Chem.* **1939**, *152*, 237.
7. a) P. Schroll, D. P. Hari, B. König, *ChemistryOpen* **2012**, *1*, 130; b) P. Schroll, C. Fehl, S. Dankesreiter, B. König, *Org. Biomol. Chem.* **2013**, *11*, 6510.
8. For Meerwein arylations mediated by organic dyes, see: a) D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958; b) T. Xiao, X. Dong, Y. Tang, L. Zhou, *Adv. Synth. Catal.* **2012**, *354*, 3195; c) D. P. Hari, T. Hering, B. König, *Org. Lett.* **2012**, *14*, 5334; d) J. Yu, L. Zhang, G. Yan, *Adv. Synth. Catal.* **2012**, *354*, 2625; e) M. Majek, A. Jacobi von Wangelin, *Chem. Commun.* **2013**, *49*, 5507; f) M. N. Hopkinson, B. Sahoo,

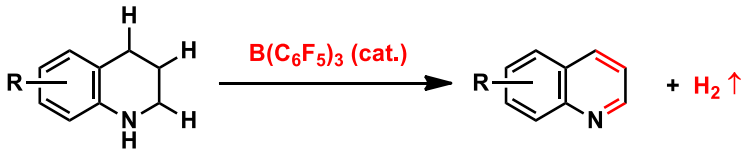
F. Glorius, *Adv. Synth. Catal,* **2014**, *356*, 2794; g) D. Kundu, S. Ahammed, B. C. Ranu, *Org. Lett.* **2014**, *16*, 1814; h) T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao, L. Zhou, *Green Chem.* **2014**, *16*, 2418; i) M. Majek, F. Filace, A. Jacobi von Wangelin, *Chem. – Eur. J.* **2015**, *21*, 4518. For recent reviews, see: j) D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688; k) M. Majek, F. Filace and A. Jacobi von Wangelin, *Beilstein J. Org. Chem.* **2014**, *10*, 981.

9. For Meerwein arylation by TEMPONa, see: M. Hartmann, Y. Li, A. Studer, *J. Am. Chem. Soc.* **2012**, *134*, 16516.
10. For Meerwein arylation by iodide, see: a) M. Hartmann, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 8180; b) D. Kosynkin, T. M. Bockman, J. K. Kochi, *J. Am. Chem. Soc.* **1997**, *119*, 4846.
11. For Meerwein arylation by ascorbic acid, see: F. P. Crisóstomo, T. Martín, R. Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181.
12. For Meerwein arylation by benzoyl peroxide, see: a) Z. H. Xia, J. B. Huang, Y. M. He, J. J. Zhao, J. Lei, Q. Zhu, *Org. Lett.* **2014**, *16*, 2546; b) S. Tang, D. Zhou, Y.-C. Wang, *Eur. J. Org. Chem.* **2014**, 3656; c) F. Y. Mo, Y. B. Jiang, D. Qiu, Y. Zhang, J. B. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 1846.
13. For Meerwein arylation by bases, see: a) W. Erb, A. Hellal, M. Albini, J. Rouden, J. Blanchet, *Chem. – Eur. J.* **2014**, *20*, 6608; b) U. M. V. Basavanag, A. Dos Santos, L. El Kaim, R. Gamez-Montano, L. Grimaud, *Angew. Chem. Int. Ed.* **2013**, *52*, 7194; c) Z. H. Xia, Q. Zhu, *Org. Lett.* **2013**, *15*, 4110; d) C. Molinaro, J. Mowat, F. Gosselin, P. D. O'Shea, J. F. Marcoux, R. Angelaud, I. W. Davies, *J. Org. Chem.* **2007**, *72*, 1856; e) R. A. Abramovitch, J. G. Saha, *Tetrahedron* **1965**, *21*, 3297.
14. For Meerwein arylation by methanol, see: C. J. Zhao, D. Xue, Z. H. Jia, C. Wang, J. L. Xiao, *Synlett* **2014**, *25*, 1577.
15. Metal-free porphyrins have been reported to act as electron mediators in artificial photosynthesis processes. For relevant reviews, see: a) D. Gust, T. A. Moore, A. L. Moore, *Acc. Chem. Res.* **2009**, *42*, 1890; b) Balzani, A. Credi, M. Venturi, *ChemSusChem* **2008**, *1*, 26; c) H. Imahori, Y. Mori, Y. Matano, *J. Photochem. Photobiol. C* **2003**, *4*, 51; d) D. Gust, T. A. Moore, A. L. Moore, *Acc. Chem. Res.* **2001**, *34*, 40; e) M. R. Wasielewski, *Chem. Rev.* **1992**, *92*, 435; see also: f) T. Nagasawa, S. I. Allakhverdiev, Y. Kimura, T. Nagata, *Photochem. Photobiol. Sci.* **2009**, *8*, 174.
16. Metal-free porphyrins are suggested to work as electron mediators in Fenton-type reactions in the absence of light irradiation. For examples, see: a) J. C. Koningsberger, B. S. van Asbeck, J. van Hattum, L. J. J. M. Wiegman, G. P. van Berge Henegouwen, J. J. M. Marx, *Eur. J. Clin. Invest.* **1993**, *23*, 716; b) M.

Fukushima, M. Kawasaki, A. Sawada, H. Ichikawa, K. Morimoto, K. Tatsumi, S. Tanaka, *J. Mol. Catal. A – Chem.* **2002**, *187*, 201.

17. Solubility of **4e** is more than 10 times greater than that of **4d** according to the solubility evaluation (experimental section, section 3c). It is also reported that **4d** is not soluble in common organic solvents. For details, see: N. Datta-Gupta, T. J. Bardos, *J. Heterocyclic Chem.* **1966**, *3*, 495.
18. For reviews on transition-metal-free cross coupling reactions, see: a) C.-L. Sun, Z.-J. Shi, *Chem. Rev.* **2014**, *114*, 9219; b) T. L. Chan, Y. Wu, P. Y. Choy, F. Y. Kwong, *Chem. – Eur. J.* **2013**, *19*, 15802; c) V. P. Mehta, B. Punji, *RSC Adv.* **2013**, *3*, 11957; d) E. Shirakawa, T. Hayashi, *Chem. Lett.* **2012**, *41*, 130; e) S. Yanagisawa, K. Itami, *ChemCatChem* **2011**, *3*, 827.
19. M. Kojima, K. Oisaki, M. Kanai, *Chem. Commun.* **2015**, *51*, 9718.
20. Recently, Gryko reported that metal-free porphyrins work as photoredox catalyst. For details, see: a) K. Rybicka-Jasińska, W. Shan, K. Zawada, K. M. Kadish, D. Gryco, *J. Am. Chem. Soc.* **2016**, *138*, 15451; b) K. Rybicka-Jasińska, B. König, D. Gryco, *Eur. J. Org. Chem.* **2017**, *early view*. DOI: 10.1002/ejoc.201601518.
21. Preliminary investigations revealed that Meerwein-type C-H arylation of furan with 4-bromobenzenediazonium tetrafluoroborate **2f** is possible in the presence of catalytic amounts of 5,10,15,20-tetrakis(4-aminophenyl)porphyrin **4c**. For details, see section 4 of the experimental section.

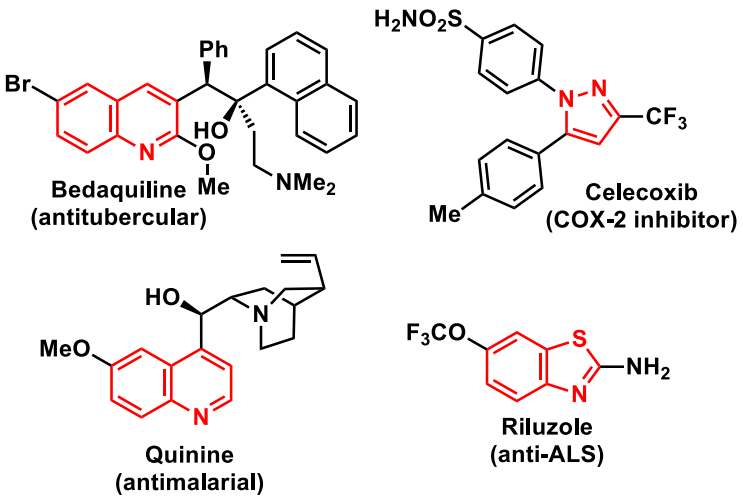
3. Tris(pentafluorophenyl)borane-catalyzed acceptorless dehydrogenation of N-heterocycles



3-1. Research background

3-1-1. N-Heteroarenes in pharmaceuticals

Nitrogen containing N-heteroarenes have long been of primary interest in synthetic organic chemistry. For example, a quinoline derivative bedaquiline is an antitubercular drug which is effective for the multidrug resistant tuberculosis.[1] Quinine is also a quinoline derived pharmaceutical which has long been utilized for the treatment of malaria. Celecoxib, with pyrazole structure in its skeleton, is a newly developed anti-inflammatory agent which has reduced side effects compared to classical nonsteroidal anti-inflammatory drugs.[2] A benzothiazole derivative riluzole is the first approved drug for treatment of amyotrophic lateral sclerosis (ALS).[3] Due to the significant importance of these N-heteroarenes in medicinal chemistry, development of a new and efficient method for the preparation of this compound class is a central research theme in modern synthetic chemistry.



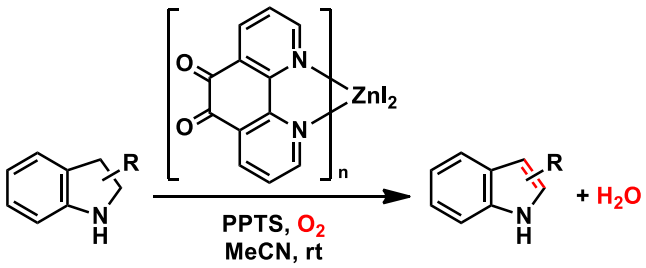
Scheme 20. N-Heteroarenes in pharmaceuticals

3-1-2. Catalytic dehydrogenation of N-heterocycles

Recently, catalytic dehydrogenation of (partially) saturated N-heterocycles via *sp*^{3} C-H functionalization has emerged as a new and atom economical[4] tool for the preparation of N-heteroarenes.[5] Among all, aerobic dehydrogenation and acceptorless dehydrogenation are typically attractive in terms of environmental friendliness.

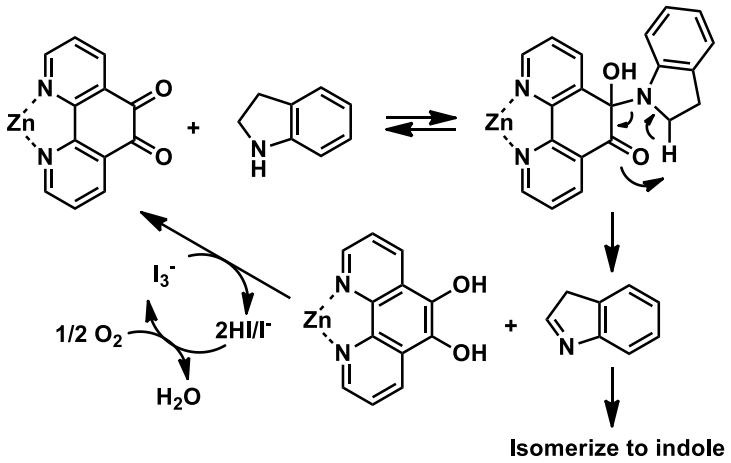
3-1-2-1. Aerobic dehydrogenation of N-heterocycles

Catalytic aerobic dehydrogenation of saturated N-heterocycles is more environmentally benign than the dehydrogenation mediated by stoichiometric chemical oxidants, because molecular oxygen is abundant and only harmless water is produced as a byproduct.[6] There are several transition-metal-catalyzed methods,[6a-6e, 6g-6i] while more desirable transition-metal-free catalytic methods remain rare. For example of transition-metal-free dehydrogenation catalysis, Stahl reported aerobic dehydrogenation of saturated N-heterocycles using ZnI_2/phd (phd = 1,10-phenanthroline-5,6-dione) system (Scheme 21).[6d]



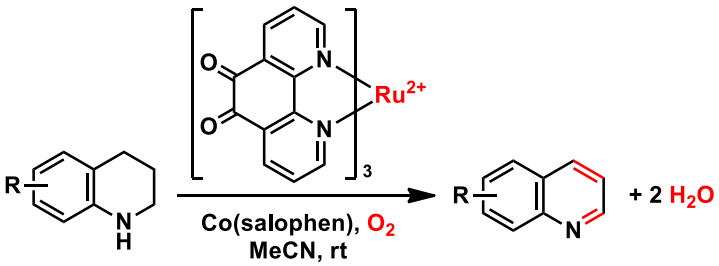
Scheme 21. Aerobic dehydrogenation of N-heterocycles by ZnI_2/phd[6d]

This system can be characterized as biomimetic catalysis because the reaction mechanisms of the catalytic system are similar to that of quinone mediated dehydrogenation by copper amine oxidase enzymes (Scheme 22). After comprehensive mechanistic studies, Stahl proposed that secondary amines are dehydrogenated by quinone/hydroquinone redox cycle through hemiaminal intermediate, while the iodine/iodide redox cycle reoxidizes the hydroquinone and regenerate the quinone catalyst. Finally, molecular oxygen works as a terminal oxidant and reoxidizes iodide. This ZnI_2/phd system is applicable for the dehydrogenation of secondary amines, and successfully applied to the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinazolines and indolines. On the other hand, dehydrogenation of 1,2,3,4-tetrahydroquinoline was unsuccessful under this catalytic conditions.



Scheme 22. Reaction mechanisms of the dehydrogenation by ZnI_2/phd

Soon after, Stahl disclosed $[Ru(phd)_3]^{2+}$/Co(salophen) catalytic system for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines (Scheme 23).[6g] It is reported that utilization of ruthenium instead of zinc facilitates the more efficient dehydrogenation. However, requirements for the precious and toxic ruthenium is disadvantageous compared to transition-metal-free methods.

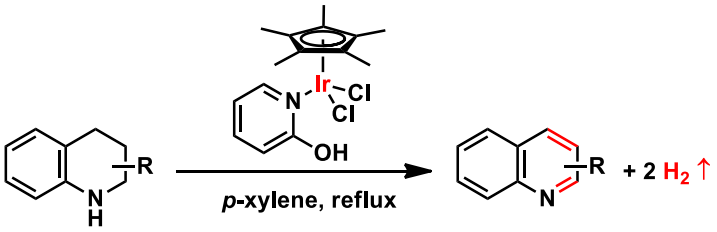


Scheme 23. Aerobic dehydrogenation of tetrahydroquinolines by $[Ru(phd)_3]^{2+}$/Co(salophen)[6g]

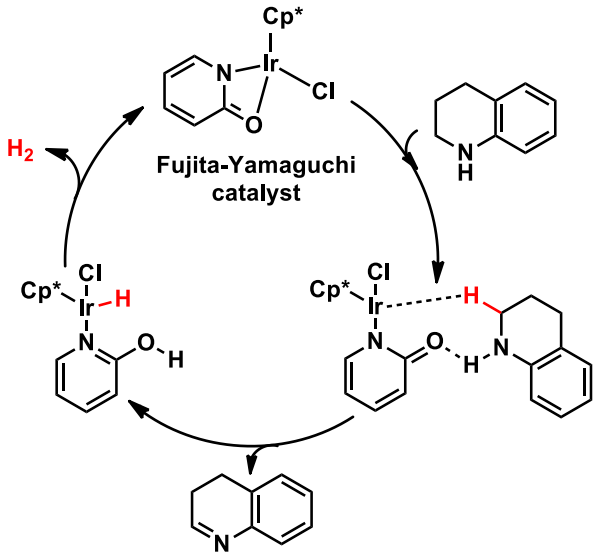
3-1-2-2. Acceptorless dehydrogenation of N-heterocycles

Catalytic acceptorless dehydrogenation can be considered to be an ideal way to desaturate organic compounds because no external reagent is necessary and valuable molecular hydrogen is expelled during the desaturation.[7] Historically, synthetically relevant conditions were accomplished by homogeneous transition metal catalysts.[8-9] Yamaguchi and Fujita are the pioneers in this class of reactions, and first reported the acceptorless dehydrogenation of 1,2,3,4-tetrahydroquinolines by [IrCp*(2-hydroxypyridine)] catalyst (Scheme 24).[9a] The following computational study

suggested that 2-hydroxypyridine ligand assists deprotonation of amines while iridium center abstracts hydride from sp^3 C-H bonds alpha to nitrogen atom. The subsequent protonolysis of iridium-hydride by 2-hydroxypyridine allows the release of molecular hydrogen and regeneration of the catalyst (Scheme 25).[9h]

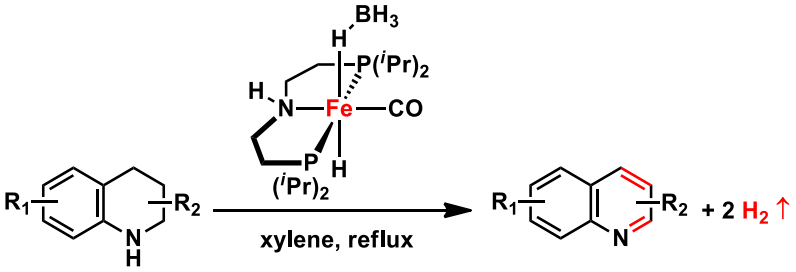


Scheme 24. Acceptorless dehydrogenation of tetrahydroquinolines by [IrCp*(2-hydroxypyridine)] catalyst[9a]



Scheme 25. Proposed mechanisms of acceptorless dehydrogenation by [IrCp*(2-hydroxypyridine)] catalyst[9h]

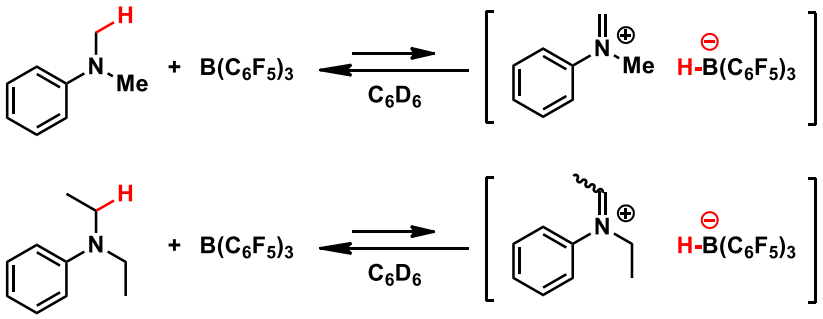
Following this report, Xiao[9b,g] and Crabtree[9e] also developed iridium-catalyzed acceptorless dehydrogenations of saturated N-heterocycles. However, necessity for costly iridium is a common drawback of these precedents. Interestingly, Jones reported relevant acceptorless dehydrogenation reactions by iron[9d] or cobalt[9f] catalysis (Scheme 26). Although the relative abundance of these first row transition metals could be an advantage, substrate scope and functional group tolerance of these catalytic systems has not been thoroughly investigated so far.



Scheme 26. Iron-catalyzed acceptorless dehydrogenation of N-heterocycles[9d]

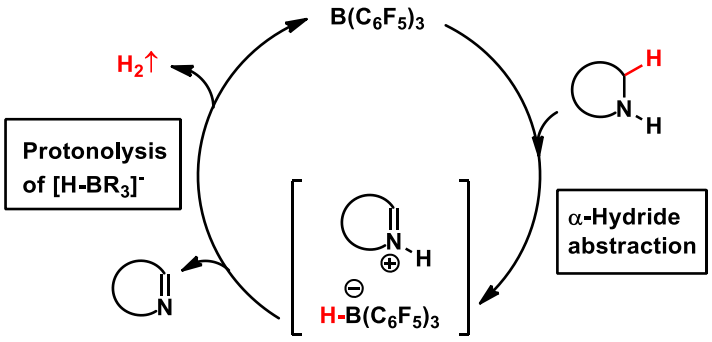
3-2. Reaction design

In order to establish a more synthetically-benign catalyst for acceptorless dehydrogenation of N-heterocycles, I focused on the chemistry of electrophilic organoboranes.[10] Electrophilic organoboranes are common cocatalysts for olefin polymerization, and investigation of their chemical behavior has long been of interest in a field of inorganic chemistry. In early 2000s, Basset was working on the mechanistic investigations of olefin polymerization catalysts by means of multinuclear NMR analysis. In one of his publications, he described a unique reactivity of an electrophilic organoborane. It was reported that tris(pentafluorophenyl)borane abstracted hydride from sp^3 C-H bonds of dialkylanilines, and reversibly formed iminium-borohydride complex (Scheme 27).[11a]



Scheme 27. Hydride abstraction from sp^3 C-H bonds of amines by an electrophilic organoborane[11a]

Based on this discovery, I hypothesized that novel catalytic acceptorless dehydrogenation could be realized as described in Scheme 28. First, hydride abstraction[11] from sp^3 C-H bonds of amines by an electrophilic borane produces iminium-borohydride complex. Second, protonolysis of the borohydride produces the desaturated amines and releases molecular hydrogen, regenerating the oraganoborane catalyst.[12-13]

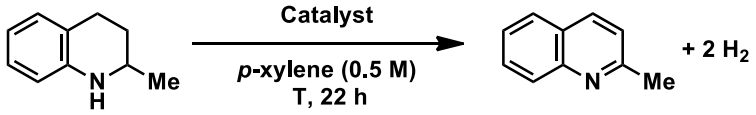


Scheme 28. Reaction design

3-3. Reaction development

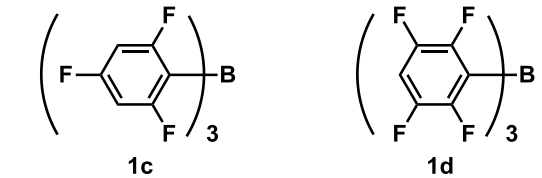
In order to evaluate the validity of my hypothesis, catalytic acceptorless dehydrogenation of 2-methyl-1,2,3,4-tetrahydroquinoline **2a** was investigated in the presence of catalytic amounts of electrophilic organoboranes **1** (Scheme 29). Gratifyingly, desired product **3a** was obtained in 42% yield with 2.5 mol% of tris(pentafluorophenyl)borane **1a** (Scheme 29, entry 1). Fluoroarylboranes **1c** or **1d** with reduced Lewis acidity compared to tris(pentafluorophenyl)borane resulted in low activity (entries 2-3). Phosphinoborane **1e**, which has comparable Lewis acidity compared to tris(pentafluorophenyl)borane afforded **3a** in modest yield (entry 4). More Lewis acidic phosphonium borane **1f** or chloroaryl boranes **1g**, **1h** showed almost no reactivity (entries 5-7). From these results, tris(pentafluorophenyl)borane **1a** was identified as the most reactive catalyst for the catalytic dehydrogenation.

Lewis basic additives **1i** and **1j** made no positive effects for the transformation (entries 8-9). Survey of the reaction temperature revealed that the highest yield (92%) was obtained when the reaction was run at 150 °C (entry 10), while catalytic dehydrogenation under lower temperature resulted in limited success (entries 11-12). From these observations, I have identified that the conditions of entry 10 is optimal for the borane-catalyzed acceptorless dehydrogenation of 1,2,3,4-tetrahydroquinoline derivatives.



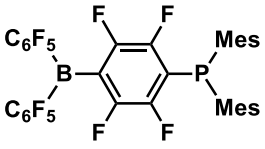
2a 3a

Entry	Catalyst (mol%)	T [°C]	Yield [%][a]
1	$B(C_6F_5)_3$ (**1a**) (2.5)	150	42
2	**1c** (2.5)	150	3
3	**1d** (2.5)	150	1
4	**1e** (2.5)	150	23
5	**1f** (2.5)	150	1
6	**1g** (2.5)	150	0
7	**1h** (2.5)	150	0
8	**1a** (2.5) + **1i** (2.5)	150	4
9	**1a** (2.5) + **1j** (2.5)	150	3
10	**1a** (5)	150	98 (92)[b]
11	**1a** (5)	100	30
12	**1a** (5)	120	41

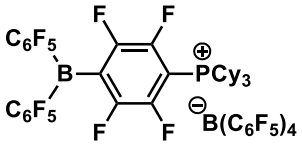


1c

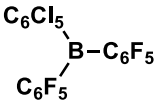
1d



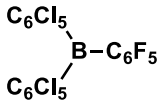
1e



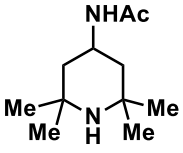
1f



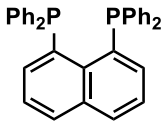
1g



1h



1i



1j

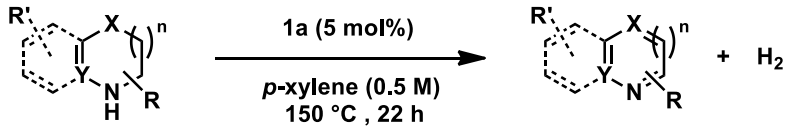
2a (0.25 mmol) and the catalyst were dissolved in *p*-xylene (0.5 mL) and heated in a screw-capped tube (diameter = 25 mm, height = 200 mm) for 22 hours. [a] ^{1}H NMR yield. [b] Isolated yield.

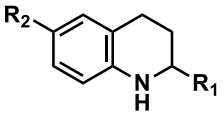
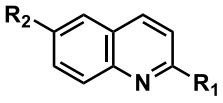
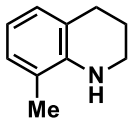
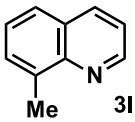
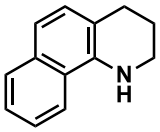
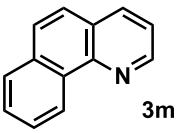
Scheme 29. Optimization of reaction conditions

3-4. Substrate scope study

3-4-1. Quinoline derivatives

With the optimized conditions in hand, substrate scope of the borane-catalyzed dehydrogenation for the synthesis of quinoline derivatives has been investigated (Scheme 30). For the substituent of the 2-position of quinolines, methyl, butyl, and aryl groups were tolerated (Scheme 30, entries 1-3). As for functional groups on 2-aryl rings, electron donating methyl and withdrawing chloro group made minor differences in the catalytic activity (entries 4-5). It is worthwhile to note that thioether group, which could be sensitive to the common oxidative reaction conditions, was compatible in the standard conditions (entry 6). Functional groups on 6-position of quinolines such as methyl, methoxy, fluoro, chloro and bromo were all compatible in the dehydrogenation reaction (entries 7-11). The relatively lower yield of the methoxy substituted quinoline could be due to catalyst deactivation by strong coordination of oxygen to the borane (entry 2h). 8-Substituted quinolines could also be synthesized from the respective tetrahydroquinoline in good yield under relevant conditions (entries 12-13). These results prove that the borane-catalyzed dehydrogenation is highly general for the preparation of the substituted quinoline derivatives.



Entry	N-Heterocycle (2)	Product (3): Yield [%]
		
1	**2a**: R_1 = Me, R_2 = H	**3a**: 92
2	**2b**: R_1 = Bu, R_2 = H	**3b:** 98
3	**2c**: R_1 = Ph, R_2 = H	**3c**: 90
4	**2d**: R_1 = 4-Me-C_6H_4, R_2 = H	**3d**: quant.
5	**2e**: R_1 = 4-Cl-C_6H_4, R_2 = H	**3e**: 85
6	**2f**: R_1 = 4-SMe-C_6H_4, R_2 = H	**3f**: 67
7	**2g**: R_1 = Me, R_2 = Me	**3g**: 91
8	**2h**: R_1 = Me, R_2 = OMe	**3h**: 70
9	**2i**: R_1 = Me, R_2 = F	**3i**: 96
10	**2j**: R_1 = Me, R_2 = Cl	**3j**: 90
11	**2k:** R_1 = Me, R_2 = Br	**3k:** 89
12	 **2l**	 **3l: 70**
13	 **2m**	 **3m: 90[a]**

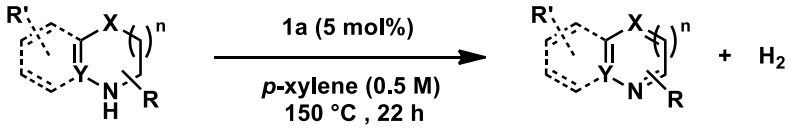
[a] 10 mol% of **1a** was used.

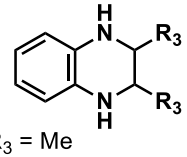
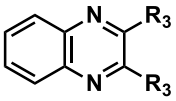
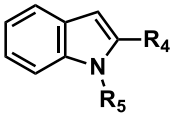
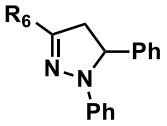
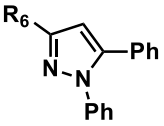
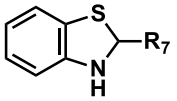
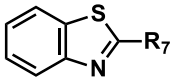
Scheme 30. Scope of 1,2,3,4-tetrahydroquinoline derivatives

3-4-1. Other N-heterocycles

Encouraged by these results, substrate scope of other N-heterocycles was investigated (Scheme 31). Qunoxalines are important N-heteroarenes in medicinal chemistry,[14] and their synthesis by catalytic dehydrogenation would be beneficial for the preparation of these N-heteroarenes. Using the optimal conditions for the quinoline synthesis, tetrahydroquinoxalines with methyl or phenyl group on 2,3-positions were dehydrogenated in good yield (Scheme 31, entries 1-2). Considering that there are several established methods for the synthesis of indolines,[15] catalytic dehydrogenation of indolines should provide reliable synthetic routes to indoles. While catalytic

dehydrogenation of an unsubstituted indoline produced the desired product in modest yield even after prolonged reaction time (entry 3), 2-methylindole and N-methylindole were synthetized in excellent yield under standard conditions from the respective indolines (entries 4-5). It is worthwhile to note that **3r** was successfully dehydrogenated under the borane catalysis because **2r** was not dehydrogenated in good yield by the transition-metal-free aerobic dehydrogenation conditions.[6d] Pyrazoles are usually synthesized by the dehydrogenation of pyrazolines, which are readily synthesized from the condensation of enone and hydrazine. With 5 mol% or 10 mol% of the borane catalyst, pyrazoles were synthesized from the respective pyrazolines in good to excellent yield (entries 6-7). The modest reactivity of **2s** could be due to the limited catalyst turnovers by strong coordination of its nitrogen lone pair of the product **3s** to the borane. Benzothiazoles are another ubiquitous N-heteroarenes in medicinal chemistry. Nevertheless, catalytic acceptorless dehydrogenation of benzothiazolines by homogeneous metal catalysts is especially challenging because the sulfur atom works as a catalyst poison. However, with 10 mol% of the borane catalyst, benzothiazoles were synthesized in good to excellent yield by the catalytic dehydrogenation of benzothiazolines (entries 8-10).



Entry	N-Heterocycle (2)	Product (3): Yield [%]
		
1	**2n**: R_3 = Me	**3n**: 93
2	**2o**: R_3 = Ph	**3o**: 71
		
3	**2p**: R_4 = H, R_5 = H	**3p**: 45[b]
4	**2q**: R_4 = Me, R_5 = H	**3q**: 90
5	**2r**: R_4 = H, R_5 = Me	**3r**: 91
		
6	**2s**: R_6 = Me	**3s**: 75[a]
7	**2t**: R_6 = Ph	**3t**: 91
		
8	**2u**: R_7 = Ph	**3u**: 91[a]
9	**2v**: R_7 = 1-naph	**3v**: 92[a]
10	**2w**: R_7 = CH_2CH_2Ph	**3w**: 74[a]

[a] 10 mol% of **1a** was used. [b] The reaction was run for 48 hours.

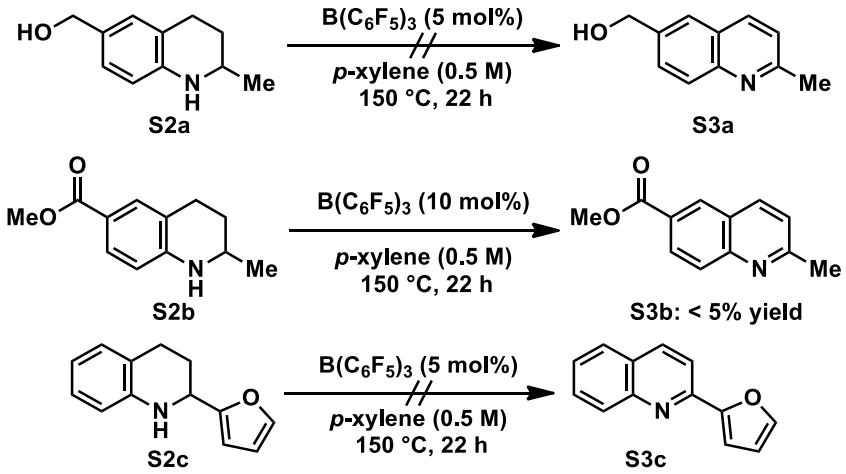
Scheme 31. Scope of other N-heterocycles

3-4-2. Current limitations

3-4-2-1. Tolerance to other oxygen functionalities

Some partially saturated N-heterocycles were not effectively dehydrogenated in the present catalytic conditions. For example, when 1,2,3,4-tetrahydroquinoline derivatives with alcohol **S2a** was subjected to standard dehydrogenation conditions, significant decomposition of starting material was observed, and no desired product **S3b** was obtained (Scheme 32, upper row). On the other hand, when 1,2,3,4-tetrahydroquinoline

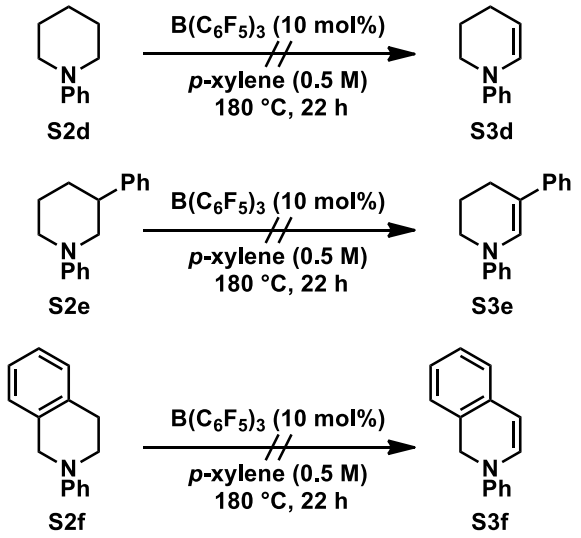
S2b with an ester functionality was subjected to dehydrogenation in the presence of 10 mol% of $B(C_6F_5)_3$, formation of quinoline ester **S3b** was observed only in a trace amount (Scheme 32, middle row). In addition, when substrate **S2c** was subjected to standard dehydrogenation conditions, only decomposition of **S2c** was observed, possibly due to the limited stability of the furyl group under the reaction conditions (Scheme 32, lower row). Thus, the limited tolerance to benzyl alcohol, ester, or 5-membered oxygen heterocycle is limitation of the present protocol.



Scheme 32. Borane-catalyzed dehydrogenation of oxygen containing substrates

3-4-2-2. Dehydrogenation of piperidine derivatives

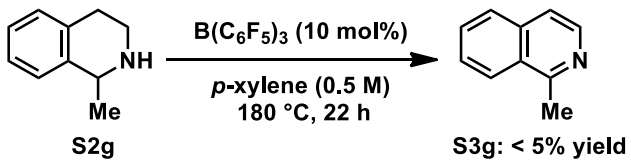
Stephan and Crudden reported hydride abstraction from Hantzsch ester derivatives by tris(pentafluorophenyl)borane in a stoichiometric fashion.[16] Thus, we evaluated whether the dehydrogenation of piperidine derivatives could take place under the present reaction conditions (Scheme 33). Three kinds of N-phenyl piperidine derivatives **S2d**, **S2e**, and **S2f** were subjected to the catalytic dehydrogenation in the presence of 10 mol% borane catalyst under 180 °C. However, no dehydrogenated products were obtained from any of these cyclic amines, and the starting materials were recovered. These results indicate the limited applicability of our protocol for the dehydrogenation of 1-phenylpiperidine derivatives.



Scheme 33. Borane-catalyzed dehydrogenation of N-phenylpiperidine derivatives

3-4-2-3. Dehydrogenation of 1-methyl-1,2,3,4-tetrahydroisoquinoline

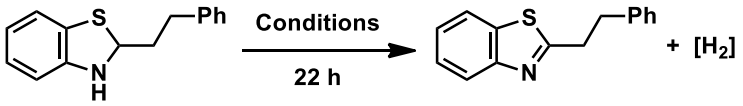
Catalytic dehydrogenation of 2-methyl-1,2,3,4-tetrahydroisoquinoine **S2g** was also tried since isoquinolines are an important class of N-heterocycles in organic synthesis (Scheme 34). However, even at 180 °C in the presence of 10 mol% of the borane catalyst, only very small conversion to isoquinoline was observed. We tentatively assume that strong coordination of tetrahydroisoquinoline or isoquinoline to tris(pentafluorophenyl)borane might inhibit efficient catalytic turnovers.



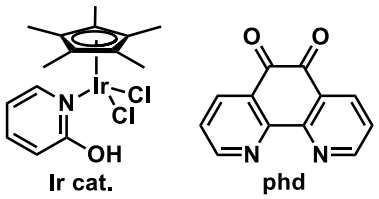
Scheme 34. Borane-catalyzed dehydrogenation of tetrahydroisoquinoline

3-5. Comparison of reactivity

The high reactivity of the borane catalyst for the dehydrogenation of a benzothiazoline **2w** (Scheme 35, entry 1) suggests that the borane catalyst should have high compatibility to sulfur containing compounds compared to metal-based dehydrogenation catalysis. In order to prove the hypothesis, catalytic acceptorless dehydrogenation of **2w** by Cp*Ir(2-hydroxypyridine)[9a] was attempted with 10 mol% of the iridium catalyst. As a result, the desired product **3w** was obtained in 38% yield (entry 2). On the other hand, transition-metal-free aerobic oxidation of **2w** by ZnI_2/phd catalyst[6d] afforded **3w** in 7% yield (entry 3). These results suggest that tris(pentafluorophenyl)borane has a uniquely high tolerance toward sulfur functionalities compared to the metal-catalyzed counterparts.



Entry	Conditions (mol%)	Yield [%]
1	$B(C_6F_5)_3$ (10), *p*-xylene, 150 °C	74
2	Ir cat. (10), *p*-xylene, 150 °C	38
3	phd (10), ZnI_2 (5), MeCN, O_2, rt	7

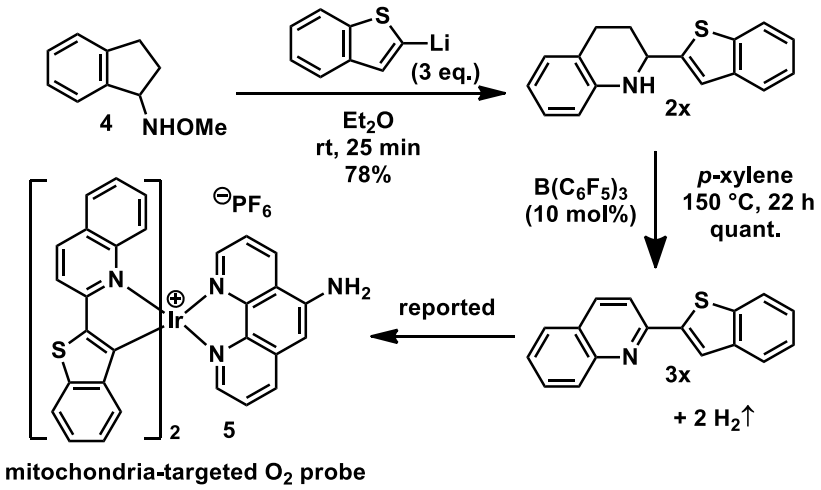


Ir cat. phd

Scheme 35. Comparison of dehydrogenation reactivity

3-6. Application study

In order to evaluate the synthetic utility of the present reaction, the borane-catalyzed dehydrogenation was applied to the synthesis of a functional molecule (Scheme 36). Tobita reported that iridium complex **5** worked as a mitochondria-targeted oxygen probe in HeLa cells.[17] The heterobiaryl **3x** is a precursor for **5**, and was previously synthesized by palladium-catalyzed Suzuki-Miyaura coupling. I envisioned that **3x** could be synthesized by the catalytic dehydrogenation of a respective partially saturated N-heterocycle **2x**. According to the method by Miyata,[18] treatment of readily available hydroxylamine methyl ether **4** with organolithium reagent afforded **2x** in 78% yield. Then, catalytic dehydrogenation of **2x** by $B(C_6F_5)_3$ proceeded smoothly, and **3x** was obtained in quantitative yield. For the preparation of synthetic drugs or probe molecules for chemical biology, contamination of toxic transition metal is a severe problem. In that sense, these transition metal free transformations should constitute a valuable new method for the preparation of 2-subsituted quinolines not only for materials science but also for synthesis of biologically active substances.

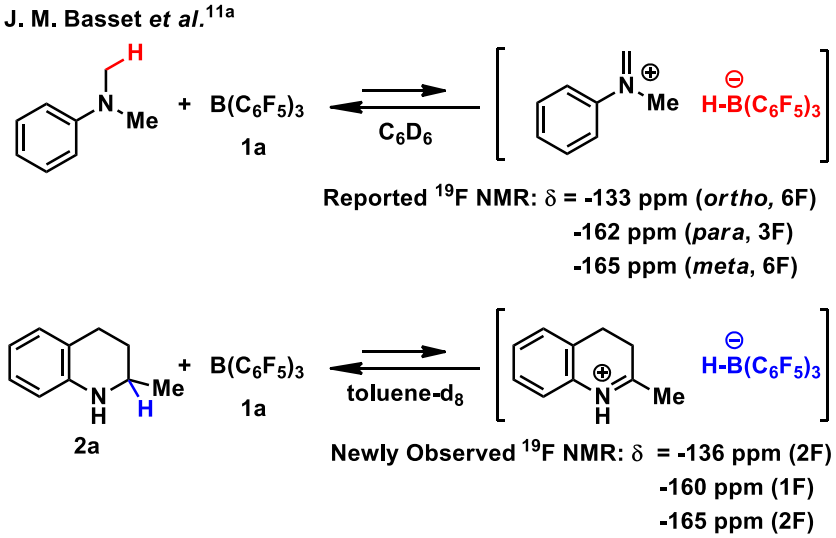


Scheme 36. Transition metal free synthesis of heterobiaryl **3x**

3-7. Mechanistic discussions

3-7-1. Confirmation of hydride abstraction by NMR study

According to the precedential reports,[11a,11h] tris(pentafluorophenyl)borane **1a** can reversibly abstract hydride from sp^3 C-H bonds of saturated amines (Scheme 37, upper row). Based on these literature precedents, it is expected that **1a** would abstract hydride from cyclic amine **2a** and form the iminium-borohydride complex, whose ^{19}F NMR resonances are expected to be similar to the reported values of iminium-borohydride complex (δ = –133, –162, –165 ppm). Indeed, in the NMR analysis of the mixture of 2-methyl-1,2,3,4-tetrahydroquinoline **2a** and tris(pentafluorophenyl)borane **1a** in toluene-d8, the relevant ^{19}F NMR resonances (δ = –136, –160, –165 ppm) were observed (Scheme 37, lower row). Since chemical shifts and relative integrations of the signals observed in the NMR experiment were in good agreement with the literature values,[11a] these results support that iminium-borohydride intermediate is formed from **2a** and **1a** in the reaction mixture.

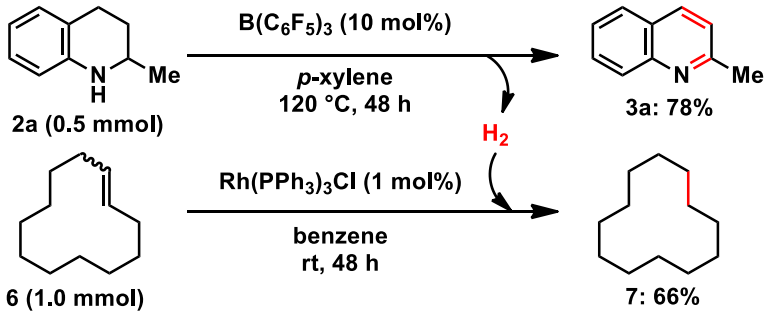


Scheme 37. Comparison between the reported and our NMR studies

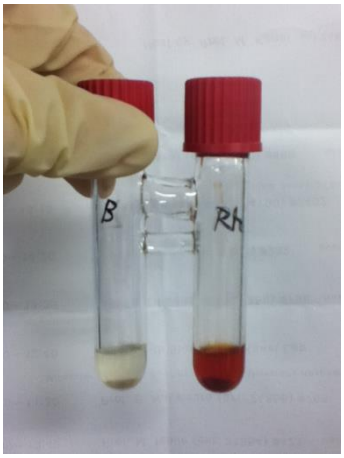
3-7-2. Confirmation of H_2 gas release by dual reactions

In order to confirm that molecular hydrogen is expelled during the desaturation of N-heterocycles, a dual reactions experiment was conducted (Scheme 38). In one side of a COware (Scheme 39), a two-chamber reaction vessel,

2-methyl-1,2,3,4-tetrahydroquinoline **2a** and catalytic amounts of tris(pentafluorophenyl)borane **1a** was dissolved in *p*-xylene. In the other side of the apparatus, benzene solution of cyclododecene **6** and Wilkinson's catalyst was placed. These two reactions share the same atmosphere and only gaseous components can be transferred to the other side of the reaction. After 48 hours of the reaction, 2-methylquinoline **3a** was obtained in 78% yield and cyclododecane **7** was obtained in 66% yield, respectively. Formation of **7** clearly indicates the release of H_2 during the desaturation of **2a**, which was transferred to the other side of the apparatus and utilized in rhodium-catalyzed hydrogenation of **6**.



Scheme 38. Confirmation of the release of gaseous H_2 via a dual reaction

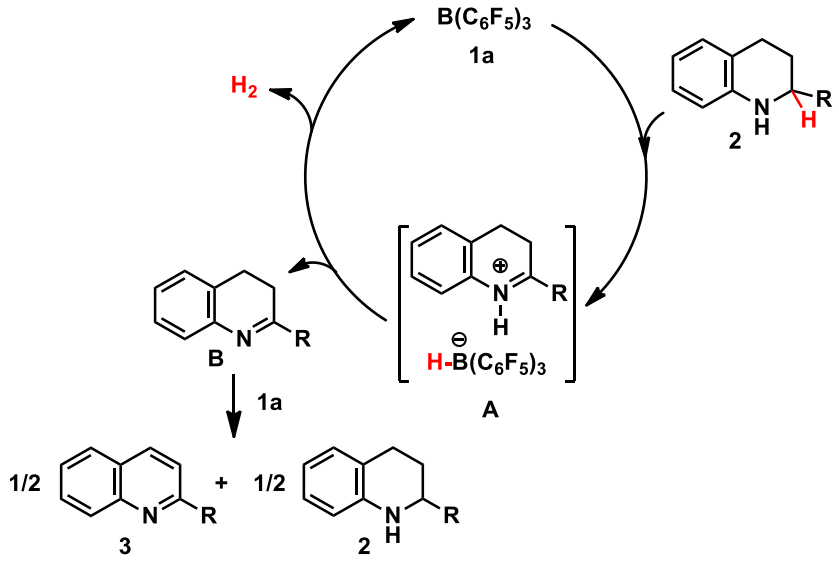


Scheme 39. Appearance of COware

3-7-3. Plausible catalytic cycle for dehydrogenation of 1,2,3,4-tetrahydroquinolines

Based on the NMR studies, it is reasonable to assume that the present dehydrogenation reaction proceeds via borohydride intermediate. Evolution of gaseous hydrogen was also confirmed by the dual reactions experiment. Supported by these

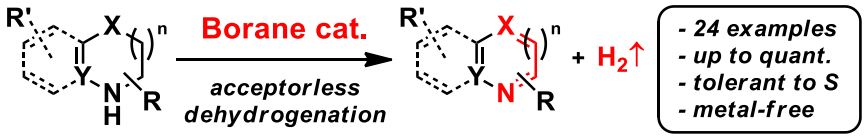
experimental results, a plausible catalytic cycle is suggested as shown in Scheme 40. Electrophilic borane **1a** abstracts hydride from *sp*^{3} C-H bond alpha to the nitrogen atom of substrates **2**, and forms borohydride-iminium complex **A**. Protonolysis of the complex releases partially desaturated N-heterocycle **B** along with molecular hydrogen and regenerates the borane catalyst. It is reported that 3,4-dihydroquinoline undergoes disproportionation into quinoline **3** and 1,2,3,4-tetrahydroquinoline under acidic conditions.[19] Since the borane works as a Lewis acid, this process may be also accelerated by **1a**. The overall catalytic process could be hampered when a substrate forms a stable Lewis adduct with **1a** and deactivates the borane catalyst, leading to the limited reactivity of 1,2,3,4-tetrahydroisoquinoline **S2g**.



Scheme 40. Plausible catalytic cycle

3-8. Conclusion

In conclusion, tris(pentafluorophenyl)borane **1a** realized the first metal-free acceptorless dehydrogenation of N-heterocycles (Scheme 41). The scope of the borane-catalyzed acceptorless dehydrogenation is quite broad, and several kinds of synthetically valuable N-heteroarenes were produced in up to quantitative yield. The present borane catalysis exhibited high tolerance to sulfur functionalities, and demonstrated superior reactivity for the dehydrogenative synthesis of benzothiazole compared to conventional metal-catalyzed dehydrogenation methods. Considering the abundance and inherently low toxicity of boron compared to transition metals,[20] the present boron catalysis provides explicit advantages compared to metal-catalyzed systems.[21] Thus, the present catalytic reaction demonstrates a new way of utilizing organoboranes in synthetic organic chemistry. Application of the borane catalysis to other types of sp^3 C-H functionalizations is currently in progress.



Scheme 41. Tris(pentafluorophenyl)borane-catalyzed acceptorless dehydrogenation of N-heterocycles

3-9. References

1. a) K. Andries, P. Verhasselt, J. Guillemont, H. W. H. Göhlmann, J.-M. Neefs, H. Winkler, J. V. Gestel, P. Timmerman, M. Zhu, E. Lee, P. Williams, D. de Chaffoy, E. Huitric, S. Hoffner, E. Cambau, C. Truffot-Pernot, N. Lounis, V. Jarlier, *Science* **2005**, *307*, 223; b) A. Koul, N. Dengouga, K. Vergauwen, B. Molenberghs, L. Vranckx, R. Willebrords, Z. Ristic, H. Lill, I. Dorange, J. Guillemont, D. Bald, K. Andries, *Nat. Chem. Biol.* **2007**, *3*, 323.
2. T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. Nita, Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347.
3. G. Bensimon *et al. N. Engl. J. Med.* **1994**, *330*, 585.
4. B. M. Trost, *Science* **1991**, *254*, 1471.
5. For related reviews, see: a) C. A. Girard, H. Huang, F. Zhou, G.-J. Deng, C.-J. Li, *Org. Chem. Front.* **2015**, *2*, 279; b) G. X. Giustra, J. S. A. Ishibashi, S.-Y. Liu, *Coord. Chem. Rev.* **2016**, *314*, 134.
6. For selected examples, see: a) S.-I. Murahashi, Y. Okano, H. Sato, T. Nakae, N. Komiya, *Synlett* **2007**, 1675; b) H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 13970; c) H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *Adv. Synth. Catal.* **2012**, *354*, 2899; d) A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 506; e) A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 11910; f) A. V. Iosub, S. S. Stahl, *Org. Lett.* **2015**, *17*, 4404; g) X. Cui, Y. Li, S. Bachmann, M. Scalone, A.-E. Surkus, K. Junge, C. Topf, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 10652.
7. a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 249. Catalytic acceptorless dehydrogenation of N-heterocycles is also a key reaction in hydrogen storage technology. For related reviews, see: b) R. H. Crabtree, *Energy Environ. Sci.* **2008**, *1*, 134; c) Q.-L. Zhu, Q. Xu, *Energy Environ. Sci.* **2015**, *8*, 478.
8. For selected reviews of ruthenium-catalyzed acceptorless dehydrogenation of organic compounds, see: a) C. Gunanathan, D. Milstein, *Chem. Rev.* **2014**, *114*, 12024; b) S. Werkmeister, J. Neumann, K, Junge, M. Beller, *Chem. – Eur. J.* **2015**, *21*, 12226. For selected examples, see: c) S. Muthaiah, S. H. Hong, *Adv. Synth. Catal.* **2012**, *354*, 3045; d) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 11384; e) M. Nielsen, E. Alberico, W. Baumann, H.-J. Drexler, H. Junge,

S. Gladiali, M. Beller, *Nature* **2013**, *495*, 85; f) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028; g) A. Khalafi-Hezhad, F. Panahi, *ACS Catal.* **2014**, *4*, 1686.

9. a) R. Yamaguchi, C. Ikeda, Y. Takahashi, K. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 8410; b) J. Wu, D. Talwar, S. Johnston, M. Yan, J. Xiao, *Angew. Chem. Int. Ed.* **2013**, *52*, 6983; c) K. Fujita, Y, Tanaka, M. Kobayashi, R. Yamaguchi, *J. Am. Chem. Soc.* **2014**, *136*, 4829; d) S. Chakraborty, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2014**, *136*, 8564; e) M. G. Manas, L. S. Sharninghausen, E. Lin, R. H. Crabtree, *J. Organomet. Chem.* **2015**, *792*, 184; f) R. Xu, S. Chakraborty, H. Yuan, W. D. Jones, *ACS Catal.* **2015**, *5*, 6350; g) D. Talwar, A. Gonzalez-de-Castro, H. Y. Li, J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5223; h) X.-B. Zhang, Z. Xi, *Phys. Chem. Chem. Phys.* **2011**, *13*, 3997. A related catalytic acceptorless dehydrogenation of heterocycles was also reported by Nozaki, see: i) S. Kusumoto, M. Akiyama, K. Nozaki, *J. Am. Chem. Soc.* **2013**, *135*, 18726.
10. Electrophilic organoboranes are commonly used in Frustrated Lewis Pair (FLP) chemistry. For selected reviews, see: a) D. W. Stephan, *Org. Biomol. Chem.* **2008**, *6*, 1535; b) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46; c) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018; d) D. W. Stephan, *Acc. Chem. Res.* **2015**, *48*, 306; e) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2015**, *54*, 6400.
11. For selected examples of hydride abstraction from organic molecules by the electrophilic borane, see: a) N. Millot, C. C. Santini, B. Fenet, J. M. Basset, *Eur. J. Inorg. Chem.* **2002**, 3328; b) J. M. Farrell, Z. M. Heiden, D. W. Stephan, *Organometallics* **2011**, *30*, 4497; c) J. D. Webb, V. S. Laberge, S. J. Geier, D. W. Stephan, C. M. Crudden, *Chem. – Eur. J.* **2010**, *16*, 4895; d) I. Chatterjee, M. Oestreich, *Angew. Chem. Int. Ed.* **2015**, *54*, 1965; e) I. Chatterjee, Z.-W. Qu, S. Grimme, M. Oestreich, *Angew. Chem. Int. Ed.* **2015**, *54*, 12158; f) A. Simonneau, M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 11905; g) S. Keess, A. Simonneau, M. Oestreich, *Organometallics* **2015**, *34*, 790. For a related review, see: h) F. Focante, P. Mercandelli, A. Sironi, L. Resconi, *Coord. Chem. Rev.* **2006**, *250,* 170. Borane-catalyzed hydride abstraction is also a key step in transfer hydrosilylation chemistry. For a review, see: h) M. Oestreich, *Angew. Chem. Int. Ed.* **2016**, *55*, 494.
12. For selected reviews on borane-mediated hydrogenations, see: a) D. W. Stephan, S. Greenberg, T. W. Graham, P. Chase, J. J. Hastie, S. J. Geier, J. M. Farrell, C. C. Brown, Z. M. Heiden, G. C. Welch, M. Ullrich, *Inorg. Chem.* **2011**, *50*, 12338; b) D. W. Stephan, *Org. Biomol. Chem.* **2012**, *10*, 5740; c) J. Paradies, *Synlett* **2013**, *24*, 777; d) J. Paradies, *Angew. Chem. Int. Ed.* **2014**, *53*, 3552; e) X. Feng, H. Du,

Tetrahedron Lett. **2014**, *55*, 6959; f) L. J. Hounjet, D. W. Stephan, *Org. Process Res. Dev.* **2014**, *18*, 385; g) M. Oestreich, J. Hermeke, J. Mohr, *Chem. Soc. Rev.* **2015**, *44*, 2202; h) J. Mohr, D. Porwal, I. Chatterjee, M. Oestreich, *Chem. – Eur. J.* **2015**, *21*, 17583. For selected examples on the hydrogenation of C=N bonds, see: i) P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 8050; j) P. A. Chase, T. Jurca, D. W. Stephan, *Chem. Commun.* **2008**, 1701; k) P. Spies, S. Schwendemann, S. Lange, G. Kehr, R. Fröhlich, G. Erker, *Angew. Chem. Int. Ed.* **2008**, *47*, 7543; l) V. Sumerin, F. Schultz, M. Atsumi, C. Wang, M. Nieger, M. Leskelä, T. Repo, P. Pyykkö, B. Rieger, *J. Am. Chem. Soc.* **2008**, *130*, 14117; m) D. Chen, J. Klankermayer, *Chem. Commun.* **2008**, 2130; n) G. Erős, H. Mehdi, I. Pápai, T. A. Rokob, P. Király, G. Tárkányi, T. Soós, *Angew. Chem. Int. Ed.* **2010**, *49*, 6559; o) S. J. Geier, P. A. Chase, D. W. Stephan, *Chem. Commun.* **2010**, *46*, 4884; p) D. Chen, Y. Wang, J. Klankermayer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9475; q) T. Mahdi, Z. M. Heiden, S. Grimme, D. W. Stephan, *J. Am. Chem. Soc.* **2012**, *134*, 4088; r) Y. Liu, H. Du, *J. Am. Chem. Soc.* **2013**, *135*, 6810; s) Y. Liu, H. Du, *J. Am. Chem. Soc.* **2013**, *135*, 12968; t) D. J. Scott. M. J. Fuchter, A. E. Ashley, *Angew. Chem. Int. Ed.* **2014**, *53*, 10218; u) J. Mohr, M. Oestreich, *Angew. Chem. Int. Ed.* **2014**, *53*, 13278; v) D. J. Scott, M. J. Fuchter, A. E. Ashley, *Angew. Chem. Int. Ed.* **2014**, *53*, 10218; w) Z. Zhang, H. Du, *Angew. Chem.* **2015**, *127*, 633; *Angew. Chem. Int. Ed.* **2015**, *54*, 623; x) J. M. Farrell, R. T. Posaratnanathan, D. W. Stephan, *Chem. Sci.* **2015**, *6*, 2010; y) P. Eisenberger, B. P. Bestvater, E. C. Keske, C. M. Crudden, *Angew. Chem. Int. Ed.* **2015**, *54*, 2467; z) M. Lindqvist, K. Borre, K. Axenov, B. Kótai, M. Nieger, M. Leskelä, I. Pápai, T. Repo, *J. Am. Chem. Soc.* **2015**, *137*, 4038.

13. For related precedents, see: a) A. J. M. Miller, J. E. Bercaw, *Chem. Commun.* **2010**, *46*, 1709; b) C. Appelt, J. C. Slootweg, K. Lammertsma, W. Uhl, *Angew. Chem.* **2013**, *125*, 4350; *Angew. Chem. Int. Ed.* **2013**, *52*, 4256; c) Z. Lu, L. Schweighauser, H. Hausmann, H. A. Wegner, *Angew. Chem. Int. Ed.* **2015**, *54*, 15556; d) Z. Mo, A. Rit, J. Campos, E. L. Kolychev, S. Aldridge, *J. Am. Chem. Soc.* **2016**, *138*, 3306.
14. M. A. Ibrahim, *Heterocycles* **2011**, *83*, 2689.
15. D. Liu, G. Zhao, L. Xiang, *Eur. J. Org. Chem.* **2010**, 3975.
16. J. D. Webb, V. S. Laberge, S. J. Geier, D. W. Stephan, C. M. Crudden, *Chem. – Eur. J.* **2010**, *16*, 4895.
17. T. Yoshihara, S. Murayama, T. Masuda, T. Kikuchi, K. Yoshida, M. Hosaka, S. Tobita, *J. Photochem. Photobiol. A: Chem.* **2015**, *299*, 172.
18. M. Ueda, S. Kawai, M. Hayashi, T. Naito, O. Miyata, *J. Org. Chem.* **2010**, *75*, 914.
19. T. P. Forrest, G. A. Dauphinee, S. A. Deraniyagala, *Can. J. Chem.* **1985**, *63*, 412.

20. According to the ICH harmonized guideline for elemental impurities, the permitted concentrations for palladium or iridium in drug products for parenteral dose is 1 μg/g. A value for boron has not been established due to its inherently low toxicity. For details, see: https://www.pmda.go.jp/files/000197758.pdf (accessed on January 4th, 2017).
21. a) M. Kojima, M. Kanai, *Angew. Chem. Int. Ed.* **2016**, *55*, 12224. A few days after the acceptance of this manuscript, Grimme and Paradies reported a conceptually relevant dehydrogenation reaction. See: b) A. F. G. Maier, S. Tussing, T. Schneider, U. Flörke, Z.-W. Qu, S. Grimme, J. Paradies, *Angew. Chem. Int. Ed.* **2016**, *55*, 12219.

Experimental section

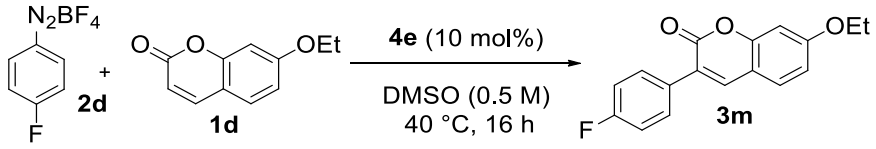
Experimental section for section 2

Contents

1. General Method

^{1}H NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR), and JEOL ECS400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 368 MHz for ^{19}F NMR) spectrometer. For ^{1}H NMR and ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. For ^{19}F NMR, chemical shifts were reported relative to hexafluorobenzene ($\delta = -164.90$ ppm) as an external reference. Electrospray ionization (ESI)-mass spectra were measured on a JEOL JMS-T100LC AccuTOF spectrometer for HRMS. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. Microwave irradiation was performed with Biotage Initiator. ICP analysis was conducted with Shimadzu ICPS-7510. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). Gel permeation chromatography (GPC) purification was conducted on a Japan Analytical Industry Co., Ltd. LC9210NEXT equipped with JAIGEL-1H and JAIGEL-2H, and $CHCl_3$ was used as an eluent. All non-commercially available compounds were prepared and characterized as described in Section 5 of this experimental section. Other reagents were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd. and were used as received.

2. General Procedure for the Arylation of Coumarins

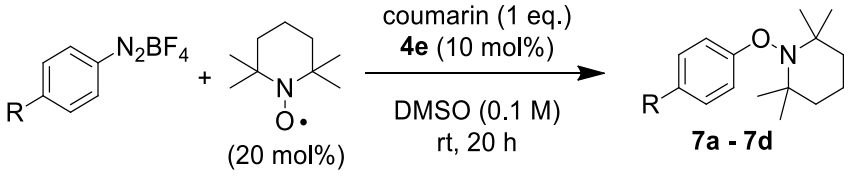


4-Fluorobenzenediazonium tetrafluoroborate (**2d**) (52.5 mg, 0.25 mmol), 7-ethoxycoumarin (**1d**) (238 mg, 1.25 mmol) and 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (**4e**) (22.5 mg, 0.025 mmol) were added in a dry test tube under argon atmosphere. Degassed DMSO (0.5 mL) was added into the tube, and the reaction mixture was stirred for 16 hours at 40 °C. After cooling the reaction to room temperature, the mixture was absorbed in silica gel and subjected to column chromatography (EtOAc/*n*-hexane = 2/13), which afforded pure **3m** (47.9 mg, 0.169 mmol) in 67% yield as white solid.

3. Mechanistic Studies

a) Details of the aryl radical trapping experiment

Considering that Meerwein arylation proceeds *via* an aryl radical intermediate, an aryl radical trapping experiment was performed in order to see whether aryl radicals involve in the present reaction (Scheme S1).

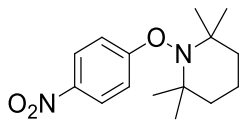


R	product	yield (based on ArN_2BF_4)
NO_2	**7a**	16%
CO_2Et	**7b**	14%
H	**7c**	12%
OMe	**7d**	decomposed

Scheme S1. Detection of an aryl radical intermediate

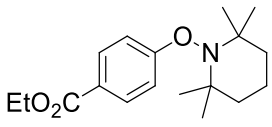
To a stirred solution of TEMPO (6.2 mg, 0.040 mmol), coumarin (29.2 mg, 0.20 mmol) and **4e** (18.0 mg, 0.020 mmol) in DMSO (1.0 mL) was added a solution of aryldiazonium tetrafluoroborate (0.20 mmol) in DMSO (1.0 mL). After 20 hours, water (20 mL) was added, and products were extracted with EtOAc (20 mL x 3). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography. Attempts to isolate **7d** with column chromatography (with SiO_2, neutral silica or alumina) or GPC were unsuccessful possibly because of facile decomposition of **7d**. 3-Arylcoumarins were not observed in all the cases. The efficient TEMPO-trapping as well as the absence of 3-arylcoumarin products support that aryl radicals are the key intermediate for the present C-C bond formation.

2,2,6,6-tetramethyl-1-(4-nitrophenoxy)piperidine (7a)



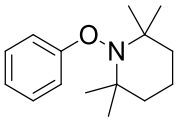
NMR spectra of the obtained product were consistent with the reported one.[1]

4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)benzoate (7b)



^{1}H NMR ($CDCl_3$): δ = 7.91 (2H, d, *J* = 9.2 Hz), 7.19 (2H, s), 4.31 (2H, q, *J* = 7.2 Hz), 1.67-1.54 (6H, m), 1.34 (3H, t, *J* = 7.2 Hz), 1.21 (6H, s), 0.97 (6H, s); ^{13}C NMR ($CDCl_3$): δ = 167.38, 166.56, 130.99, 122.31, 113.69, 60.56, 60.42, 39.67, 32.35, 20.42, 16.95, 14.41; HRMS (ESI): *m/z* calcd for $C_{18}H_{27}NO_3Na$ $[M+Na]^+$ 328.1883 Found 328.1885; IR (KBr): 2977, 2932, 1715, 1602, 1501, 1272, 1252, 1150, 1109, 1095 cm^{-1}

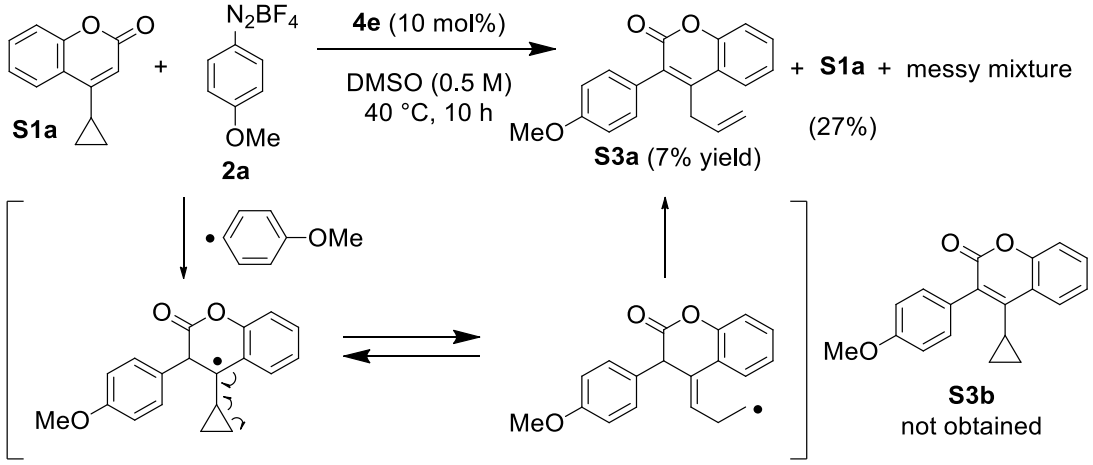
2,2,6,6-tetramethyl-1-phenoxypiperidine (7c)



NMR spectra of the obtained product were consistent with the reported one.[2]

b) Details of the benzyl radical detection experiment

Compound **S1a** was subjected to the reaction conditions in order to determine the presence of benzyl radical intermediate (Scheme S2). Based on a concept of "radical clock,"[3a,3b] cyclopropane opening should occur if benzyl radical intermediate was generated. As the observed product **S3a** is formed through ring-opening of cyclopropane, benzyl radical intermediate is likely to have involved in the present reaction.[3c] Product with the cyclopropane moiety remained (**S3b**) was not obtained. These results also indicate that 4-methoxybenzenediazonium tetrafluoroborate reacts via radical pathway.

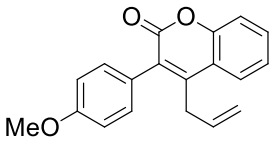


Scheme S2. A radical clock experiment

4-methoxybenzenediazonium tetrafluoroborate (**2a**) (22.2 mg, 0.10 mmol),

4-cyclopropyl-2*H*-chromen-2-one (**S1a**) (18.6 mg, 0.10 mmol) and 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (**4e**) (9.0 mg, 0.010 mmol) were added in a dry test tube under argon atmosphere. Degassed DMSO (0.2 mL) was added into the tube, and the reaction mixture was stirred for 10 hours at 40 °C. After cooling the reaction to room temperature, the mixture was absorbed in silica gel and subjected to column chromatography (EtOAc/*n*-hexane = 1/5) and then subjected to GPC, which afforded pure **S3a** (2.0 mg, 0.0068 mmol) in 7% yield as white solid.

4-allyl-3-(4-methoxyphenyl)-2*H*-chromen-2-one (S3a)



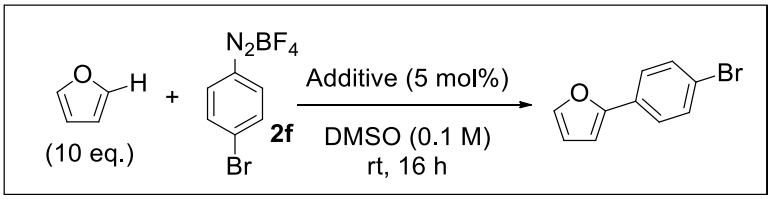
^{1}H NMR ($CDCl_3$): δ = 7.65 (1H, dd, *J* = 7.4, 1.4 Hz), 7.50 (1H, dt, *J* = 7.9, 1.4 Hz), 7.36 (1H, dd, *J* = 8.2, 1.1 Hz), 7.29-7.23 (3H, m), 6.95 (2H, d, *J* = 9.0 Hz), 5.93 (1H, m), 5.14 (1H, dd, *J* = 10.7, 1.4 Hz), 4.99 (1H, dd, *J* = 17.6, 1.2 Hz), 3.83 (3H, s), 3.44 (2H, d, *J* = 5.7 Hz), ; ^{13}C NMR ($CDCl_3$): δ = 161.43, 159.58, 152.95, 148.46, 134.21, 131.13, 130.81, 127.85, 126.27, 125.87, 124.15, 119.61, 117.85, 116.97, 113.87, 55.29, 33.93; HRMS (ESI): *m/z* calcd for $C_{19}H_{16}O_3Na$ $[M+Na]^+$ 315.0992 Found 315.0994; IR (KBr): 1711, 1595, 1509, 1449, 1248, 1164, 1148, 835 cm^{-1}

c) Solubility measurement of 4d and 4e

In order to rationalize the difference in reactivity between **4d** and **4e**, their solubility in DMSO was evaluated. To an Eppendorf tube, **4d** or **4e** (50 mg) and DMSO (1 mL) were added. The tube was subjected to vortex mixing for 5 minutes and centrifuged (100,000 rpm for 5 minutes). Then 0.1 mL of their supernatant was transferred to a glass vial, which was freezed with liquid nitrogen and dried under high vacuum. After the removal of solvent, solid from the supernatant of **4d** weighed 0.33 mg whereas that from **4e** weighed 4.10 mg. These results suggested that the solubility of **4d** is 3.3 g/L (= 4.2 mM) and **4e** is 41.0 g/L (= 46 mM). Therefore, their maximum concentration in the standard reaction conditions (0.5 M to aryldiazonium tetrafluoroborate) corresponds to 0.84 mol% for **4d** and 9.2 mol% for **4e**. This inherent difference in solubility could be one crucial factor for the catalytic reactivity.

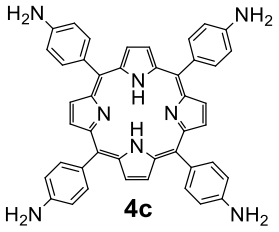
4. Arylation of Other Substrate

Along with the study of the C(3)-H arylation of coumarins, Meerwein-type arylation of other substrates were investigated. As a preliminary result, it was confirmed that Meerwein arylation of furan with 4-bromobenzenediazonium tetrafluoroborate **2f** occurred in the presence of 5 mol% of 5,10,15,20-tetrakis(4-aminophenyl)porphyrin **4c** (Scheme S3). This result implies that catalytic activity of tetrakis(4-aminophenyl)porphyrin derivatives are not specific to the arylation of coumarins. Optimization of the reaction conditions and investigation of substrate scope are currently underway.



Entry	Additive	Yield [%][a]
1	**4c**	51
2	none	5

[a] ^{1}H NMR yield.



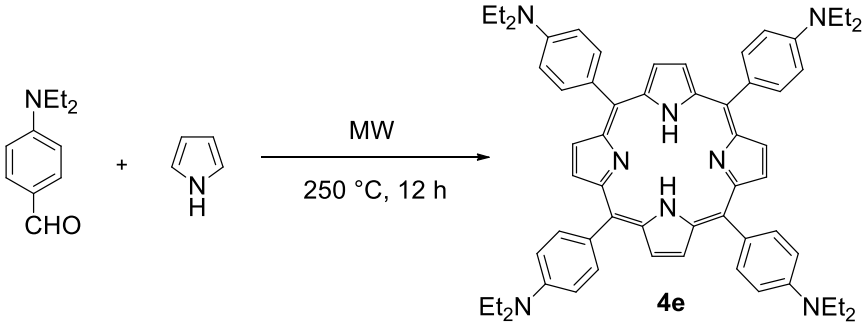
4c

Scheme S3.C-H Arylation of furan with **4c**

5. Syntheses of Catalysts and Substrates

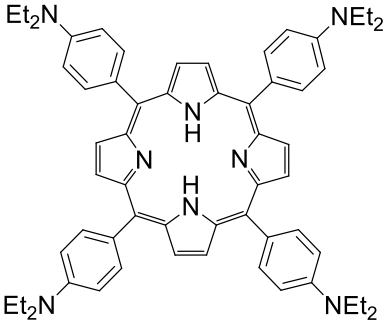
a) Synthesis of 4e

5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (4e)



4e can be synthesized as was reported previously.[4] We also developed a new procedure for shorter reaction time and better reproducibility. 4-Diethylaminobenzaldehyde (2.5 g, 14.1 mmol) and freshly distilled pyrrole (0.875 mL, 12.6 mmol) were heated to 250 °C under microwave irradiation in a sealed tube for 12 hours. Then the reaction mixture was cooled to room temperature and was suspended into acetone (125 mL). The suspension was filtered and washed several times with acetone. The solid was dried under vacuum and pure 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin was obtained (206.7 mg, 0.230 mmol) in 7% yield as black solid.

5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (4e)



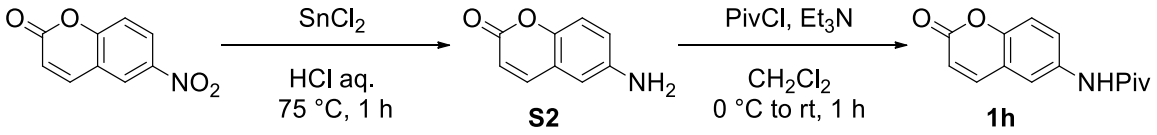
^{1}H NMR ($CDCl_3$): δ = 8.92 (8H, s), 8.08 (8H, d, *J*= 8.8 Hz), 7.04 (8H, d, *J*= 9.1 Hz), 3.61 (16H, q, *J*= 7.1 Hz), 1.39 (24H, t, *J*= 7.1 Hz), – 2.54 (2H, s); ^{13}C NMR ($CDCl_3$): δ = 147.21, 136.15, 129.71, 128.90, 120.41, 110.01, 44.57, 12.86 (one aromatic carbon is overlapped or unidentified); HRMS (ESI): *m/z* calcd for $C_{60}H_{67}N_8$ $[M+H]^+$ 899.5483 Found 899.5484; IR (KBr): 2968, 1606, 1519, 1353, 1265, 1194, 800 cm^{-1}.

b) Synthesis of aryldiazonium tetrafluoroborates

All the aryldiazonium tetrafluoroborates were synthesized according to the reported procedure.[5]

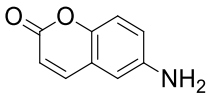
c) Synthesis of 1h

N-(2-oxo-2*H*-chromen-6-yl)pivalamide (1h)



6-Nitrocoumarin (1.91 g, 10 mmol) and $SnCl_2$ (6.17 g, 33 mmol) were suspended in concentrated HCl (100 mL) and heated to 75 °C for 1 hour. Then the reaction mixture was cooled to 0 °C on ice bath and basified with saturated NH_3 aqueous solution (120 mL). The resulting suspension was filtered, washed with H_2O and extracted with acetone. Concentration of the acetone extract afforded 6-aminocoumarin (**S2**) (1.22 g, 7.5 mmol) in 75% yield as yellow solid.

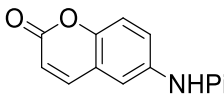
6-aminocoumarin (S2)



NMR spectra of the obtained product were consistent with the reported one.[6]

A solution of 6-aminocoumarin (600 mg, 3.73 mmol) and Et_3N (0.624 mL, 4.48 mmol) in CH_2Cl_2 (7.5 mL) were cooled to 0 °C and PivCl (0.483 mL, 3.92 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 3 hours. Then the reaction mixture was washed with water three times. The organic layer was dried with Na_2SO_4, filtered and concentrated to afford *N*-(2-oxo-2*H*-chromen-6-yl)pivalamide (**1h**) (815 mg, 3.07 mmol) in 82% yield as white solid.

N-(2-oxo-2*H*-chromen-6-yl)pivalamide (1h)

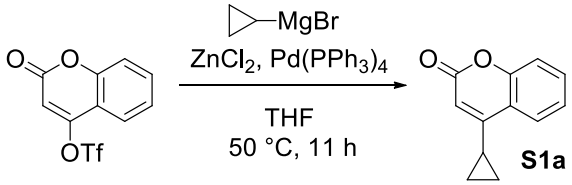


^{1}H NMR ($CDCl_3$): δ = 8.04 (1H, d, *J* = 2.3 Hz), 7.65 (1H, d, *J* = 9.8 Hz), 7.38 (1H, s), 7.37 (1H, dd, *J* = 8.9, 2.3 Hz), 7.26 (1H, d, *J* = 8.9 Hz), 6.41 (1H, d, *J* = 9.8 Hz), 1.32 (9H, s); ^{13}C NMR ($CDCl_3$): δ = 177.03, 160.77, 150.24, 143.48, 134.62, 123.90, 118.83, 118.76, 116.97, 116.93, 39.59, 27.46; HRMS (ESI): *m/z* calcd for

$C_{18}H_{18}O_2Na$ $[M+Na]^+$ 268.0944 Found 268.0934; IR (KBr): 3262, 2984, 1735, 1650, 1573, 1536, 1435, 1156, 822 cm^{-1}

d) Synthesis of S1a

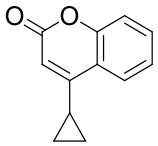
4-cyclopropyl-2*H*-chromen-2-one (S1a)



To a flame-dried flask was added $ZnCl_2$ (1M in diethyl ether: 4.0 mL, 4.0 mmol) and cyclopropyl magnesium bromide (0.5 M in THF: 8.0 mL, 4.0 mmol). The resulting suspension was stirred at 50 °C for 40 minutes. The suspension was cooled to room temperature and its supernatant was used for the reaction.

2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate was prepared as reported previously.[7] To a stirred suspension of $Pd(PPh_3)_4$ (46.0 mg, 0.040 mmol) and 2-oxo-2*H*-chromen-4-yl trifluoromethanesulfonate (58.8 mg, 0.20 mmol) in dry THF (0.5 mL), the supernatant (1.8 ml, 0.6 mmol of cyclopropyl zinc chloride) was added. The mixture was stirred at 50 °C for 11 hours. After cooling to room temperature, the reaction was quenched with 1N HCl. After extraction with EtOAc, the combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10 to 1/5) afforded 4-cyclopropyl-2*H*-chromen-2-one (**S1a**) (15.2 mg, 0.082 mmol) in 41% yield as white solid.

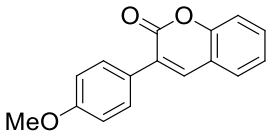
4-cyclopropyl-2*H*-chromen-2-one (S1a)



^1H NMR ($CDCl_3$): δ = 7.79 (1H, d, *J* = 8.6 Hz), 6.87 (1H, dd, *J* = 8.6, 2.6 Hz), 6.80 (1H, d, *J* = 2.6 Hz), 5.87 (1H, s), 3.86 (3H, s), 2.08-2.02 (1H, m), 1.13-1.09 (1H,m), 0.83-0.80 (1H, m); ^{13}C NMR ($CDCl_3$): δ = 161.44, 157.66, 153.37,131.62, 124.63, 124.12, 120.17, 117.07, 110.33, 11.95, 8.01; HRMS (ESI): *m/z* calcd for $C_{12}H_{10}O_2Na$ $[M+Na]^+$ 209.0573 Found 209.0557; IR (KBr): 1719, 1609, 1408, 1281, 1208, 1137, 841 cm^{-1}

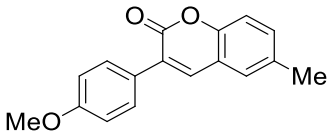
6. Characterization of Target Compounds

3-(4-methoxyphenyl)-2*H*-chromen-2-one (3a)



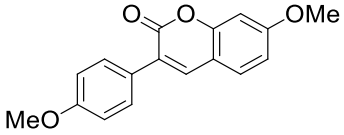
NMR spectra of the obtained product were consistent with the reported one.[8]

3-(4-methoxyphenyl)-6-methyl-2*H*-chromen-2-one (3b)



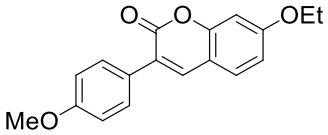
NMR spectra of the obtained product were consistent with the reported one.[8]

7-methoxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (3c)



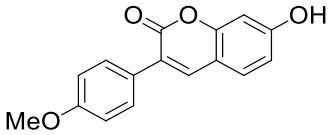
NMR spectra of the obtained product were consistent with the reported one.[8]

7-ethoxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (3d)



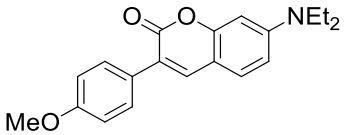
NMR spectra of the obtained product were consistent with the reported one.[8]

7-hydroxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (3e)



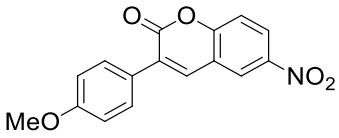
NMR spectra of the obtained product were consistent with the reported one.[9]

7-(diethylamino)-3-(4-methoxyphenyl)-2*H*-chromen-2-one (3f)



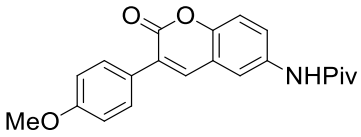
NMR spectra of the obtained product were consistent with the reported one.[8]

3-(4-methoxyphenyl)-6-nitro-2*H*-chromen-2-one (3g)



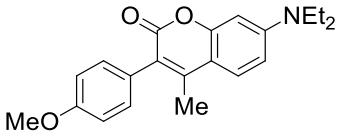
NMR spectra of the obtained product were consistent with the reported one.[10]

***N*-(3-(4-methoxyphenyl)-2-oxo-2*H*-chromen-6-yl)pivalamide (3h)**



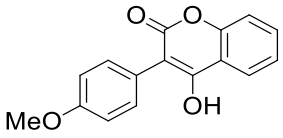
^{1}H NMR ($CDCl_3$): δ = 8.05 (1H, d, *J* = 2.5 Hz), 7.68 (1H, s), 7.63 (2H, d, *J* = 9.2 Hz), 7.44 (1H, s), 7.36 (1H, dd, *J* = 9.0, 2.5 Hz), 7.26 (1H, d, *J* = 8.9 Hz), 6.95 (2H, d, *J* = 9.2 Hz), 3.83 (3H, s), 1.32 (9H, s); ^{13}C NMR ($CDCl_3$): δ = 176.85, 160.72, 160.21, 149.69, 138.31, 134.46, 129.83, 128.31, 126.95, 122.97, 119.99, 118.51, 116.59, 113.94, 55.35, 39.65, 27.57; HRMS (ESI): *m/z* calcd for $C_{21}H_{21}NO_4Na$ $[M+Na]^+$ 374.1363 Found 374.1363; IR (KBr): 3282, 2967, 1725, 1649, 1514, 1253, 826 cm^{-1}

7-(diethylamino)-3-(4-methoxyphenyl)-4-methyl-2*H*-chromen-2-one (3i)



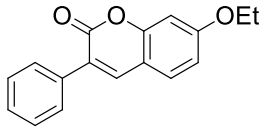
^{1}H NMR ($CDCl_3$): δ = 7.42 (1H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 9.0 Hz), 6.94 (2H, d, *J* = 10 Hz), 6.59 (1H, dd, *J* = 9.0, 2.5 Hz), 6.52 (1H, d, *J* = 2.5 Hz), 3.40 (4H, q, *J* = 7.2 Hz), 1.19 (6H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.25, 158.87, 154.91, 150.03, 148.06, 131.58, 127.44, 125.98, 120.65, 113.65, 109.53, 108.47, 97.39, 55.20, 44.66, 16.26, 12.39; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}NO_3Na$ $[M+Na]^+$ 360.1570 Found 360.1587; IR (KBr): 2966, 1703, 1617, 1578, 1524, 1273, 1248, 1073 cm^{-1}

4-hydroxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (3j)



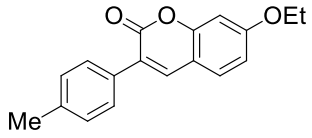
NMR spectra of the obtained product were consistent with the reported one.[11]

7-ethoxy-3-phenyl-2*H*-chromen-2-one (3k)



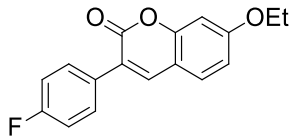
^{1}H NMR ($CDCl_3$): δ = 7.73 (1H, s), 7.66 (2H, d, *J* = 7.1 Hz), 7.43-7.33 (4H, m), 6.85-6.79 (2H, m), 4.08 (2H, q, *J* = 7.2 Hz), 1.44 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 161.97, 160.90, 155.28, 140.03, 135.03, 128.78, 128.37, 128.35, 124.61, 113.17, 113.11, 100.83, 64.15, 14.53 (one carbon is overlapped); HRMS (ESI): *m/z* calcd for $C_{17}H_{14}O_3Na$ $[M+Na]^+$ 289.0835 Found 289.0844; IR (KBr): 2977, 1711, 1604, 1274, 823, 783, 692 cm^{-1}

7-ethoxy-3-(*p*-tolyl)-2*H*-chromen-2-one (3l)



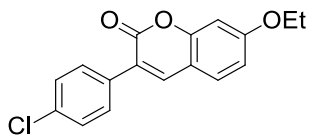
^{1}H NMR ($CDCl_3$): δ = 7.70 (1H, s), 7.57 (2H, d, *J* = 8.2 Hz), 7.38 (1H, d, *J* = 8.5 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 6.82 (1H, dd, *J* = 8.5, 2.3 Hz), 6.81 (1H, d, *J* = 2.5 Hz), 4.08 (2H, q, *J* = 7.1 Hz), 2.37 (3H, s), 1.44 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 161.81, 161.00, 155.17, 139.40, 138.34, 132.13, 129.08, 128.66, 128.22, 124.62, 113.27, 113.04, 100.82, 64.13, 21.22, 14.54; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3Na$ $[M+Na]^+$ 303.0992 Found 303.0994; IR (KBr): 1704, 1606, 1268, 1180, 1123, 1038, 822 cm^{-1}

7-ethoxy-3-(4-fluorophenyl)-2*H*-chromen-2-one (3m)



^{1}H NMR ($CDCl_3$): δ = 7.70 (1H, s), 7.64 (2H, dd, *J* = 9.2, 5.5 Hz), 7.39 (1H, d, *J* = 8.7 Hz), 7.09 (2H, dd, *J* = 8.9, 8.9 Hz), 6.83 (1H, dd, *J* = 8.7, 2.5 Hz), 6.80 (1H, d, *J* = 2.3 Hz), 4.08 (2H, q, *J* = 7.2 Hz), 1.44 (3H, t, *J* = 7.2 Hz); ^{19}F NMR ($CDCl_3$): δ = -115.96 (s, 1F); ^{13}C NMR ($CDCl_3$): δ = 162.76 (d, *J* = 252 Hz), 162.06, 160.87, 155.26, 139.88, 131.03 (d, *J* = 3.8 Hz), 130.17 (d, *J* = 8.1 Hz), 128.78, 123.56, 115.34 (d, *J* = 21.5 Hz), 113.21, 113.04, 100.84, 64.18, 14.52; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3FNa$ $[M+Na]^+$ 307.0741 Found 307.0741; IR (KBr): 1706, 1604, 1513, 1274, 1240, 1177, 822 cm^{-1}

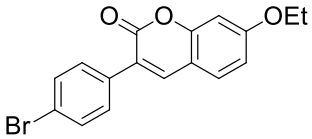
3-(4-chlorophenyl)-7-ethoxy-2*H*-chromen-2-one (3n)



^{1}H NMR ($CDCl_3$): δ = 7.73 (1H, s), 7.62 (2H, d, *J* = 8.7 Hz), 7.40 (1H, d, *J* = 8.7 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 6.84 (1H, dd, *J* = 8.7, 2.3 Hz), 6.81 (1H, d, *J* =

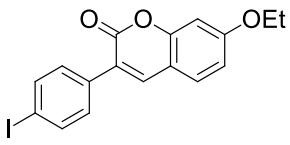
2.3 Hz), 4.09 (2H, q, *J* = 7.2 Hz), 1.45 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.22, 160.69, 155.37, 140.11, 134.37, 133.45, 129.66, 128.88, 128.59, 123.37, 113.31, 112.99, 100.87, 64.22, 14.54; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3Na$ $[M+Na]^+$ 323.0445 Found 323.0438; IR (KBr): 1713, 1611, 1508, 1363, 1270, 818 cm^{-1}

3-(4-bromophenyl)-7-ethoxy-2*H*-chromen-2-one (3o)



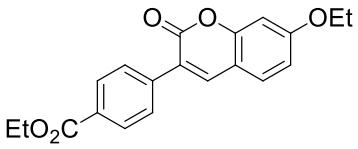
^{1}H NMR ($CDCl_3$): δ = 7.73 (1H, s), 7.57-7.52 (4H,m), 7.40 (1H, d, *J* = 8.6 Hz), 6.84 (1H, dd, *J* = 8.6, 2.6 Hz), 6.81 (1H, d, *J* = 2.3 Hz), 4.06 (2H, q, *J* = 7.1, Hz), 1.45 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.25, 160.62, 155.39, 140.11, 133.93, 131.55, 129.94, 128.90, 123.40, 122.60, 113.33, 113.00, 100.88, 64.23, 14.54; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3BrNa$ $[M+Na]^+$ 366.9940 Found 366.9947; IR (KBr): 1711, 1611, 1507, 1363, 1270, 1176, 817 cm^{-1}

7-ethoxy-3-(4-iodophenyl)-2*H*-chromen-2-one (3p)



^{1}H NMR ($CDCl_3$): δ = 7.73 (2H, d, *J* = 8.6 Hz), 7.72 (1H, s), 7.41 (2H, d, *J* = 8.6 Hz), 7.39 (1H, d, *J* = 8.6 Hz), 6.83 (1H, dd, *J* = 8.6, 2.3 Hz), 6.80 (1H, d, *J* = 2.3 Hz), 4.08 (2H, q, *J* = 7.1 Hz), 1.44 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.25, 160.53, 155.38, 140.07, 137.50, 134.51, 130.08, 128.91, 123.44, 113.30, 112.98, 100.87, 94.27, 64.22, 14.53; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3INa$ $[M+Na]^+$ 414.9802 Found 414.9809; IR (KBr): 1713, 1611, 1506, 1362, 1269, 1176, 816 cm^{-1}

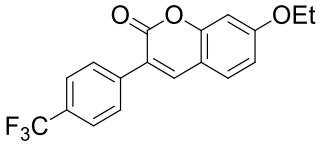
ethyl 4-(7-ethoxy-2-oxo-2*H*-chromen-3-yl)benzoate (3q)



^{1}H NMR ($CDCl_3$): δ = 8.06 (2H, d, *J* = 8.9 Hz), 7.79 (1H, s), 7.75 (2H, d, *J* = 8.7 Hz), 7.41 (1H, d, *J* = 8.9 Hz), 6.84 (1H, dd, *J* = 8.9, 2.5 Hz), 6.80 (1H, d, *J* = 2.5 Hz), 4.37 (2H, q, *J* = 7.3 Hz), 4.08 (2H, q, *J* = 7.2 Hz), 1.44 (3H, t, *J* = 7.2 Hz), 1.38 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 166.20, 162.42, 160.45, 155.51, 140.90, 139.38, 130.09, 129.54, 129.07, 128.21, 123.40, 113.33, 112.90, 100.83, 64.22, 61.00,

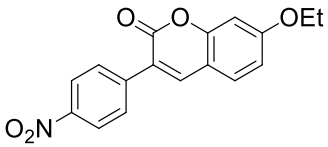
14.50, 14.29; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}O_5Na$ $[M+Na]^+$ 361.1046 Found 361.1057; IR (KBr): 1715, 1609, 1366, 1276, 1186, 1109, 783 cm^{-1}

7-ethoxy-3-(4-(trifluoromethyl)phenyl)-2*H*-chromen-2-one (3r)



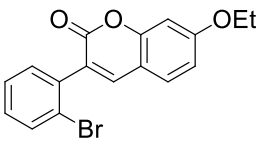
^1H NMR ($CDCl_3$): δ = 7.79 (1H, s), 7.79 (2H, d, *J* = 8.2 Hz), 7.66 (2H, d, *J* = 8.7 Hz), 7.43 (1H, d, *J* = 8.7 Hz), 6.86 (1H, dd, *J* = 8.7, 2.5 Hz), 6.82 (1H, d, *J* = 2.3 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 1.45 (3H, t, *J* = 7.1 Hz); ^{19}F NMR ($CDCl_3$): δ = -65.51 (s, 3F); ^{13}C NMR ($CDCl_3$): δ = 162.55, 160.53, 155.59, 141.07, 138.58 (q, *J* = 1.3 Hz), 130.25 (q, *J* = 33.2 Hz), 129.11, 128.69, 125.33 (q, *J* = 3.8 Hz), 124.04 (q, *J* = 276 Hz), 123.11, 113.45, 112.85, 100.91, 64.29, 14.52; HRMS (ESI): *m/z* calcd for $C_{18}H_{13}O_3F_3Na$ $[M+Na]^+$ 367.0709 Found 357.0710; IR (KBr): 1713, 1612, 1331, 1274, 178, 1117, 1071, 849 cm^{-1}

7-ethoxy-3-(4-nitrophenyl)-2*H*-chromen-2-one (3s)



^1H NMR ($CDCl_3$): δ = 8.26 (2H, d, *J* = 9.0 Hz), 7.88 (2H, d, *J* = 8.7 Hz), 7.87 (1H,s), 7.46 (1H, d, *J* = 8.7 Hz), 6.88 (1H, dd, *J* = 8.7, 2.3 Hz), 6.83 (1H, d, *J* = 2.3 Hz), 4.11 (2H, q, *J* = 7.1 Hz) 1.46 (3H, t, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.98, 160.19, 155.81, 147.41, 141.81, 141.52, 129.37, 129.14, 123.60, 122.08, 113.70, 112.67, 100.92, 64.38, 14.52; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3INa$ $[M+Na]^+$ 334.0686 Found 334.0700; IR (KBr): 1712, 1610, 1524, 1347, 1275, 1224, 1037, 852 cm^{-1}

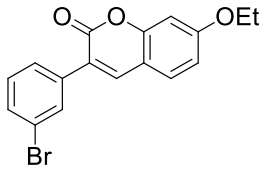
3-(2-bromophenyl)-7-ethoxy-2*H*-chromen-2-one (3t)



^1H NMR ($CDCl_3$): δ = 7.65 (1H, d, *J* = 7.8 Hz), 7.63 (1H, s), 7.40-7.34 (3H, m), 7.25-7.21 (1H, m), 6.86-6.83 (2H, m), 4.10 (2H, q, *J* = 7.0 Hz), 1.45 (3H, t, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.33, 160.11, 155.80, 142.68, 136.07, 133.03, 131.47, 129.91, 128.98, 127.40, 125.01, 123.81, 113.19, 112.45, 101.10, 64.22, 14.53; HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3BrNa$ $[M+Na]^+$ 366.9940 Found 366.9922; IR (KBr):

1734, 1615, 1356, 1274, 1180, 1125, 1036, 823 cm^{-1}

3-(3-bromophenyl)-7-ethoxy-2*H*-chromen-2-one (3u)



^{1}H NMR ($CDCl_3$): δ = 7.80 (1H, dd, *J* = 1.8, 1.8 Hz), 7.73 (1H, s), 7.62 (1H, dd, *J* = 8.0, 0.9 Hz), 7.47 (1H, dt, *J* = 8.2, 0.9 Hz), 7.40 (1H, d, *J* = 8.9 Hz), 7.27 (1H, t, *J* = 8.0 Hz), 6.84 (1H, dd, *J* = 8.7, 2.5 Hz), 6.80 (1H, d, *J* = 2.3 Hz), 4.08 (2H, q, *J* = 7.2 Hz), 1.44 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 162.35, 160.49, 155.44, 140.63, 137.02, 131.31, 131.18, 129.85, 128.99, 127.05, 123.00, 122.40, 113.33, 112.88, 100.85, 64.23, 14.52; HRMS (ESI): m/z calcd for $C_{17}H_{13}O_3BrNa$ [M+Na]+ 366.9940. Found 366.9928; IR (KBr): 1714, 1605, 1276, 1177, 822, 787, 686 cm^{-1}

7. References

1. F. P. Crisostomo, T. Martín, R. Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181.
2. M. Hartmann, Y. Li, A. Studer, *J. Am. Chem. Soc.* **2012**, *134*, 16516.
3. a) D. Lal, D. Griller, S. Husband and K. U. Ingold, *J. Am. Chem. Soc.* **1974**, *96*, 6355; b) B. Maillald, D. Forrest, K. U. Ingold, *J. Am. Chem. Soc.* **1976**, *98*, 7024; c) V. W. Bowry, J. Lusztyk, K. U. Ingold, *J. Chem. Soc., Chem. Commun.* **1990**, 923.
4. N. Datta-Gupta, T. J. Bardos, *J. Heterocyclic Chem.* **1966**, *3*, 495.
5. D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958.
6. W. Erb, A. Hellal, M. Albini, J. Rouden, J. Blanchet, *Chem. – Eur. J.* **2014**, *20*, 6608.
7. R. Brimioulle, H. Guo, T. Bach, *Chem. – Eur. J.* **2012**, *18*, 7552.
8. F. Jafarpour, H. Hazrati, N. Mohasselyazdi, M. Khoobib, A. Shafiee, *Chem. Commun.* **2013**, *49*, 10935.
9. M. D. Mertens, M. Gütschow, *Chirality* **2013**, *25*, 957.
10. G. Ferino *et al. ChemMedChem* **2013**, *8*, 956.
11. Z.-Z. Zhou, G.-H. Yan, W.-H. Chen, X.-M. Yang, *Chem. Pharm. Bull.* **2013**, *61*, 1166.

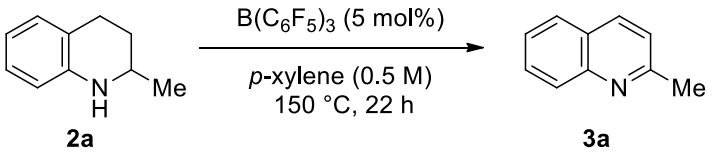
Experimental section for section 3

Contents

1. General Method

^{1}H NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR), and JEOL ECS400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 368 MHz for ^{19}F NMR) spectrometer. For ^{1}H NMR and ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. For ^{19}F NMR, chemical shifts were reported relative to hexafluorobenzene (δ = –164.9 ppm) as an external reference. Electrospray ionization (ESI)-mass spectra were measured on a JEOL JMS-T100LC AccuTOF spectrometer for HRMS. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). GPC purification was conducted on a Japan Analytical Industry Co., Ltd. LC9210NEXT equipped with JAIGEL-1H and JAIGEL-2H, and $CHCl_3$ was used as an eluent. All non-commercially available compounds were prepared and characterized as described in section 4 of this experimental section. Other reagents were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd. and were used as received. Electrophilic boranes **1c**,[1] **1d**,[2] **1e**, **1f**,[3] **1g**, **1h**[4] or Lewis base **1j**[5] were prepared according to the literature procedure.

2. General Procedure for the Dehydrogenation of N-heterocycles



2a **3a**

2-Methyl-1,2,3,4-tetrahydroquinoline (**2a**) (36.1 μL, 0.25 mmol), tris(pentafluorophenyl)borane (**1a**) (6.4 mg, 0.0125 mmol) and *p*-xylene (0.5 mL) were added in a dry screw tube (diameter = 25 mm, height = 200 mm) under argon atmosphere. The tube was capped and the reaction mixture was stirred for 22 hours at 150 °C. After cooling the reaction to room temperature, the mixture was passed through a short pad of alumina with degassed methanol under argon atmosphere and concentrated under reduced pressure. The crude mixture was subjected to column chromatography (EtOAc/*n*-hexane = 1/5), which afforded pure **3a** (32.8 mg, 0.23 mmol) in 92% yield as colorless oil.

3. Mechanistic Studies

a) Conditions for the ^{19}F NMR investigations

A solution of **2a** (36.1 μL, 0.25 mmol) and tris(pentafluorophenyl)borane **1a** (5.4 mg, 0.011 mmol) in toluene-d_8 (1.0 mL) was prepared in a flame-dried vial under inert atmosphere. The solution was transferred into a dry NMR tube, sealed, and subjected to ^{19}F NMR analysis. When the tube was warmed to 80 °C, resonances at –136 ppm, –161 ppm, –166 ppm were observed. The relative integrals of those were approximately 2 (for –136 ppm), 1 (for –160 ppm) and 2 (for –165 ppm).

b) Conditions for the confirmation of H_2 gas release by dual reactions

In one side of screwable two-chamber glass system (COware: http://www.sigmaaldrich.com/catalog/product/aldrich/744077?lang=ja&region=JP accessed on June 25th, 2016), tris(pentafluorophenyl)borane **1a** (25.6 mg, 0.050 mmol) and 2-methyl-1,2,3,4-tetrahydroquinoline **2a** (72.2 μL, 0.50 mmol) were dissolved in *p*-xylene (1.0 mL). In the other side of the apparatus, tris(triphenylphosphine)rhodium chloride (9.3 mg, 0.010 mmol) and cyclododecene **6** (191 μL, 1.0 mmol) were dissolved in benzene (1.0 mL). These two reactions share the same atmosphere so that only gaseous components can be transferred between sides. Then, the *p*-xylene solution side was heated to 120 °C while the benzene solution side was kept at room temperature. After 48 hours, each reaction mixture was cooled to room temperature and passed through a short pad of alumina with CH_2Cl_2. The solvent was removed under reduced pressure, and each reaction mixture was subjected to ^1H NMR analysis. According to the NMR spectra using 1,1,2,2-tetrachloroethane as an internal standard, yield of 2-methylquinoline **3a** was 78% and yield of cyclododecane **7** was 66%, respectively.

4. Syntheses and characterization of substrates

a) Synthesis of 2c, 2g, 2i

These compounds were prepared as reported previously.[6]

b) Synthesis of 2b, 2d, 2e

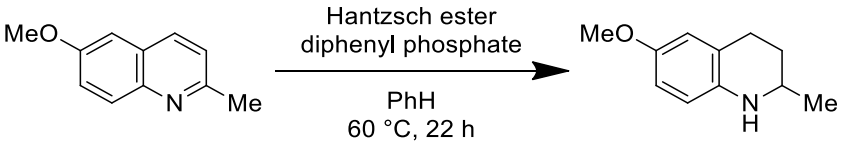
These compounds were prepared as reported previously.[7]

c) Synthesis of 2f

2f was prepared as reported previously.[8]

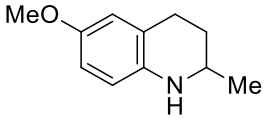
d) Synthesis of 2h

6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2h)



The compound was synthesized with a similar procedure as a previous report.[6] A suspension of 6-methoxy-2-methylquinoline (260 mg, 1.5 mmol), Hantzsch ester (912 mg, 3.6 mmol) and diphenyl phosphate (3.8 mg, 0.015 mmol) in benzene (10 mL) was stirred at 60 °C for 22 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by GPC afforded **2h** (110.3 mg, 0.62 mmol) in 41% yield as colorless oil.

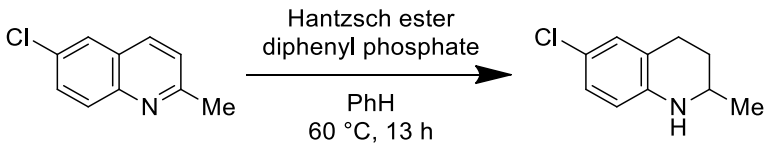
6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2h)



NMR spectra of the obtained product were consistent with the reported one.[9]

e) Synthesis of 2j

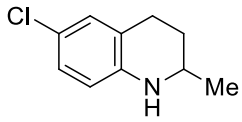
6-chloro-2-methyl-1,2,3,4-tetrahydroquinoline (2j)



The compound was synthesized with a similar procedure as a previous report.[6] A

suspension of 6-chloro-2-methylquinoline (178 mg, 1.0 mmol), Hantzsch ester (608 mg, 2.4 mmol) and diphenyl phosphate (5.0 mg, 0.020 mmol) in benzene (6.7 mL) was stirred at 60 °C for 13 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2j** (150.6 mg, 0.83 mmol) in 83% yield as white solid.

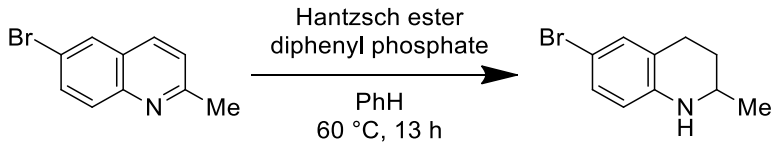
6-chloro-2-methyl-1,2,3,4-tetrahydroquinoline (2j)



NMR spectra of the obtained product were consistent with the reported one.[9]

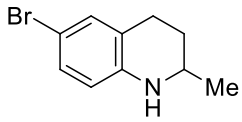
f) Synthesis of 2k

6-bromo-2-methyl-1,2,3,4-tetrahydroquinoline (2k)



The compound was synthesized with a similar procedure as a previous report.[6] A suspension of 6-bromo-2-methylquinoline (222 mg, 1.0 mmol), Hantzsch ester (608 mg, 2.4 mmol) and diphenyl phosphate (5.0 mg, 0.020 mmol) in benzene (6.7 mL) was stirred at 60 °C for 13 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2k** (195.1 mg, 0.86 mmol) in 86% yield as white solid.

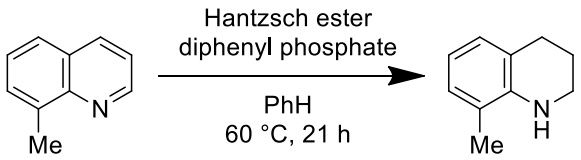
6-bromo-2-methyl-1,2,3,4-tetrahydroquinoline (2k)



NMR spectra of the obtained product were consistent with the reported one.[9]

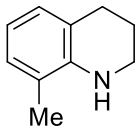
g) Synthesis of 2l

8-methyl-1,2,3,4-tetrahydroquinoline (2l)



The compound was synthesized with a similar procedure as a previous report.[6] A suspension of 8-methylquinoline (0.136 ml, 1.0 mmol), Hantzsch ester (608 mg, 2.4 mmol) and diphenyl phosphate (2.5 mg, 0.010 mmol) in benzene (6.7 mL) was stirred at 60 °C for 21 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2l** (131.4 mg, 0.89 mmol) in 89% yield as pale yellow oil.

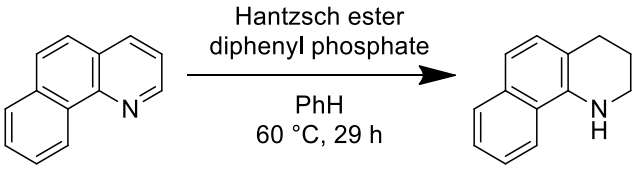
8-methyl-1,2,3,4-tetrahydroquinoline (2l)



NMR spectra of the obtained product were consistent with the reported one.[10]

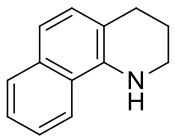
h) Synthesis of 2m

1,2,3,4-tetrahydrobenzo[*h*]quinoline (2m)



The compound was synthesized with a similar procedure as a previous report.[6] A suspension of benzo[*h*]quinoline (269 mg, 1.5 mmol), Hantzsch ester (912 mg, 3.6 mmol) and diphenyl phosphate (3.8 mg, 0.015 mmol) in benzene (10 mL) was stirred at 60 °C for 29 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2m** (210.7 mg, 1.15 mmol) in 77% yield as white solid.

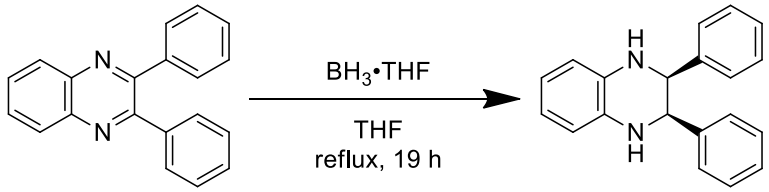
1,2,3,4-tetrahydrobenzo[*h*]quinoline (2m)



NMR spectra of the obtained product were consistent with the reported one.[8]

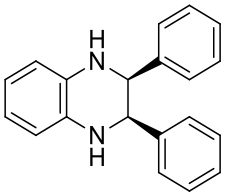
i) Synthesis of 2o

***cis*-2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline (2o)**



To a stirred solution of 2,3-diphenylquinoxaline (424 mg, 1.5 mmol) in THF (5 mL), BH_3•THF (1 M in THF; 6.0 mL: 6.0 mmol) was added. The mixture was heated to reflux and stirred for 19 hours. After cooled to room temperature, volatiles were removed under reduced pressure. The crude was suspended in 10% HCl aq. and stirred at 60 °C for 1 hour. Then, the mixture was basified with 10% NaOH aq. and extraction was performed three times with CH_2Cl_2. The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2o** (357 mg, 1.25 mmol) in 83% yield as white solid.

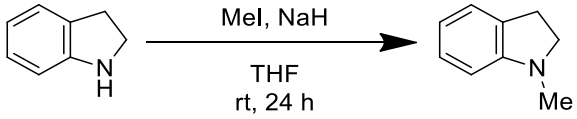
***cis*-2,3-diphenyl-1,2,3,4-tetrahydroquinoxaline (2o)**



NMR spectra of the obtained product were consistent with the reported one.[11]

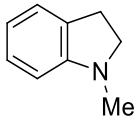
j) Synthesis of 2r

1-methylindoline (2r)



To a stirred suspension of indoline (562 µL, 5.0 mmol) and sodium hydride (60% in mineral oil; 300 mg, 7.5 mmol) in THF (10 mL), indomethane (467 µL, 7.5 mmol) was added dropwise. After 24 hours, water was added, and organic phase was extracted with CH_2Cl_2 three times. The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (Et_3N/ CH_2Cl_2/*n*-hexane = 1/50/50) afforded **2r** (167 mg, 1.26 mmol) in 25% yield as yellow oil.

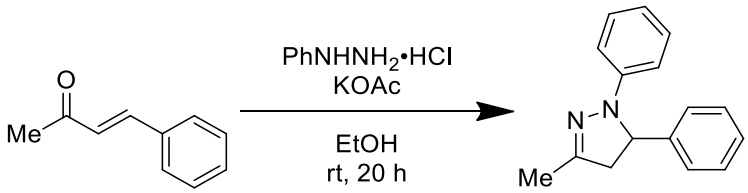
1-methylindoline (2r)



NMR spectra of the obtained product were consistent with the reported one.[12]

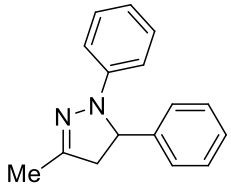
k) Synthesis of 2r

3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (2s)[13]



To a suspension of phenylhydrazine hydrochloride (795 mg, 5.5 mmol) and potassium acetate (491 mg, 5.0 mmol) in EtOH (25 mL), benzalacetone (746 mg, 5.0 mmol) was added. After 20 hours, water was added and the formed precipitate was filtered and washed with water. The crude product was purified by column chromatography (CH_2Cl_2/*n*-hexane = 2/3 to 1/1) to afford **2s** (328 mg, 1.39 mmol) in 28% yield as orange solid.

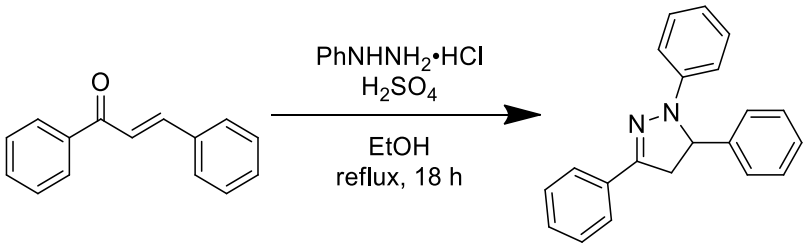
3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (2s)



NMR spectra of the obtained product were consistent with the reported one.[13]

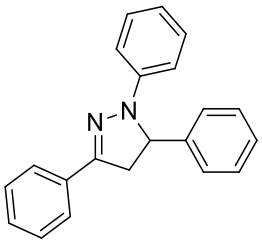
l) Synthesis of 2t

1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole (2t)



To a solution of chalcone (1041 mg, 5.0 mmol) and phenylhydrazine hydrochloride (795 mg, 5.5 mmol) in EtOH (20 mL), 3 drops of concentrated H_2SO_4 was added. The mixture was stirred under reflux for 5 hours. Then, water was added, and precipitate was filtered and washed with water. The crude product was purified by column chromatography (EtOAc/*n*-hexane = 1/20) and **2t** (1251 mg, 4.20 mmol) was obtained in 84 % yield as white solid.

1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole (2t)



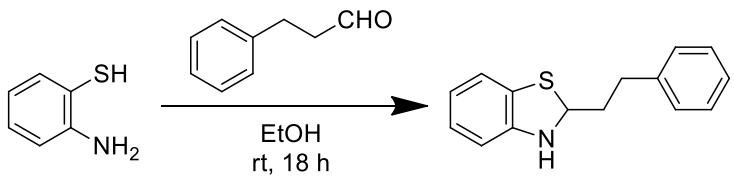
NMR spectra of the obtained product were consistent with the reported one.[14]

m) Synthesis of 2u, 2v

These compounds were prepared as reported previously.[15]

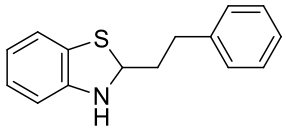
n) Synthesis of 2w

2-phenethyl-2,3-dihydrobenzo[*d*]thiazole (2w)



To a stirred solution of 2-aminobenzenethiol (1.07 mL, 10 mmol) in EtOH (40 mL), 3-phenylpropanal (1.33 mL, 10 mmol) was added. After 16 hours, volatiles were removed under reduced pressure. Purification by column chromatography (EtOAc/*n*-hexane = 1/10) afforded **2w** (1062 mg, 4.4 mmol) in 44% yield as white solid.

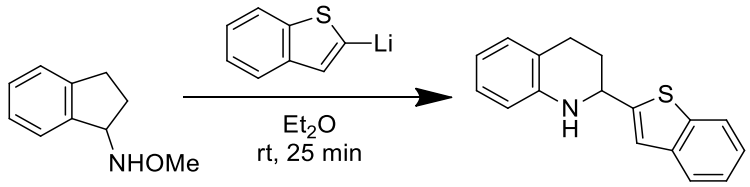
2-phenethyl-2,3-dihydrobenzo[*d*]thiazole (2w)



^{1}H NMR ($CDCl_3$): δ = 7.34-7.31 (2H, m), 7.25-7.21 (3H, m), 7.10 (1H, dd, *J* = 7.8, 1.2 Hz), 6.93 (1H, dt, *J* = 7.6, 1.5 Hz), 6.77 (1H, dt, *J* = 7.6, 1.2 Hz), 6.64 (1H, dd, *J* = 8.1, 0.9 Hz), 5.25 (1H, t, *J* = 6.5 Hz), 4.02 (1H, s), 2.84-2.72 (2H, m), 2.19 (2H, dd, *J* = 14.3, 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 146.37, 140.74, 128.45, 128.35, 127.24, 126.06, 125.08, 121.90, 120.77, 110.85, 67.84, 40.09, 32.08; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}NSNa$ $[M+Na]^+$ 264.0817 Found 264.0827; IR (KBr): 3352, 1577, 1473, 1404, 1275, 1065, 786, 735, 717, 694 cm^{-1}

o) Synthesis of 2x

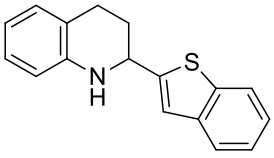
2-(benzo[*b*]thiophen-2-yl)-1,2,3,4-tetrahydroquinoline (2x)



A solution of benzo[*b*]thiophene (671 mg, 5.0 mmol) in Et_2O (3.12 mL) was cooled to 0 °C. Then, a solution of *n*-butyllithium (2.66 M in hexane: 1.88 mL, 5.0 mmol) was added dropwise. After warmed to room temperature, the solution was stirred for 1 hour. The solution of benzo[*b*]thiophen-2-yllithium was used for the next reaction.

N-(2,3-Dihydro-1*H*-inden-1-yl)-*O*-methylhydroxylamine was prepared according to the method reported by Miyata.[7] To a stirred solution of *N*-(2,3-dihydro-1*H*-inden-1-yl)-*O*-methylhydroxylamine (106 mg, 0.65 mmol) in Et_2O (20 ml), the solution of benzo[*b*]thiophen-2-yllithium (1 M in Et_2O/hexane: 1.95 mL, 1.95 mmol) was added dropwise. After 25 minutes, water was added. Organic layer was separated, and water phase was extracted with $CHCl_3$ three times. The combined organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2/*n*-hexane = 1/2) afforded **2x** (136.1 mg, 0.51 mmol) in 78% yield as white solid.

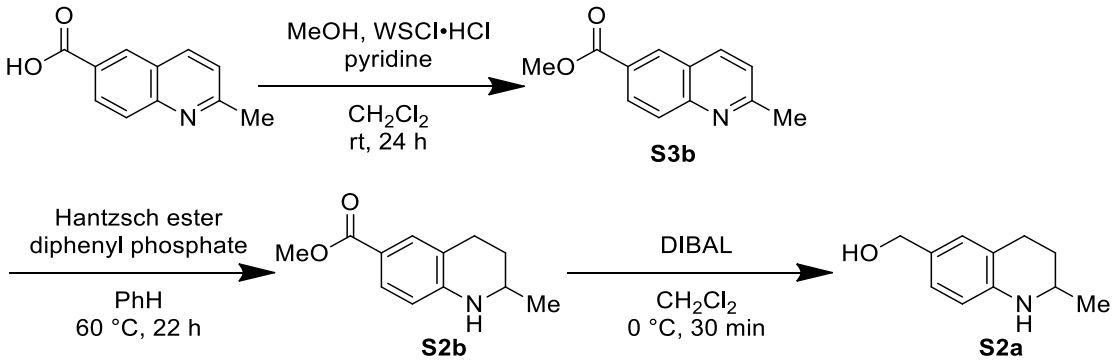
2-(benzo[*b*]thiophen-2-yl)-1,2,3,4-tetrahydroquinoline (2x)



^{1}H NMR ($CDCl_3$): δ = 7.78 (1H, d, *J* = 8.1 Hz), 7.68 (1H, d, *J* = 7.7 Hz), 7.32-7.28 (2H, m), 7.23 (1H, d, *J* = 12.9 Hz), 7.03-6.98 (2H, m), 6.68 (1H, t, *J* = 7.3 Hz), 6.58 (1H, d, *J* = 8.0 Hz), 4.81 (1H, dd, *J* = 8.3, 3.2 Hz), 2.94-2.88 (1H, m), 2.81-2.75 (1H, m), 2.28-2.24 (1H, m), 2.18-2.13 (1H, m); ^{13}C NMR ($CDCl_3$): δ = 149.60, 143.63, 139.58, 139.14, 129.29, 126.96, 124.23, 123.97, 123.23, 122.44, 120.89, 120.08, 117.76, 114.28, 52.33, 31.08, 25.69; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}NSNa$ $[M+Na]^+$ 288.0817 Found 288.0824; IR (KBr): 3349, 1584, 1480, 1309, 1254, 752 cm^{-1}

p) Synthesis of S2a

(2-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methanol (S2a)



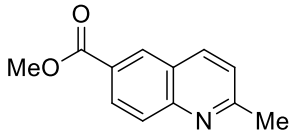
To a stirred suspension of 2-methylquinoline-6-carboxylic acid (936 mg, 5.0 mmol) and WSCI・HCl (1150 mg, 6.0 mmol) in CH_2Cl_2 (20 mL), MeOH (2 mL) and pyridine (0.80 mL, 10 mmol) were added successively. After 24 hours, the mixture was washed with water, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford **S3b** (707.7 mg, 3.52 mmol) in 70% yield as light brown solid.

S2b was synthesized with a similar procedure as a previous report.[6] A suspension of **S3b** (338 mg, 1.68 mmol), Hantzsch ester (1021 mg, 4.03 mmol) and diphenyl phosphate (4.2 mg, 0.017 mmol) in benzene (11.2 mL) was stirred at 60 °C for 22 hours. After cooled to room temperature, solvents were removed under reduced pressure. Purification by column chromatography (acetone/*n*-hexane = 1/6) afforded **S2b** (287.9 mg, 1.40 mmol) in 83% yield as white solid.

To a stirred solution of **S2b** (103 mg, 0.50 mmol) in CH_2Cl_2 (1 mL) cooled at 0 °C, a solution of DIBAL (1 M in hexane, 1.5 mL, 1.5 mmol) was added dropwise. After 20 minutes, EtOAc (5 mL) and saturated aqueous solution of Rochelle salt (10 mL) was added. After stirred for 1 hour at room temperature, the organic material was extracted

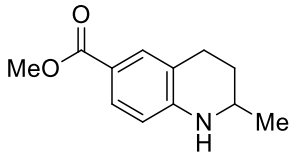
with EtOAc three times, dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford **S2a** (83.5 mg, 0.47 mmol) in 94% yield as light pink solid.

methyl 2-methylquinoline-6-carboxylate (S3b)



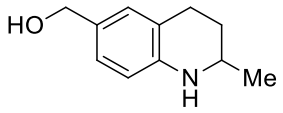
NMR spectra of the obtained product were consistent with the reported one.[16]

methyl 2-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (S2b)



NMR spectra of the obtained product were consistent with the reported one.[9]

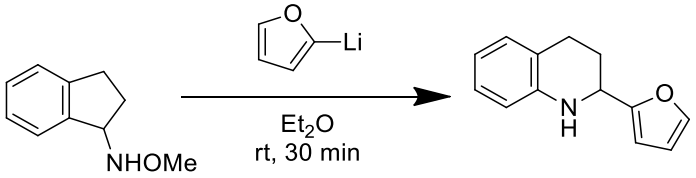
(2-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methanol (S2a)



^{1}H NMR ($CDCl_3$): δ = 6.95-6.93 (2H, m), 6.43 (1H, d, *J* = 8.1 Hz), 4.47 (2H, s), 3.40-3.35 (1H, m), 2.84-2.78 (1H, m), 2.73-2.68 (1H, m), 1.94-1.89 (1H, m), 1.59-1.52 (1H, m), 1.19 (3H, d, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 144.44, 129.36, 128.83, 126.28, 121.07, 113.94, 65.45, 47.14, 29.96, 26.47, 22.47; HRMS (ESI): *m/z* calcd for $C_{11}H_{15}NONa$ $[M+Na]^+$ 200.1046 Found 200.1036; IR (KBr): 3278, 1613, 1507, 1343, 1306, 1256, 1011, 825, 736 cm^{-1}

q) Synthesis of S2c

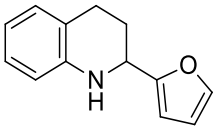
2-(furan-2-yl)-1,2,3,4-tetrahydroquinoline (S2c)



A solution of furan (600 μL, 8.3 mmol) in Et_2O (3.12 mL) was cooled to 0 °C. Then, a solution of *n*-butyllithium (2.66 M in hexane: 2.26 mL, 6.0 mmol) was added dropwise. After warmed to room temperature, the solution was stirred for 1 hour. The suspension of furan-2-yllithium was used for the next reaction.

N-(2,3-Dihydro-1*H*-inden-1-yl)-*O*-methylhydroxylamine was prepared according to the method reported by Miyata.[7] To a stirred solution of *N*-(2,3-dihydro-1*H*-inden-1-yl)-*O*-methylhydroxylamine (245 mg, 1.5 mmol) in Et_2O (30 ml), the suspension of furan-2-yllithium (1 M in Et_2O/hexane: 4.5 mL, 4.5 mmol) was added dropwise. After 30 minutes, water was added. Organic layer was separated, and water phase was extracted with $CHCl_3$ three times. The combined organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2/*n*-hexane = 1/2) afforded **S2c** (111.9 mg, 0.69 mmol) in 46% yield as yellow oil.

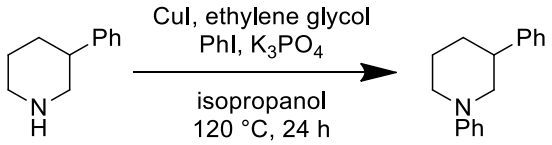
2-(furan-2-yl)-1,2,3,4-tetrahydroquinoline (S2c)



NMR spectra of the obtained product were consistent with the reported one.[8]

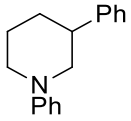
s) Synthesis of S2e

(2-methyl-1,2,3,4-tetrahydroquinolin-6-yl)methanol (S2e)



The compound was synthesized with a similar procedure as a previous report.[17] A mixture of 3-phenylpiperidine (479 µL, 3.0 mmol), CuI (38 mg, 0.2 mmol), PhI (224 µL, 2.0 mmol), K_3PO_4 (849 mg, 4.0 mmol), ethylene glycol (223 µL, 4.0 mmol) and isopropanol (1.33 mL) was heated at 120 °C in a sealed tube under argon atmosphere. After cooled to room temperature, the mixture was dissolved in a mixture of water and CH_2Cl_2. After extraction with CH_2Cl_2 three times, the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2/*n*-hexane = 1/2) afforded **S2e** (195.8 mg, 0.82 mmol) in 27% yield as colorless oil.

1,3-diphenylpiperidine (S2e)



^{1}H NMR ($CDCl_3$): δ = 7.39-7.35 (2H, m), 7.33-7.26 (5H, m), 7.00 (2H, dd, *J* =

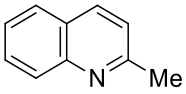
7.8, 0.9 Hz), 6.89-6.85 (1H, m), 3.82-3.78 (2H, m), 3.00-2.94 (1H, m), 2.84-2.78 (2H, m), 2.09-2.06 (1H, m), 1.93-1.83 (2H, m), 1.73-1.64 (1H, m); ^{13}C NMR ($CDCl_3$): δ = 151.52, 144.26, 129.06, 128.46, 127.22, 126.50, 119.27, 116.48, 57.01, 50.08, 42.50, 31.50, 25.39. HRMS (ESI): *m/z* calcd for $C_{17}H_{20}N$ $[M+H]^+$ 238.1590 Found 238.1583; IR (KBr): 2929, 1599, 1495, 1384, 1239, 1119, 1032, 754, 698 cm^{-1}

r) Synthesis of S2f

This compound was prepared as reported previously.[17]

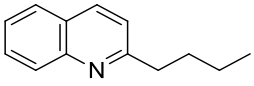
5. Characterization of Target Compounds

2-methylquinoline (3a)



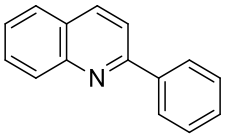
NMR spectra of the obtained product were consistent with the reported one.[18]

2-butylquinoline (3b)



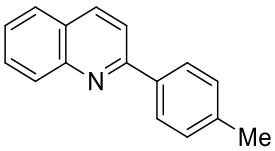
NMR spectra of the obtained product were consistent with the reported one.[18]

2-phenylquinoline (3c)



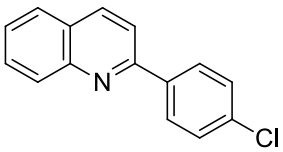
NMR spectra of the obtained product were consistent with the reported one.[8]

2-(*p*-tolyl)quinoline (3d)



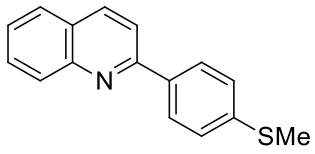
NMR spectra of the obtained product were consistent with the reported one.[19]

2-(4-chlorophenyl)quinoline (3e)



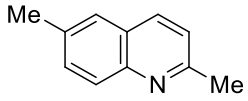
NMR spectra of the obtained product were consistent with the reported one.[19]

2-(4-(methylthio)phenyl)quinoline (3f)



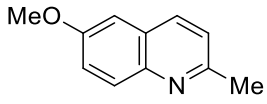
NMR spectra of the obtained product were consistent with the reported one.[8]

2,6-dimethylquinoline (3g)



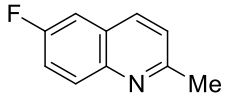
NMR spectra of the obtained product were consistent with the reported one.[16]

6-methoxy-2-methylquinoline (3h)



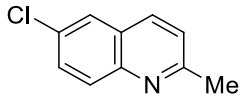
NMR spectra of the obtained product were consistent with the reported one.[16]

6-fluoro-2-methylquinoline (3i)



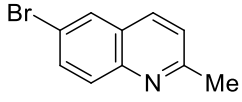
NMR spectra of the obtained product were consistent with the reported one.[16]

6-chloro-2-methylquinoline (3j)



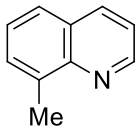
NMR spectra of the obtained product were consistent with the reported one.[16]

6-bromo-2-methylquinoline (3k)



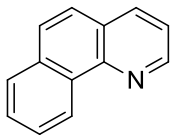
NMR spectra of the obtained product were consistent with the reported one.[16]

8-methylquinoline (3l)



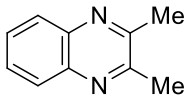
NMR spectra of the obtained product were consistent with the reported one.[8]

benzo[*h*]quinoline (3m)



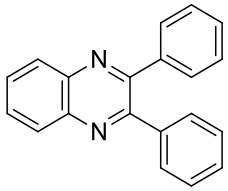
NMR spectra of the obtained product were consistent with the reported one.[8]

2,3-dimethylquinoxaline (3n)



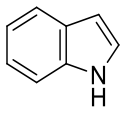
NMR spectra of the obtained product were consistent with the reported one.[11]

2,3-dimethylquinoxaline (3o)



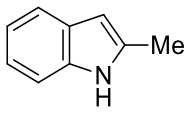
NMR spectra of the obtained product were consistent with the reported one.[20]

1*H*-indole (3p)



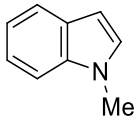
NMR spectra of the obtained product were consistent with the reported one.[21]

2-methyl-1*H*-indole (3q)



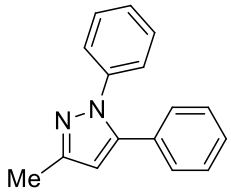
NMR spectra of the obtained product were consistent with the reported one.[22]

1-methyl-1*H*-indole (3r)



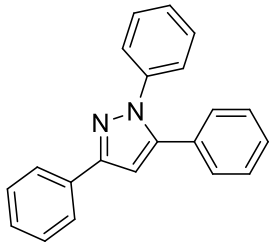
NMR spectra of the obtained product were consistent with the reported one.[22]

3-methyl-1,5-diphenyl-1*H*-pyrazole (3s)



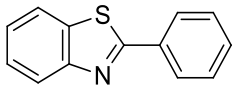
NMR spectra of the obtained product were consistent with the reported one.[23]

1,3,5-triphenyl-1*H*-pyrazole (3t)



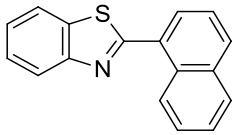
NMR spectra of the obtained product were consistent with the reported one.[24]

2-phenylbenzo[*d*]thiazole (3u)



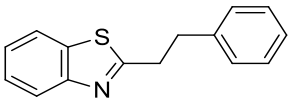
NMR spectra of the obtained product were consistent with the reported one.[25]

2-(naphthalene-1-yl)benzo[*d*]thiazole (3v)



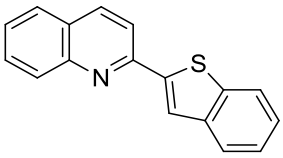
NMR spectra of the obtained product were consistent with the reported one.[26]

2-phenethylbenzo[*d*]thiazole (3w)



NMR spectra of the obtained product were consistent with the reported one.[27]

2-(benzo[*b*]thiophen-2-yl)quinoline (3x)



NMR spectra of the obtained product were consistent with the reported one.[28]

8. References

1. J. A. Nicasio, S. Steinberg, B. Inés, M. Alcarazo*, Chem. – Eur. J.* **2013**, *19*, 11016.
2. M. Ullrich, A. J. Lough, D. W. Stephan, *Organometallics* **2010**, *29*, 3647
3. G. C. Welch, L. Cabrera, P. A. Chase, E. Hollink, J. D. Masuda, P. Wei, D. W. Stephan, *Dalton Trans.* **2007**, 3407.
4. A. E. Ashley, T. J. Herrington, G. G. Wildgoose, H. Zaher, A. L. Thompson, N. H. Rees, T. Krämer, D. O'Hare, *J. Am. Chem. Soc.* **2011**, *133*, 14727.
5. H. Wang, R. Fröhlich, G. Kehr, G. Erker, *Chem. Commun.* **2008**, 5966.
6. M. Rueping, T. Theissmann, A. P. Antonchick, *Synlett* **2006**, 1071.
7. M. Ueda, S. Kawai, M. Hayashi, T. Naito, O. Miyata, *J. Org. Chem.* **2010**, *75*, 914.
8. A. V. Iosub, S. S. Stahl, *Org. Lett.* **2015**, *17*, 4404.
9. D. Talwar, H. Y. Li, E. Durham, J. Xiao, *Chem. – Eur. J.* **2015**, *21*, 5370.
10. P. Eisenberger, B. P. Bestvater, E. C. Keske, C. M. Crudden, *Angew. Chem. Int. Ed.* **2015**, *54*, 2467.
11. Z. Zhang, H. Du, *Angew. Chem. Int. Ed.* **2015**, *54*, 623.
12. A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 506.
13. N. T. Patil, V. Singh, *Chem. Commun.* **2011**, *47*, 11116.
14. N. Raghav, M. Singh, *Bioorg. Med. Chem.* **2014**, *22*, 4233.
15. C. Zhu, T. Akiyama, *Org. Lett.* **2009**, *11*, 4180.
16. Y. Matsubara, S. Hirakawa, Y. Yamaguchi, Z. Yoshida, *Angew. Chem. Int. Ed.* **2011**, *50*, 7670.
17. A. M. Nauth, N. Otto, T. Opatz, *Adv. Synth. Catal.* **2015**, *357*, 3424.
18. A. E. Wendlandt, S. S. Stahl, *J. Am. Chem. Soc.* **2014**, *136*, 11910.
19. R. P. Singh, S. K. Aithagani, M. Yadav, V. P. Singh, R. A. Vishwakarma, *J. Org. Chem.* **2013**, *78*, 2639.
20. B. Krishnakumar, M. Swaminathan, *J. Organomet. Chem.* **2010**, *695*, 2572.
21. J. Siu, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.* **2004**, *2*, 160.
22. J. A. Schiffner, T. H. Wöste, M. Oestreich, *Eur. J. Org. Chem.* **2010**, 174.
23. G. Hilt, M. Arndt, D. F. Weske, *Synthesis (Stuttgart)* **2010**, 1321.
24. N. Nakamichi, Y. Kawashita, M. Hayashi, *Synthesis (Stuttgart)* **2004**, 1015.
25. J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 3674.
26. H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737.
27. X. Fan, Y. He, X. Zhang, S. Guo, Y. Wang, *Tetrahedron* **2011**, *67*, 6369.
28. T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073.

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