The development of green catalysts for organic transformations

Guanshuo Shen

2019

Table of Contents

General Introduction 1

Green Chemistry 2

The Principles of Green Chemistry 2

Solvents 5

Catalysis 7

References 12

Chapter 1 Brønsted Acid-Catalyzed Selective C-C Bond Cleavage of 1,3-Diketones: A Facile Synthesis of 4(3*H*)-Quinazolinones in Aqueous Ethyl Lactate 14

Introduction 15

Results and Discussion 17

Conclusion 26

Experimental Section 27

References 43

Chapter 2 Cu-Catalyzed Reduction of Azaarenes and Nitroaromatics with Diboronic Acid as Reductant 48

Introduction 49

Results and Discussion 51

Conclusion 61

Experimental Section 62

References.....80

Chapter 3 Aqueous Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex under Batch and Continuous-Flow Conditions.....85

Introduction.....86

Results and Discussion.....88

Conclusion.....103

Experimental Section.....104

References.....125

Chapter 4 Asymmetric Arylative Cyclization of Alkynones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex in Water.....130

Introduction.....131

Results and Discussion.....133

Conclusion.....138

Experimental Section.....139

References.....146

Conclusion.....147

Acknowledgement.....151

General Introduction

Green Chemistry

The definition and concept of Green Chemistry were first formulated at the beginning of the 1990s nearly 30 years ago.[1] Green Chemistry emphasizes reducing or eliminating the use and generation of hazardous substances when designing of chemical products and processes.[2] To obtain the desired products and achieve green sustainability simultaneously, a lot of efforts has been made in this field. Among them, the catalytic organic transformations performed in water in replacement of organic solvents has attracted considerable attentions in recent years. Furthermore, the catalytic process can also avoid generating the stoichiometric amount of waste which further enhances the green sustainability.

The Principles of Green Chemistry

In 1998, the twelve principles of green chemistry were introduced by Paul Anastas and John Warner, which used for guiding the organic chemists to obtain the target molecules with green protocols. These principles explained the fundamental methods to achieve green chemistry goals. For the convenience of the reader, the twelve principles of green chemistry are cited below.[2a]

1. **Prevention**. It is better to prevent waste than to treat or clean up waste after it is formed.
2. **Atom Economy**. Synthetic methods should be designed to maximize

the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Synthesis**. Wherever practicable, synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.
5. **Safer Solvents and Auxiliaries.** The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.
6. **Design for Energy Efficiency**. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**. Unnecessary derivatization (use of blocking groups, protection/deprotection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can

generate waste.

9. **Catalysis**. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation.** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-Time Analysis for Pollution Prevention**. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

According to the twelve principles of green chemistry and considering the practice of synthetic chemistry, the following points should receive much more attention.

(a) Catalytic process should be designed.

(b) Organic solvents should be replaced.

(c) Atom economy should be considered.

(d) Recyclable catalysts should be employed.

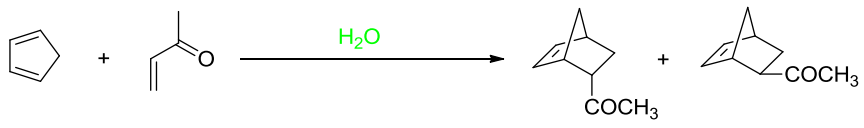
In this regard, replacement of organic solvents with water (a.k.a.

aqueous-switching), using cheaper and more-abundant elements/reagents/catalysts (ubiquitous-switching), or recycling the precious transition-metal species are highly desirable.

Solvents

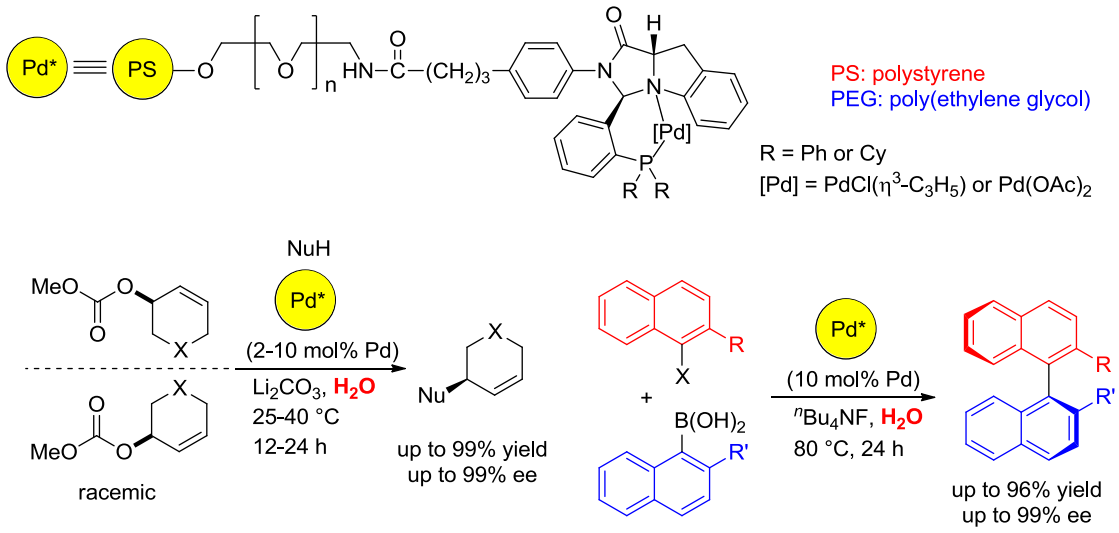
Solvents are the media of organic transformations, which plays an important role in organic synthesis. Conventionally, the hazardous and non-sustainable organic solvents which produced from petroleum feedstocks are used as the normal media and water is considered as a contaminant in the chemical synthesis. However, human's body contains around 60% of water. It's obvious that the chemical bond could be formed in the aqueous solution. In fact, the urea synthesis, commonly referred to as the starting point for organic synthesis, was performed in aqueous solution by heating silver cyanate with ammonium chloride in 1828 by Friedrich Wöhler. Another milestone of organic reactions in water is in 1980, Darryl C. Rideout and Ronald Breslow found that using water as a solvent instead of organic solvents could be greatly accelerated Diels-Alder reactions[3] (**Scheme 1**).

Scheme 1. Diels-Alder reaction performed in water



Besides Diels-Alder reactions, other examples cover almost all of the most useful reactions even the asymmetric version was realized in water. In **Scheme 2**, prof. Uozumi and coworkers have previously reported an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin supported chiral imidazoindoline-palladium catalyst, which efficiently catalyzed the asymmetric allylic substitution and the asymmetric Suzuki-Miyaura crossing coupling reactions in water under heterogeneous conditions with high recyclability.[4, 5]

Scheme 2. Asymmetric allylic substitution and asymmetric Suzuki-Miyaura coupling in water



It's obvious that use water as a green chemistry solvent has tremendous benefits, because water is eco-friendly, cheap, nontoxic, abundant and safe.[6] Therefore, the development of organic reactions in water to realize the green sustainability is highly desired.

Catalysis

The catalyst is a substance added to the reaction to accelerate the rate of the reaction, which is not consumed and produced and can continue to act repeatedly. The catalyst usually worked by lowering the activation energy to make the reaction occurred in an efficient way. Comparing with the reactions which use stoichiometric amounts of reagents, the catalytic reaction can significantly decrease the waste.[7] Based on the above-mentioned advantages such as less energy, efficient reaction pathway, less waste, the catalytic reaction has the potential to achieve the green sustainability.

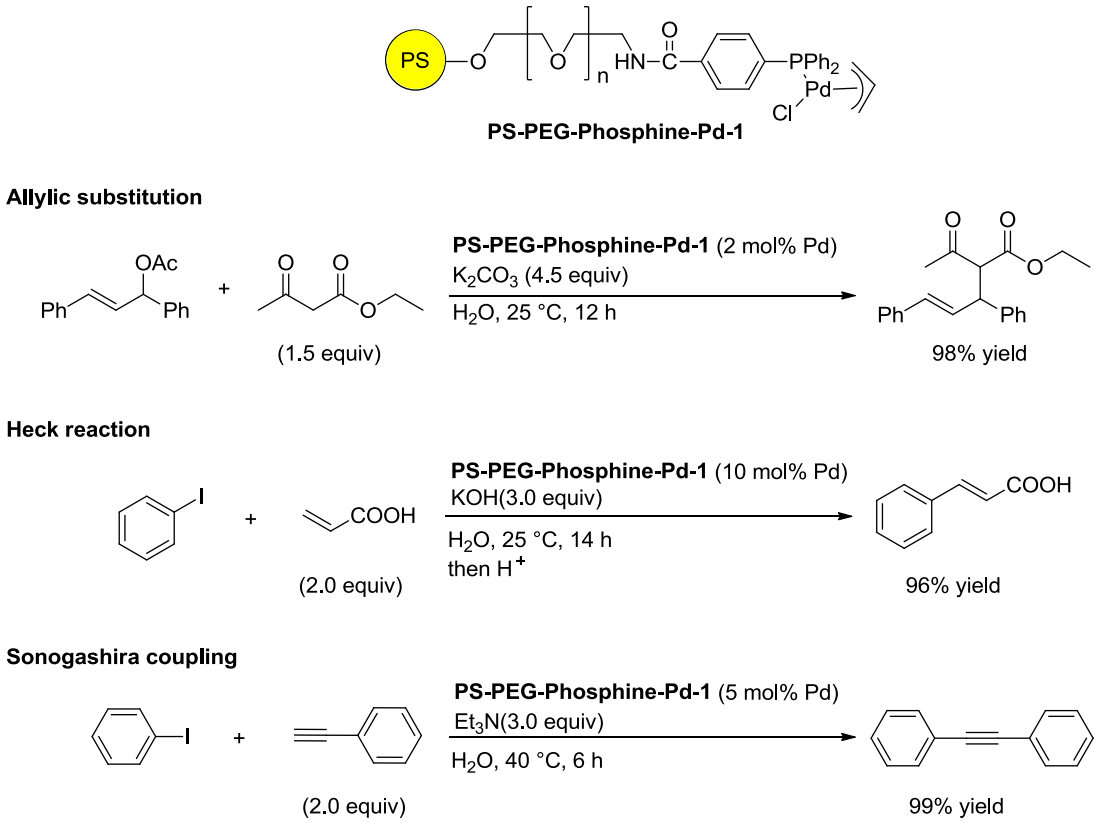
The catalysts can be classified as homogeneous catalyst or heterogeneous catalyst depending on how it worked in the reaction. In the heterogeneous reaction, the catalysts and the substrates are in the same phase. The catalyst with high activity and selectivity are usually obtained. However, heterogeneous reaction system is usually a multi-phase reaction system, which the catalyst and substrates are present in different phases. The advantages for the reactions using heterogeneous catalysts are easy separation of the catalysts from the reaction mixture and easy recycling of the catalyst.[8] The products with high purity are often obtained.

To achieve the green sustainability, both homogeneous and heterogeneous catalysts catalyzed the organic transformations should be highly considered. In fact, prof. Uozumi and coworkers have recently

developed various amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin supported transition metal catalysis and their application to the catalytic transformations in water under heterogeneous conditions.

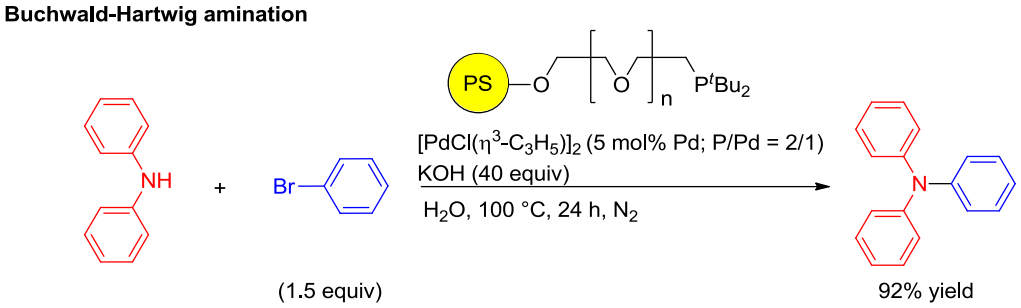
For example, prof. Uozumi and coworkers have previously reported the PS-PEG supported palladium-phosphine complex catalyzed allylic substitution[9], alkenylation (Heck reaction)[10], alkynylation (Sonogashira coupling)[11] in water (**Scheme 3**).

Scheme 3. PS-PEG supported palladium-phosphine catalyzed C-C bond forming reactions



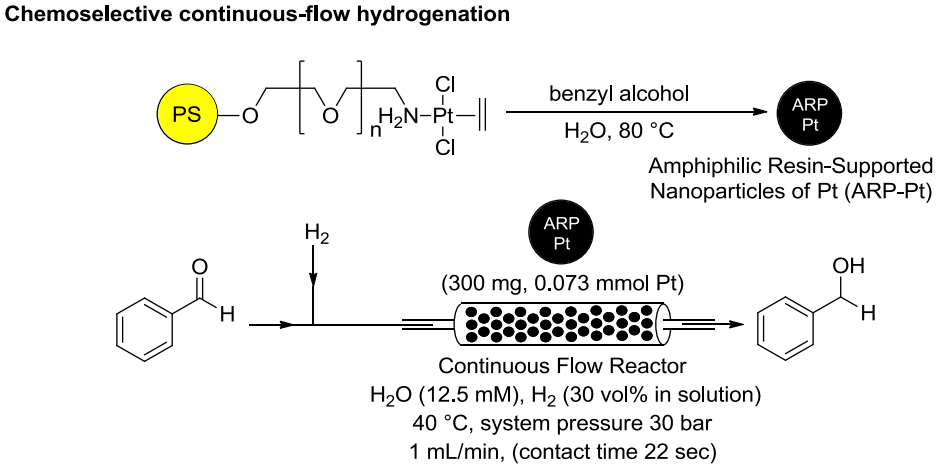
PS-PEG supported palladium-phosphine complexes also can be applied to the Buchwald-Hartwig amination of aryl halides with diphenylamine to provide the corresponding triarylamines in up to 96% yield (**Scheme 4**).[12]

Scheme 4. PS-PEG supported palladium-phosphine catalyzed Buchwald-Hartwig amination



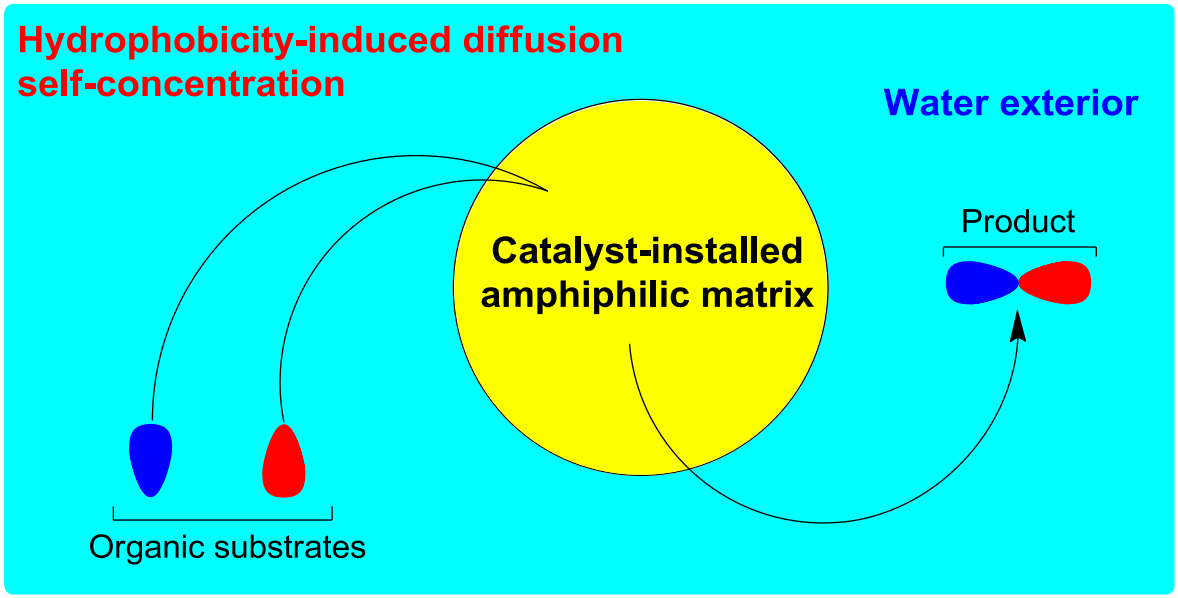
PS-PEG supported other transition metal like platinum was also designed and used for the chemoselective continuous-flow hydrogenation of aldehydes with excellent performance in the yield, selectivity and functional groups tolerance **(Scheme 5)**.[13]

Scheme 5. ARP-Pt catalyzed chemoselective continuous-flow hydrogenation of aldehyde



The high activity of these PS-PEG supported transition metal catalysts in water are due to the unique property of the reaction system. The organic substrates will be highly concentrated at the hydrophobicity of polystyrene matrix part where the active catalyst center was right there. Thus, the reactants can be efficiently transferred to the desired products (**Scheme 6**). Furthermore, from the perspective of the green chemistry, PS-PEG catalysts have several advantages such as easily recovery and recycling, and with less metal contamination of products.

Scheme 6. Schematic image of PS-PEG supported transition metal catalysts in water



From all above and continue this author group's research interests in green catalysis, this author decided to make effort in the development of green sustainable organic transformations by way of aqueous-switching, ubiquitous-switching, and recycling the precious transition-metal species.

References

(1) Collins, T. J. *Green Chemistry*, *Macmillan Encyclopedia of Chemistry,* Simon and SchusterMacmillan, New York, **1997**, *2*, 691-697.

(2) (a) Anastas, P. T. and Warner, J. C. *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**. (b) Horváth, I. T. and Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2167-2168. (c) Anastas, P. T. and Williamson, T. C. *Green Chemistry: Designing Chemistry for the Environment*, American Chemical Series Books, Washington, DC, **1996**, 1-20.

(3) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816-7817.

(4) (a) Uozumi, Y. and Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919-2910. (b) Uozumi, Y.; Tanaka, H. and Shibatomi, K. *Org. Lett.* **2004**, *6*, 281-283.

(5) For asymmetric Suzuki-Miyaura coupling: Uozumi, Y.; Matsuura, Y.; Arakawa, T. and Yamada, Y. M. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2708-2710.

(6) (a) Dixneuf, P. H.; Cadierno, V. *Metal-Catalyzed Reactions in Water*; Wiley-VCH: Weinheim, **2013**. (b) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725-748. (c) Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415-1427 and references cited therein.

(7) (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233-1246. (b) Horváth, I. T. *Encyclopedia of Catalysis*, Wiley-VCH: Weinheim, 2003.

(8) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267-278.

(9) Uozumi, Y.; Danjo, H. and Hayashi, T. *Tetrahedron Lett.* **1997**, 38, 3557-3560.

(10) Uozumi, Y.; Kimura, T. *Synlett.* **2002**, 2045-2048.

(11) Suzuka, T.; Okada, Y.; Ooshiro, K.; Uozumi, Y. *Tetrahedron*. **2010**, *66*, 1064-1069.

(12) Hirai, Y. and Uozumi, Y. *Chem. Commun.* **2010**, *46*, 1103-1105.

(13) Osako, T.; Torii, K.; Hirata, S. and Uozumi, Y. *ACS Catal*. **2017**, *7*, 7371-7377.

Chapter 1

Brønsted Acid-Catalyzed Selective C-C Bond Cleavage of 1,3-Diketones: A Facile Synthesis of 4(3*H*)-Quinazolinones in Aqueous Ethyl Lactate

Guanshuo Shen, Haifeng Zhou, Peng Du, Sensheng Liu, Kun Zou,

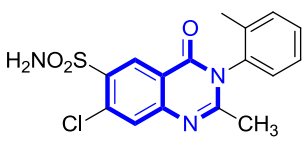
and Yasuhiro Uozumi

RSC Adv. **2015**, *5*, 85646-85651

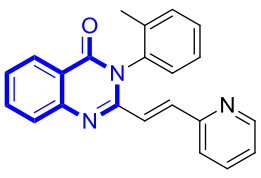
Introduction

The direct selective cleavage of unstrained C-C bond has attracted much attention and emerged as a challenging transformation in organic synthesis due to the high C-C bond strength.[1] As inexpensive and readily available starting materials, 1,3-diketones have been widely used as important substrates in organic synthesis.[2] In 2010, Lei reported the first example of CuI-catalyzed C-C bond cleavage of 1,3-diketones and arylation to give *α*-arylketones.[3a] The esters,[3b] *α*-ketoesters,[3c] amides,[3d,3e] *α*-ketoamides[3f] or *α*-amino acid esters[3g] could be obtained from the reactions of 1,3-diketones with alcohols or amines *via* C-C bond cleavage in the presence of Lewis acid, or under oxidation conditions. Recently, CuI-catalyzed tandem cyclization of *o*-halobenzoic acids,[3h] esters,[3i] or amides[3j] with 1,3-diketones leading to isocoumarins was developed. Very recently, H_2O_2-promoted reactions of aliphatic primary amines with 1,3-diketones for the synthesis of 1*H*-pyrrol-3(*2H*)-ones was also realized.[3k]

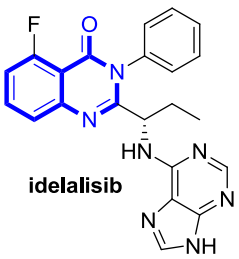
Figure 1. Selected examples of alkaloids and marketed drugs incorporating 4(3*H*)-quinazolinone cores.



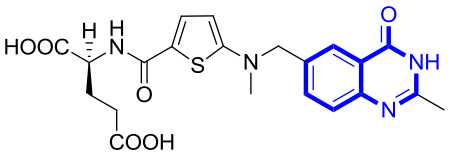
metolazone



piriqualone



idelalisib

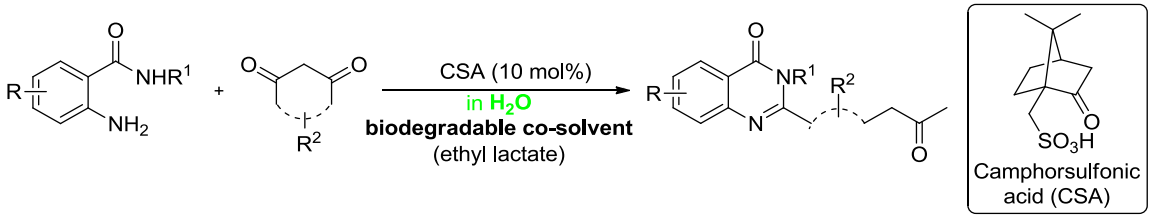


raltitrexed

4(*3H*)-quinazolinones are building blocks of many naturally occurring alkaloids and marketed drugs (**Fig 1**).[4] Owing to their importance and utility, a range of synthetic methods have been developed to construct quinazolinone derivatives.[5-7] It should be noted that most reported methods for the preparing of 4(*3H*)-quinazolinones request expensive transition-metal catalysts in the presence of oxidants and bases under harsh reaction conditions. Therefore, more environmentally benign and efficient methods to approach valuable quinazolinone derivatives are highly desirable.

Ethyl lactate is prepared by esterification of ethanol with lactic acid, both of which can be obtained by fermentation of biomass. Ethyl lactate has recently attracted much attention and has been used in organic synthesis as an environmentally benign and biodegradable solvent.[8] Continuing this author group's research interest in green catalysis,[9] this author has discovered a green approach for the synthesis of 4(3*H*)-quinazolinones by cyclization of 2-aminobenzamides with a wide range of acyclic or cyclic 1,3-diketones *via* C-C bond cleavage in the presence of camphorsulfonic acid (CSA) as a Brønsted catalyst in biodegradable ethyl lactate solution under metal-, oxidant-, and radiation-free conditions (**Scheme 1**).

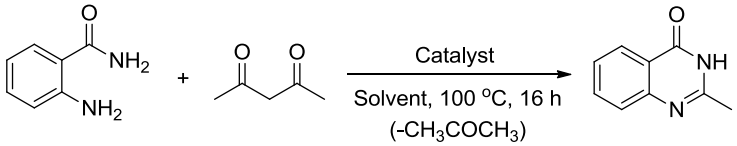
Scheme 1. A green approach to 4(3*H*)-quinazolinones



Results and Discussion

Initially, this author chose the reaction of 2-aminobenzamide (**1a**) with pentane-2,4-dione (**2A**) as a model process for optimizing the reaction conditions (**Table 1**).

Table 1. Optimization of conditions for the asymmetric 1,4-addition[a]



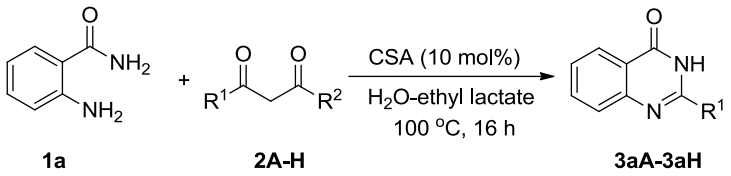
1a **2A** **3aA**

Entry	Catalyst	Solvent	Yield[b] (%)
1	None	PEG-400	NR[c]
2	$TsOH·H_2O$	PEG-400	10
3	AcOH	PEG-400	<5
4	F_3CCO_2H	PEG-400	<5
5	F_3CSO_3H	PEG-400	48
6	CSA[d]	PEG-400	61
7	CSA	PEG-200	42
8	CSA	Ethyl lactate	74
9	CSA	H_2O	43
10	CSA	Ethyl lactate-H_2O (1:1)	84
11	CSA	Ethyl lactate-H_2O (1:9)	98
12	CSA[e]	Ethyl lactate-H_2O (1:9)	81

[a]Reaction conditions: 2-aminobenzamide (**1a**; 0.2 mmol), pentane-2,4-dione (**2A**; 0.3 mmol), catalyst (10 mol%), solvent (1.0 mL), 100 °C, 16 h. [b]Isolated yield. [c]No reaction. [d]CSA: camphorsulfonic acid. [e]5 mol% of CSA was use.

No reaction was observed when amide **1a** was treated with dione **2A** in poly(ethylene glycol) (PEG-400) at 100 °C in the absence of a catalyst (**Table1**, entry 1). However, the desired product **3aA** was obtained in various yields on adding 10 mol% of a Brønsted acid catalyst to the reaction mixture (entries 2-6). Among the tested Brønsted acid catalysts, *p*-toluenesulfonic acid ($TsOH \cdot H_2O$), acetic acid (AcOH), and trifluoroacetic acid (F_3CCO_2H) gave yields of less than 10%. Moderate yields of quinazolinone **3aA** were obtained when trifluoromethanesulfonic acid (F_3CSO_3H; entry 5) or natural camphorsulfonic acid (CSA; entry 6) was used as catalyst, with CSA providing the higher yield (61%). When other green solvents such as PEG-200, ethyl lactate, and water were screened in this transformation, ethyl lactate gave the best results (entries 6-9). More delightfully, this author obtained product **3aA** in up to 98% yield by using a mixture of ethyl lactate and water as the solvent (entry 11). Decreasing the catalyst loading from 10 mol% to 5 mol% resulted in a relatively low yield (entry 12). This author therefore performed subsequent reactions of 2-aminobenzamides with various 1,3-diketones in the presence of 10 mol% camphorsulfonic acid as catalyst at 100 °C in a 1:9 (v/v) mixture of ethyl lactate and water for 16-24 hours.

Table 2. The scope of acyclic 1,3-diketones 2[a]



1a **2A-H** **3aA-3aH**

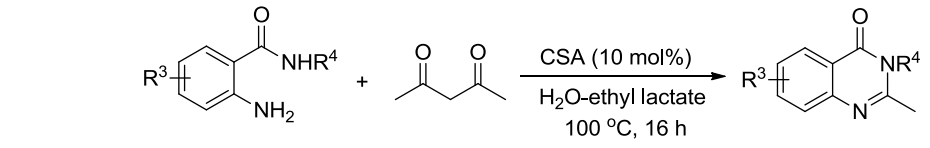
Entry	**2**		**3**	Yield[b] (%)
1	$R^1 = R^2 =$ Me	**2A**	**3aA**	98
2	$R^1 = R^2 =$ Et	**2B**	**3aB**	81
3	$R^1 = R^2 =$ *i*-Pr	**2C**	**3aC**	59
4	$R^1 = R^2 =$ *t*-Bu	**2D**	**3aD**	<1
5	$R^1 = R^2 =$ Ph	**2E**	**3aE**	79
6	$R^1 =$ Me, $R^2 =$ Ph	**2F**	**3aA**	75
7	$R^1 =$ Me, $R^2 =$ *t*-Bu	**2G**	**3aA**	71
8	$R^1 =$ Me, $R^2 = CF_3$	**2H**	**3aA**	54

[a]Reaction conditions: 2-aminobenzamide (**1a**; 0.2 mmol), pentane-2,4-dione (**2**; 0.3 mmol), CSA (10 mol%), H_2O-ethyl lactate (9:1; 1.0 mL), 100 °C, 16 h. [b]Isolated yield.

With the optimized reaction conditions in hand, this author examined the reactions of 2-aminobenzamide (**1a**) with various acyclic 1,3-diketones. As shown in **Table 2**, a lower yield of **3aB** comparing with that of **3aA** was observed when the reaction of **1a** and heptane-3,5-dione (**2B**) was carried out under the optimized conditions (**3aA**: 98%; **3aB**: 81%). The reaction of amide **1a** with sterically hindered 2,6-dimethylheptane-3,5-dione (**2C**) provided the desired product **3aC** in moderate yield (**3aC**: 59%). In

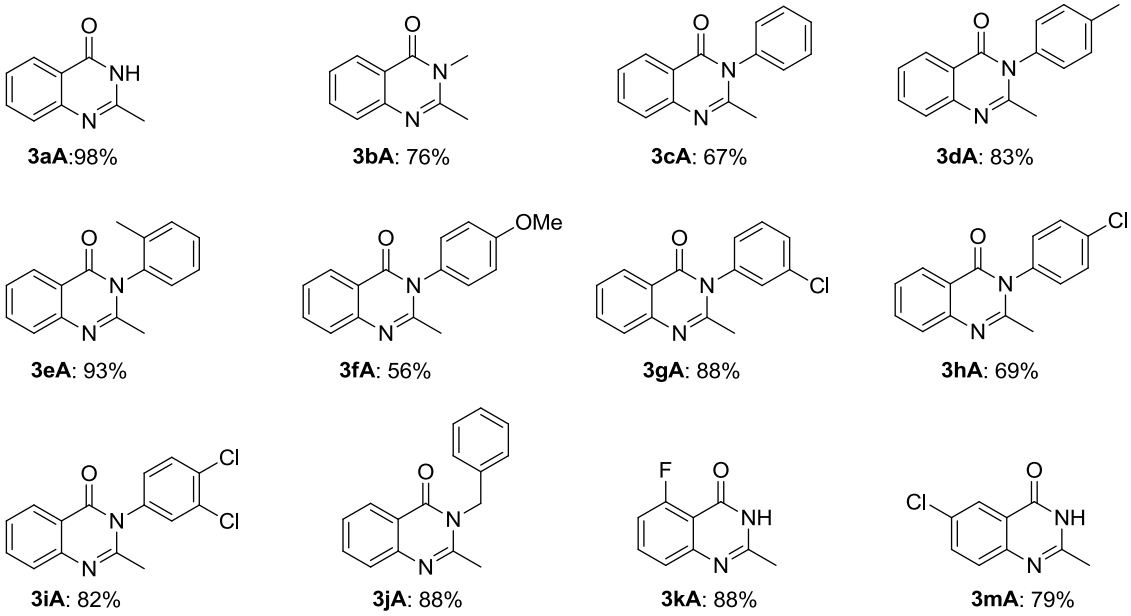
contrast, the reactants remained unchanged in the attempted reaction of amide **1a** and the more sterically hindered 2,2,6,6-tetramethylheptane-3,5-dione (**2D**), even on raising the temperature and prolonging the reaction time. 2-Phenylquinazolin-4(3*H*)-one (**3aE**) was obtained by the reaction of **1a** with 1,3-diphenylpropane-1,3-dione (**2E**) in 79% yield. Finally, the reactions of **1a** with the unsymmetrical 1,3-diketones 1-phenylbutane-1,3-dione (**2F**), 5,5-dimethylhexane-2,4-dione (**2G**), and 1,1,1-trifluoropentane-2,4-dione (**2H**) were examined, all gave the same product, **3aA**, in 54-75% yield through selective C-C bond cleavage. These results indicate that the reactivity of the acetyl group is higher than that of the benzoyl, pivaloyl, or trifluoroacetyl group.

Scheme 2. The scope of 2-aminobenzamides 1[a]



1a-m **2A** **3aA-3mA**

a: $R^3 = R^4 = H$
b: $R^3 = H$, $R^4 = Me$
c: $R^3 = H$, $R^4 = Ph$
d: $R^3 = H$, $R^4 = 4\text{-}CH_3C_6H_4$
e: $R^3 = H$, $R^4 = 2\text{-}CH_3C_6H_4$
f: $R^3 = H$, $R^4 = 4\text{-}CH_3OC_6H_4$
g: $R^3 = H$, $R^4 = 3\text{-}ClC_6H_4$
h: $R^3 = H$, $R^4 = 4\text{-}ClC_6H_4$
i: $R^3 = H$, $R^4 = 3,4\text{-}Cl_2C_6H_4$
j: $R^3 = H$, $R^4 = CH_2Ph$
k: $R^3 = 6\text{-}F$, $R^4 = H$
m: $R^3 = 5\text{-}Cl$, $R^4 = H$

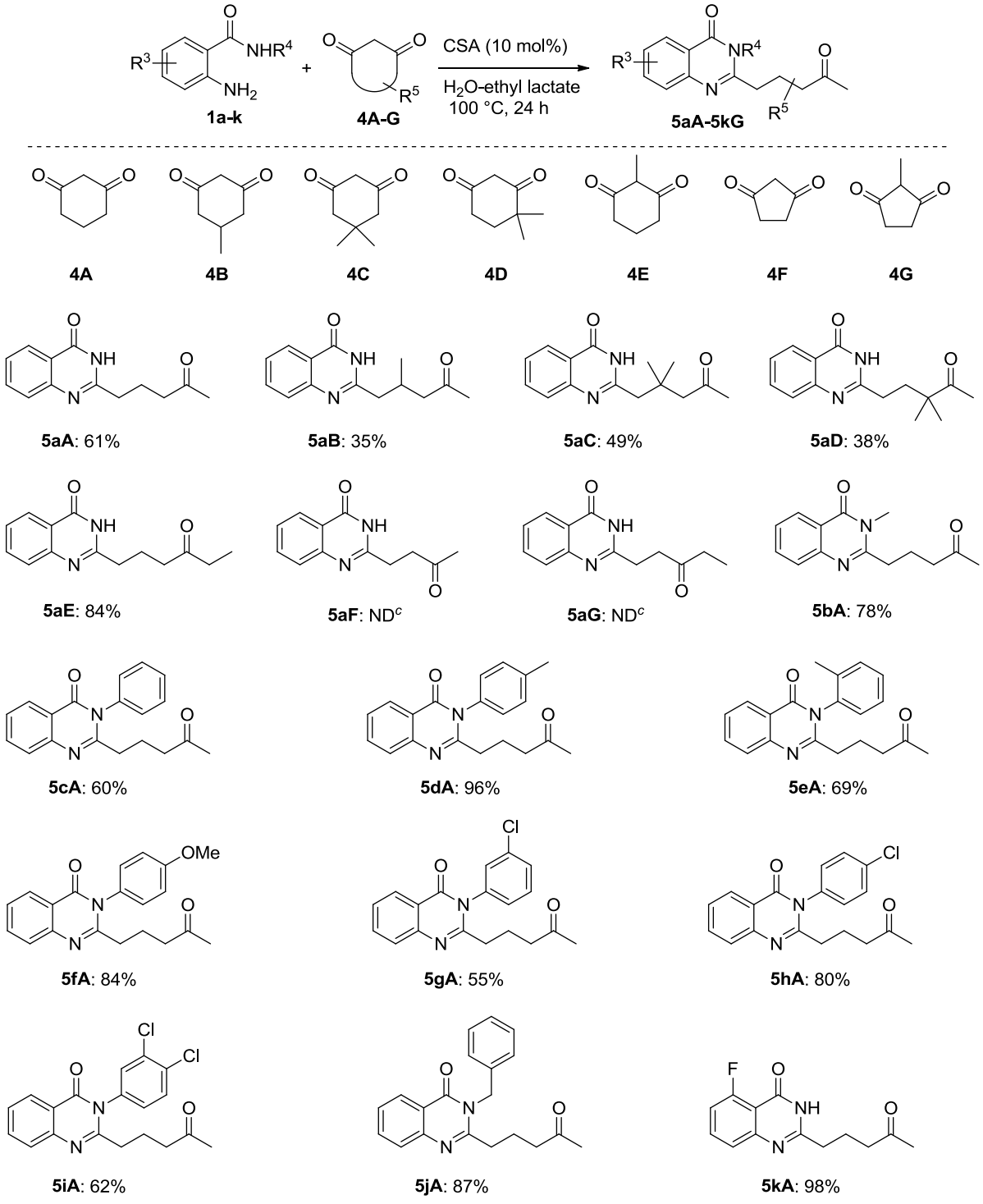


[a]Reaction conditions: 2-aminobenzamide (**1**; 0.2 mmol), pentane-2,4-dione (**2A**; 0.3 mmol), CSA (10 mol%), H_2O-ethyl lactate (9:1; 1.0 mL), 100 °C, 16 h, isolated yield.

Next, this author examined the scope of the reaction with respect to the 2-aminobenzamides. Various *N*-substituted 2-aminobenzamides **1a-m** were treated with pentane-2,4-dione (**2A**) under the optimized conditions (**Scheme 2**). From the reaction of 2-amino-*N*-methylbenzamide (**1b**), the desired product 2,3-dimethylquinazolin-4(*3H*)-one (**3bA**) was isolated in 76% yield. The *N*-aryl-2-aminobenzamides with electron-donating groups

(**1d**; 4-Me, **1e**; 2-Me, and **1f**; 4-OMe) or electron-withdrawing groups (**1g**; 3-Cl, **1h**; 4-Cl, and **1i**; 3,4-Cl_2) on the benzene ring also underwent the transformation to give the corresponding products **3cA**-**3iA** in 56-93% yield. 3-Benzyl-2-methylquinazolin-4(3*H*)-one (**3jA**) was prepared in 88% yield by the reaction of 2-amino-*N*-benzylbenzamide with pentane-2,4-dione (**2A**). The corresponding reactions of 2-amino-6-fluorobenzamide and 2-amino-5-chlorobenzamide gave quinazolinones **3kA** and **3mA** in 88% and 79% yield, respectively.

Scheme 3. Synthesis of 2-(4-oxoalkyl)quinazolinones 5[a]

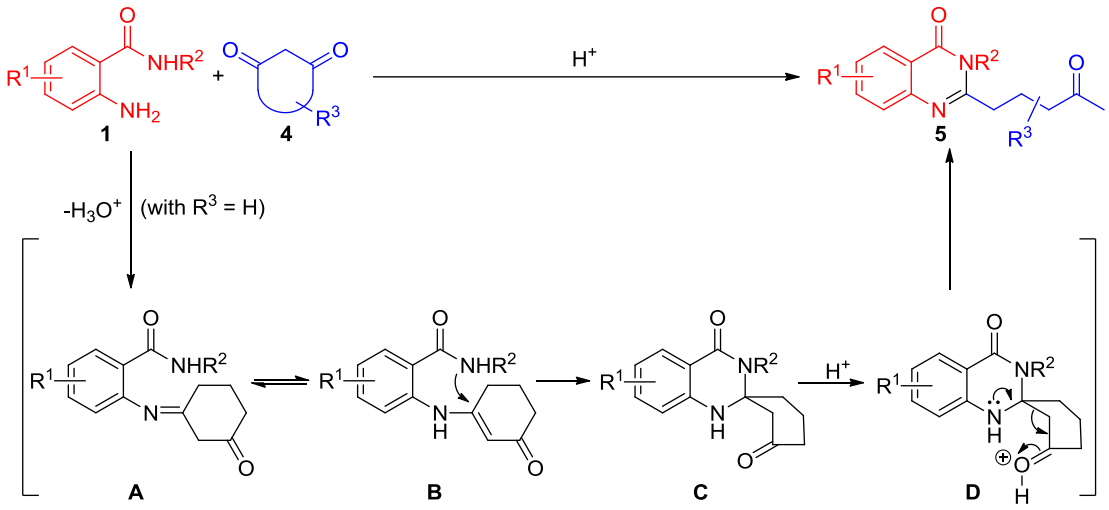


[a]Reaction conditions: 2-aminobenzamide **1** (0.2 mmol), cyclic 1,3-diketone **5** (0.3 mmol), CSA (10 mol%), 1:9 (v/v) ethyl lactate-H_2O (1.0 mL), 100 °C, 24 h. [b]Isolated yield. [c]Not detected.

Encouraged by these results, this author extended the scope of diketone reactant to include cyclic 1,3-diketones **4A-G** (**Scheme 3**). Treatment of 2-aminobenzamide (**1a**) with 1.5 equivalents of cyclohexane-1,3-dione (**4A**) in the presence of 10 mol% natural CSA in a 1:9 (v/v) mixture of ethyl lactate and water at 100 °C for 24 h gave 2-(4-oxopentyl)quinazolin-4(*3H*)-one (**5aA**) in 61% yield with full atom efficiency. When reactions of **1a** with other substituted cyclohexane-1,3-diones **4B-E** were carried out under the optimized conditions, the corresponding products **5aB-5aE** were obtained in 35–84% yield. Interestingly, 2-methylcyclohexane-1,3-dione (**4E**) exhibited a higher reactivity than 5-methylcyclohexane-1,3-dione (**4B**) (**4aB** and **4aE**). In contrast, cyclopentane-1,3-dione (**4F**) and 2-methyl-1,3-cyclopentane-1-3-dione (**4G**), which contain a five-membered ring, did not give the desired products **5aF** and **5aG** when treated with **1a** (**4aF** and **4aG**). This author then examined the scope of the reaction with respect to the 2-aminobenzamides **1**. In general, various 2-aminobenzamides **1** reacted with cyclohexane-1,3-dione (**4A**) under the optimized conditions to give the corresponding products **5bA-5kA** in 55–98% yield. With *N*-alkyl-substituted 2-aminobenzamides, products **5bA** and **5jA** were obtained in 78% and 87% yield, respectively. *N*-Aryl-substituted 2-aminobenzamides also underwent this transformation. 2-aminobenzamides with an electron-rich substituent on the aryl group gave products **5eA** and **5fA** in relatively high yields, whereas electron-deficient aryl group-

substituted 2-aminobenzamides gave products **5gA** and **5iA** in relatively low yields. Finally, 2-amino-6-fluorobenzamide also reacted with cyclohexane-1,3-dione (**4A**) to give the corresponding product **5kA** in 98%.

Scheme 4. A proposed reaction pathway



Based on the results obtained above and the literature[10], a proposed reaction mechanism was shown in **Scheme 4**. The Brønsted acid-catalyzed condensation reaction of the 2-aminobenzamide **1** with the 1,3-diketone would take place to generate a ketimine intermediate **A**, followed by tautomerization to give the enaminone intermediate **B**. Then, the intramolecular nucleophilic addition of **B** would produce adduct **C**. The C-C bond cleavage reaction would finally occur to generate the desired product **5**.

Conclusion

In summary, this author has developed an efficient, metal- and oxidant-free green approach for the synthesis of 4(3*H*)-quinazolinones. Various 2-aryl-, 2-alkyl-, and 2-(4-oxoalkyl)quinazolinones were prepared by successive condensation of 2-aminobenzamides with a wide range of acyclic or cyclic 1,3-diketones, intramolecular nucleophile addition, and selective C-C bond cleavage, catalyzed by camphorsulfonic acid in an aqueous ethyl lactate solution.

Experimental Section

General Methods. All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise stated. Analytic thin-layer chromatography (TLC) was carried out with silica gel GF 254-coated plates. All products were isolated by column chromatography on silica gel (300-400 mesh) using petroleum ether (PE; bp 60-90 °C) and ethyl acetate. All compounds were characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ESI-MS. All ^{1}H NMR shifts are reported in δ units (ppm) relative to the signals for residual $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm) in the corresponding deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.60 ppm). NMR data were recorded on a Bruker 400 MHz instrument. HRMS data were recorded with ESI ionization sources on a Bruker Apex II instrument. Melting points were determined on an X-4 apparatus.

2-Methylquinazolin-4(3*H*)-one (3aA); typical procedure

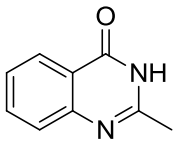
A flask was charged with 2-aminobenzamide (**1a**; 27.2 mg, 0.2 mmol), pentane-2,3-dione (**2A**; 30.0 mg, 0.3 mmol), CSA (4.6 mg, 0.02 mmol), and 1:9 (v/v) ethyl lactate-H_2O (1.0 mL). The flask was sealed and the mixture was stirred at 100 °C for 16 h. When the reaction was complete (TLC), the mixture was cooled to room temperature, extracted with EtOAc

(3 × 20 mL), and washed with H_2O. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) to give the product **3aA** (31.7 mg, 98%) as white solid.

2-(4-Oxopentyl)quinazolin-4(3*H*)-one (5aA); typical procedure

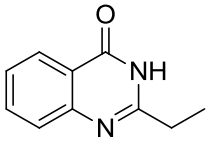
A fask was charged with 2-aminobenzamide (**1a**; 27.2 mg, 0.2 mmol), cyclohexane-1,3-dione (**4A**; 33.6 mg, 0.3 mmol), CSA (4.6 mg, 0.02 mmol), and 1:9 (v/v) ethyl lactate-H_2O (1.0 mL). The fask was sealed and the mixture was stirred at 100 °C for 24 h. When the reaction was complete (TLC), the mixture was cooled to r.t., extracted with EtOAc (3×20 mL), and washed with H_2O. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) to give the product **5aA** (28.1 mg, 61%) as white solid.

2-Methylquinazolin-4(*3H*)-one (3aA)



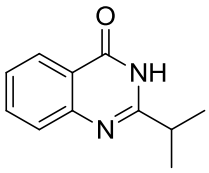
CAS: 1769-24-0; White solid, mp 176-177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.61 (s, 3H), 7.47 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.76 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.28 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 12.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.1, 120.2, 126.2, 126.4, 127.0, 134.9, 149.4, 153.3, 164.4; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_8N_2O$ 161.0709; found 161.0714.

2-Ethylquinazolin-4(*3H*)-one (3aB)



CAS: 3137-64-2; White solid, mp 232-233 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (t, J = 7.6 Hz, 3H), 2.84 (q, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.78 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 8.29 (d, J = 7.6 Hz, 1H), 11.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.5, 29.2, 120.5, 126.2, 126.4, 127.2, 134.8, 149.4, 157.5, 164.2 ; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{10}N_2O$ 175.0866; found 175.0871.

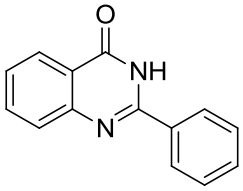
2-Isopropylquinazolin-4(*3H*)-one (3aC)



CAS: 13182-64-4; White solid, mp 232-233 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (d, J = 6.8 Hz, 6H), 2.97-3.08 (m, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.70-7.79 (m, 2H), 8.29

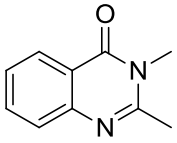
(d, J = 7.6Hz, 1H), 10.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.5, 35.0, 120.8, 126.3, 126.4, 127.4, 134.7, 149.4, 160.5, 163.7; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{11}H_{12}N_2O$ 189.1022; found 189.1027.

2-Phenylquinazolin-4(*3H*)-one (3aE)



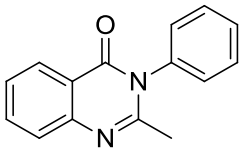
CAS: 1022-45-3; White solid, mp 122-123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.59-7.60 (m, 3H), 7.79-7.86 (m, 2H), 8.15-8.17 (m, 2H), 8.33 (d, J=7.6 Hz, 1H), 10.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 126.5, 126.9, 127.1, 128.1, 129.2, 131.8, 132.8, 134.9, 149.4, 151.4, 163.1; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{10}N_2O$ 223.0866; found 223.0871.

2,3-Dimethylquinazolin-4(*3H*)-one (3bA)



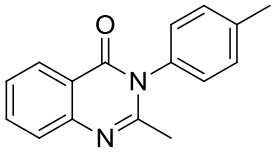
CAS: 1769-25-1; White solid, mp 110-111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.63 (s, 3H), 3.63 (s, 3H), 7.44 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.71 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6, 31.1, 120.2, 126.5, 126.5, 126.8, 134.3, 147.1, 154.6, 162.3, ppm; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{10}H_{10}N_2O$ 175.0866; found 175.0870.

2-Methyl-3-phenylquinazolin-4(*3H*)-one (3cA)



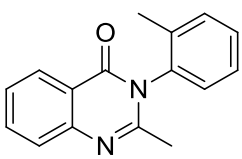
CAS: 2385-23-1; White solid, mp 147-148 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.25 (s, 3H), 7.27-7.28 (m, 2H), 7.45-7.59 (m, 4H), 7.68 (d, J = 7.6 Hz, 1H), 7.77 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.28 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.4, 120.8, 126.7, 126.8, 127.1, 128.0, 129.3, 130.0, 134.6, 137.8, 147.5, 154.2, 162.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{12}N_2O$ 237.1022; found 237.1028.

2-Methyl-3-(p-tolyl)quinazolin-4(*3H*)-one (3dA)



CAS: 22316-59-2; White solid, mp 150-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.25 (s, 3H), 2.45 (s, 3H), 7.14 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.76 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.3, 24.4, 120.8, 126.5, 126.7, 127.1, 127.7, 130.6, 134.5, 135.1, 139.3, 147.5, 154.5, 162.4; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{16}H_{14}N_2O$ 251.1179; found 251.1185.

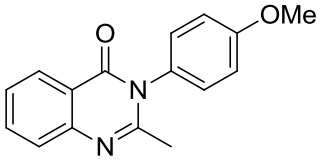
2-Methyl-3-(*o*-tolyl)quinazolin-4(*3H*)-one (3eA)



CAS: 72-44-6; White solid, mp 119-121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13 (s, 3H), 2.19 (s, 3H), 7.16

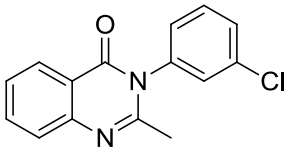
(d, J = 7.6 Hz, 1H), 7.35-7.42 (m, 3H), 7.48 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.78 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.29 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.4, 23.9, 120.7, 126.6, 126.8, 127.1, 127.6, 127.9, 129.6, 131.5, 134.6, 135.3, 136.8, 147.6, 154.3, 161.7; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{16}H_{14}N_2O$ 251.1179; found 251.1186.

3-(4-Methoxyphenyl)-2-methylquinazolin-4(*3H*)-one (3fA)



CAS: 53574-77-9; White solid, mp 169-171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (s, 3H), 3.88 (s, 3H), 7.05 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.76 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.26 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.4, 55.5, 115.2, 120.8, 126.6, 126.7, 127.1, 129.0, 130.2, 134.5, 147.5, 154.8, 159.9, 162.5; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{16}H_{14}N_2O_2$ 267.1128; found 267.1135.

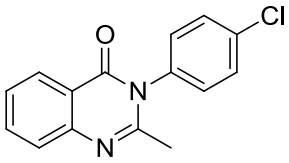
3-(3-Chlorophenyl)-2-methylquinazolin-4(*3H*)-one (3gA)



CAS: 340-94-3; White solid, mp 130-131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (s, 3H), 7.18-7.20 (m, 1H), 7.31 (s, 1H), 7.46-7.51 (m, 3H), 7.68 (d, J = 8.4 Hz, 1H), 7.79 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 8.26 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C

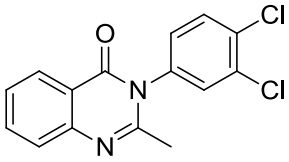
NMR ($CDCl_3$, 100 MHz): δ = 24.4, 120.6, 126.5, 126.9, 126.9, 127.1, 128.6, 129.7, 131.0, 134.8, 135.6, 138.8, 147.4, 153.5, 162.1; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{11}ClN_2O$ 271.0633; found 271.0641.

3-(4-Chlorophenyl)-2-methylquinazolin-4(*3H*)-one (3hA)



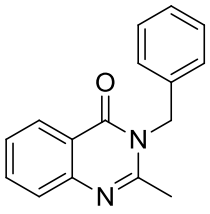
CAS: 1788-93-8; White solid, mp 157-158 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.25 (s, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.48 (t, d = 8.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.4, 120.6, 126.8, 127.1, 129.5, 130.3, 134.8, 135.4, 136.2, 147.4, 153.7, 162.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{11}ClN_2O$ 271.0633; found 271.0639.

3-(3,4-Dichlorophenyl)-2-methylquinazolin-4(*3H*)-one (3iA)



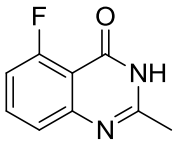
CAS: 4285-67-0; White solid, mp 164-165 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (s, 3H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.61-7.67 (m, 2H), 7.77 (t, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.3, 120.3, 126.9, 126.9, 126.9, 127.6, 130.2, 131.6, 133.9, 134.0, 134.9, 136.8, 147.2, 153.1, 161.9 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{10}Cl_2N_2O$ 305.0243; found 305.0252.

3-Benzyl-2-methylquinazolin-4(*3H*)-one (3jA)



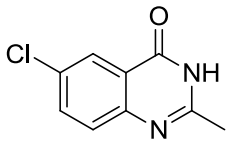
CAS: 4260-34-8; White solid, mp 123-124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.59 (s, 3H), 5.44 (s, 2H), 7.24 (d, J = 7.2 Hz, 2H), 7.31-7.38 (m, 3H), 7.51 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.79 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.35 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.4, 47.1, 120.3, 126.5, 126.5, 126.7, 127.1, 127.7, 128.9, 134.4, 135.8, 147.3, 154.6, 162.4; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{16}H_{14}N_2O$ 251.1179; found 251.1185.

5-Fluoro-2-methylquinazolin-4(*3H*)-one (3kA)



CAS: 143745-24-8; White solid, mp 252-253 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.56 (s, 3H), 7.10 (t, J = 9.2 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.67-7.72 (m, 1H), 11.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 110.2, 113.0, 123.0, 135.2, 151.3, 154.2, 160.1, 162.6; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_7FN_2O$ 179.0615; found 179.0621.

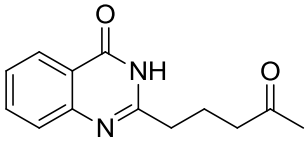
6-chloro-2-methylquinazolin-4(*3H*)-one (3lA)



CAS: 7142-09-8; White solid, mp 286-287 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (s, 3H), 7.59 (d, J = 8.8 Hz, 1H), 7.79 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 12.40

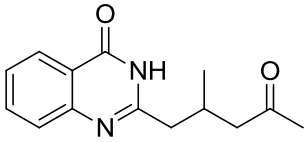
(s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.9, 122.3, 125.1, 129.3, 130.5, 134.8, 148.1, 155.4, 161.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_9H_7ClN_2O$ 195.0320; found 195.0325.

2-(4-Oxopentyl)quinazolin-4(*3H*)-one (5aA)



CAS: 86663-60-7; White solid, mp 145-146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.13-2.20 (m, 2H), 2.18 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 7.48 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.77 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 8.29 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 11.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.1, 30.0, 34.7, 42.3, 120.6, 126.3, 126.5, 127.2, 134.8, 149.2, 155.8, 163.8, 208.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{14}N_2O_2$ 231.1128; found 231.1134.

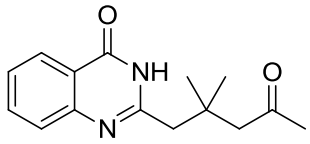
2-(2-Methyl-4-oxopentyl)quinazolin-4(*3H*)-one (5aB)



CAS: none; White solid, mp 154-157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (d, J = 6.0 Hz, 1H), 2.19 (s, 3H), 2.47-2.53 (m, 1H), 2.68-2.83 (m, 4H), 7.51 (t, J = 7.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.81 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 8.33 (dd, J_1 = 7.6 Hz, J_2 = 0.4 Hz, 1H), 11.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1, 28.6, 30.5, 42.4, 50.0, 120.7, 126.3, 126.5, 127.3, 134.8, 149.2, 155.3, 163.9, 208.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_2$

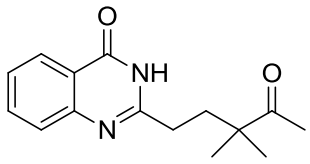
245.1285; found 245.1284.

2-(2,2-Dimethyl-4-oxopentyl)quinazolin-4(*3H*)-one (5aC)



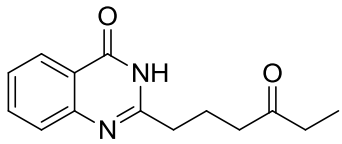
CAS: 86663-57-2; White solid, mp 159-160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 6H), 2.30 (s, 3H), 2.46 (s, 2H), 2.73 (s, 2H), 7.45(t, J = 7.2 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.74 (dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 10.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 29.0, 33.6, 35.5, 45.4, 51.5, 121.1, 126.4, 126.4, 127.2, 134.4, 149.0, 154.0, 162.1, 212.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{18}N_2O_2$ 259.1441; found 259.1447.

2-(3,3-Dimethyl-4-oxopentyl)quinazolin-4(*3H*)-one (5aD)



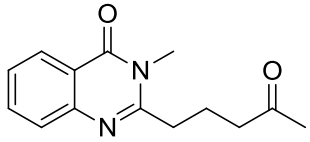
CAS: none; White solid, mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (s, 6H), 2.11-2.16 (m, 2H), 2.28 (s, 3H), 2.70-2.74 (m, 2H), 7.52 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.81 (dt, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.30 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 11.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.4, 25.2, 31.6, 36.8, 47.6, 120.7, 126.3, 126.6, 127.2, 134.8, 149.3, 156.3, 163.9, 213.5; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{15}H_{18}N_2O_2$ 259.1441; found 259.1440.

2-(4-Oxopentyl)quinazolin-4(*3H*)-one (5aE)



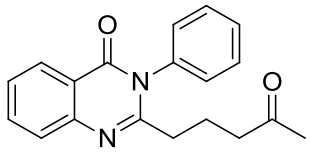
CAS: none; White solid, mp 149-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.04 (t, *J* = 7.2 Hz, 3H), 2.14-2.21 (m, 2H), 2.45 (q, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 7.47 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.77 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 8.28 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 11.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.7, 21.2, 34.8, 36.0, 41.0, 120.6, 126.3, 126.5, 127.2, 134.8, 149.2, 155.9, 163.8, 211.0; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_2$ 245.1285; found 245.1292.

3-methyl-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5bA)



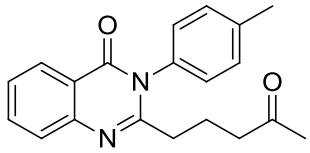
CAS: 1616629-16-3; Pale yellow oily liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.08-2.15 (m, 2H), 2.17 (s, 3H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 7.43 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.71 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.4, 30.2, 30.6, 34.6, 42.3, 120.3, 126.5, 126.8, 126.8, 134.1, 147.1, 156.4, 162.6, 208.4; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{14}H_{16}N_2O_2$ 245.1285; found 245.1292.

2-(4-Oxopentyl)-3-phenylquinazolin-4(*3H*)-one (5cA)



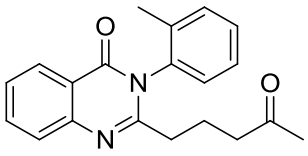
CAS: none; Pale yellow solid, mp 131-134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.96-2.02 (m, 2H), 2.07 (s, 3H), 2.43 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 7.25-7.28 (m, 3H), 7.45-7.58 (m, 4H), 7.69 (dd, J_1 = 8.0 Hz, J_2 = 0.4 Hz, 1H), 7.76 (dt, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H), 8.27 (q, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 29.9, 34.8, 42.5, 120.9, 126.7, 127.1, 128.3, 129.3, 130.0, 134.5, 137.2, 147.4, 156.0, 162.5, 208.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{18}N_2O_2$ 307.1441; found 307.1449.

2-(4-Oxopentyl)-3-(p-tolyl)quinazolin-4(*3H*)-one (5dA)



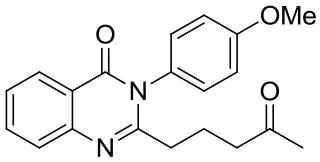
CAS: none; Pale yellow solid, mp 97-99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94-2.02 (m, 2H), 2.08 (s, 3H), 2.42-2.46 (m, 3H), 2.42 (s, 3H), 2.50 (t, J = 7.2 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.45 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.75 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.26 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 21.3, 29.9, 34.7, 42.6, 120.9, 127.0, 127.1, 128.0, 130.6, 134.5, 134.5, 139.4, 147.4, 156.2, 162.6, 208.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1598; found 321.1602.

2-(4-Oxopentyl)-3-(o-tolyl)quinazolin-4(*3H*)-one (5eA)



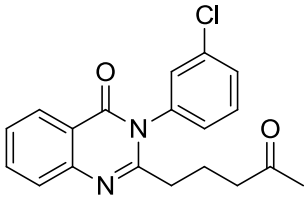
CAS: none; White solid, mp 113-115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.98-2.04 (m, 2H), 2.08 (s, 3H), 2.10 (s, 3H), 2.27-2.41 (m, 2H), 2.47-2.53 (m, 2H), 7.16 (d, J = 7.2 Hz, 1H), 7.34-7.41 (m, 3H), 7.47 (t, J = 7.6 Hz, 1H), 7.64-7.72 (m, 1H), 7.77 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.28 (q, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.5, 20.3, 30.0, 34.3, 42.6, 120.8, 126.7, 127.1, 127.6, 128.3, 129.6, 131.6, 134.5, 135.5, 136.2, 147.6, 156.0, 161.8, 208.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1598; found 321.1603.

3-(4-Methoxyphenyl)-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5fA)



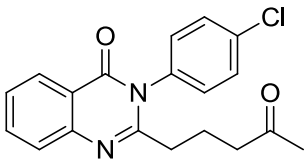
CAS: none; Pale yellow solid, mp 125-127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94-2.01 (m, 2H), 2.08 (s, 3H), 2.44 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 3.87 (s, 3H), 7.03-7.06 (m, 2H), 7.14-7.17 (m, 2H), 7.45 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.75 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.24 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 29.9, 34.8, 42.5, 55.6, 115.2, 120.8, 126.6, 127.0, 127.1, 129.3, 129.6, 134.5, 147.4, 156.5, 160.0, 162.7, 208.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_3$ 337.1547; found 337.1554.

3-(3-Chlorophenyl)-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5gA)



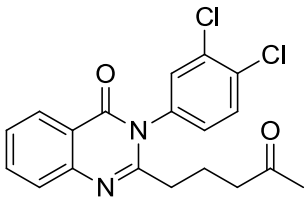
CAS: none; Pale yellow oily liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.98-2.01 (m, 2H), 2.08 (s, 3H), δ = 2.42 (t, J = 7.2 Hz, 2H), 2.51-2.56 (m, 2H), 7.18-7.21 (m, 1H), 7.30 (s, 1H), 7.45-7.50 (m, 3H), 7.68 (d, J = 7.6 Hz, 1H), 7.77 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 8.24 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.4, 29.9, 34.7, 42.4, 120.7, 126.8, 126.9, 127.1, 127.2, 128.8, 129.7, 130.9, 134.7, 135.6, 138.3, 147.3, 155.4, 162.3, 208.1; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{17}ClN_2O_2$ 341.1051; found 341.1060.

3-(4-Chlorophenyl)-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5hA)



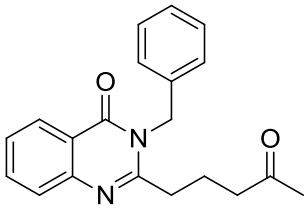
CAS: none; Pale yellow oily liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94-2.02 (m, 2H), 2.08 (s, 3H), 2.41 (t, J = 7.6 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 7.21-7.24 (m, 2H), 7.47 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.51-7.56 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.77 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.4, 29.9, 34.8, 42.4, 120.7, 122.1, 126.9, 127.1, 127.2, 129.2, 129.8, 130.3, 134.7, 135.4, 135.7, 147.3, 155.5, 162.4, 208.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{17}ClN_2O_2$ 341.1051; found 341.1058.

3-(3,4-Dichlorophenyl)-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5iA)



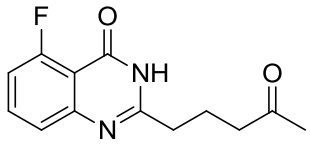
CAS: none; Pale yellow oily liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.97-2.04 (m, 2H), 2.09 (s, 3H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.54-2.57 (m, 2H), 7.15 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.42-7.50 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.77 (dt, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 8.25 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 30.0, 34.7, 42.3, 120.5, 127.0, 127.1, 127.2, 128.0, 130.6, 131.7, 134.0, 134.9, 136.4, 147.2, 155.0, 162.2, 208.1; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{19}H_{16}Cl_2N_2O_2$ 375.0662; found 375.0671.

3-Benzyl-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5jA)



CAS: 161629-15-2; Pale yellow solid, mp 122-124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.04-2.08 (m, 2H), 2.11 (s, 3H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 5.48 (s, 2H), 7.19 (d, *J* = 6.8 Hz, 2H), 7.27-7.35 (m, 3H), 7.47 (dt, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.75 (dt, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.32 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9, 30.0, 34.1, 42.3, 46.3, 120.4, 126.4, 126.6, 127.0, 127.2, 127.6, 128.9, 134.4, 136.3, 147.3, 156.6, 162.6, 208.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{20}H_{20}N_2O_2$ 321.1598; found 321.1605.

5-Fluoro-2-(4-oxopentyl)quinazolin-4(*3H*)-one (5kA)



CAS: none; White solid, mp 156-157 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.10-2.16 (m, 2H), 2.17 (s, 3H), 2.64 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 7.09 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.65-7.71 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.0, 30.0, 34.6, 42.5, 113.1, 123.2, 135.2, 151.3, 157.0, 160.0, 161.3, 162.7, 208.3; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{13}FN_2O_2$ 249.1034; found 249.1039.

References

(1) For selected recent reviews, see: (a) Meijere, A. de *Chem. Rev.* **2003**, *103*, 931-932. (b) Boom, M. E. and Milstein, D. *Chem. Rev.* **2003**, *103*, 1759-1792. (c) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610-618. (d) Rubin, M; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3179. (e) Park, Y. J.; Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222-234. (f) Tobisu, M. and Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300-307. (g) Horino, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2144-2146. (h) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120. (i) Najera, C. and Sansano, J. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2452-2456. (j) Bonesi, S. M. and Fagnoni, M. *Chem. Eur. J.* **2010**, *16*, 13572-13589. (k) Rybtchinski, B. and Milstein, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 870-883. (l) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245-269.

(2) (a) Zhao, J.; Zhao, Y.; Fu, H. *Org. Lett.* **2012**, *14*, 2710-2713. (b) Liu, W. P.; Liu, J.; Ogawa, D.; Nishihara, Y.; Guo, X.; Li, Z. *Org. Lett.* **2011**, *13*, 6272-6275. (c) Biswas, A.; Sarkar, S. De; Fröhlich, R.; Studer, A. *Org. Lett.* **2011**, *13*, 4966-4969. (d) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080-4083. (e) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979-981. (f) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M.; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 4026-4029. (g) Liu, Y. and Sun, J.-W. *J. Org.*

Chem. **2012**, *77*, 1191. (h) Meng, L.-G.; Hu, B.; Wu, Q.-P.; Liang, M.; Xue, S. *Chem.*, *Commun.* **2009**, *0*, 6089-6091.

(3) For selected examples, see: (a) He, C.; Guo, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273-8275. (b) Kawata, A.; Takata, K.; Kuninobu, Y.; Takai, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 7793-7795. (c) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257-15262. (d) Sun, X.; Wang, M.; Li, P.; Zhang, X.; Wang, L. *Green Chem.* **2013**, *15*, 3289-3294. (e) Wang, S.; Yu, Y.; Chen, X.; Zhu, H.; Du, P.; Liu, G.; Lou, L.; Li, H.; Wang, W. *Tetrahedron. Lett.* **2015**, *56*, 3093-3096. (f) Zhang, X.B.; Wang, M.; Zhang, Y.; Wang, L. *RSC Adv.* **2013**, *3*, 1311-1316. (g) Zhang, J.; Shao, Y.; Wang, Y.; Li, H.; Xu, D.; Wan, X. *Org. Biomol. Chem.* **2015**, *13*, 3982-3987. (h) Cai, S.; Wang, F.; Xi, C. *J. Org. Chem.* **2012**, *77*, 2331-2336. (i) Fan, X.; He, Y.; Cui, L.; Guo, S.; Wang, J.; Zhang, X. *Eur. J. Org. Chem.* **2012**, 673-677. (j) Kavala, V.; Wang, C. C.; Barange, D. K.; Kuo, C. W.; Lei, P. M.; Yao, C. F. *J. Org. Chem.* **2012**, *77*, 5022-5029. (k) Sun, X.; Li, X.; Zhang, X.; Wang, L. *Org. Lett.* **2014**, *16*, 2126-2129. (l) Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Org. Lett.* **2014**, *16*, 764-767.

(4) (a) Wattanapiromsakul, C.; Forster, P. I.; Waterman, P. G. *Phytochemistry* **2003**, *64*, 609-615. (b) Abdel Gawad, N. M.; Georgey, H. H.; Youssef, R. M.; El-Sayed, N. A. *Eur. J. Med. Chem.* **2010**, *45*, 6058-6067.

(5) For selected recent reviews, see: (a) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659-677. (b) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153-10202. (c) He, L.; Li, H.; Chen, J.; Wu, X.-F. *RSC Adv*. **2014**, *4*, 12065-12077.

(6) For selected recent examples, see: (a) Wang, G. W.; Miao, C. B.; Kang, H. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 1426-1430. (b) Mulakayala, N.; Kandagatla, B.; Ismail, R.; Rapolu, K.; Rao, P.; Mulakayala, C.; Kumar, C. S.; Iqbal, J. and Orugani, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5063-5066. (c) Zhan, D.; Li, T.; Zhang, X.; Dai, C.; Wei, H.; Zhang, Y.; Zeng, Q. *Synth. Commun*. **2013**, *43*, 2493-2500. (d) Sharif, M.; Opalach, J.; Langer, P.; Beller, M.; Wu, X.-F. *RSC Adv.* **2014**, *4*, 8-17. (e) Zhou, J.; Fang, J. *J. Org. Chem.* **2011**, *76*, 7730-7736. (f) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. *J. Org. Biomol. Chem.* **2012**, *10*, 240-243. (g) Hikawa, H.; Ino, Y.; Suzuki, H.; Yokoyama, Y. *J. Org. Chem.* **2012**, *77*, 7046-7051. (h) Ge, W.; Zhu, X.; Wei, Y. *RSC Adv.* **2013,** *3*, 10817-10822. (i) Zhu, Y.-P.; Fei, Z.; Liu, M.; Jia, F.; Wu, A. *Org. Lett.* **2013**, *15*, 378-381. (j) Li, Q.; Huang, Y.; Chen, T.; Zhou, Y.; Xu, Q.; Yin, S.-F.; Han, L.-B. *Org. Lett.* **2014**, *16*, 3672-3675. (k) Zhao, D.; Wang, T.; Li, J.-X. *Chem. Commun.* **2014**, *50*, 6471-6474. (l) Kumar, D.; Jadhavar, P. S.; Nautiyal, M.; Sharma, H.; Meena, P. K.; Adane, L.; Pancholia, S.; Chakraborti, A. K. *RSC.Adv.* **2015**, *5*, 30819-30825. (m) Lu, L.; Zhang, M.-M.; Jiang, H.; Wang, X.-S. *Tetrahedron*

Lett. **2013**, *54*, 757-760. (n) Yang, X.; Cheng, G.; Shen, J.; Kuai, C.; Cui, X. *Org. Chem. Front.* **2015**, *2*, 366-368.

(7) Carbonylative construction of quinazolinones, see: (a) Wu, X.-F.; He, L.; Neumann, H. and Beller, M. *Chem.-Eur. J.* **2013**, *19*, 12635-12638. (b) Li, H.; He, L.; Neumann, H.; Beller, M. and Wu, X. F. *Green Chem.* **2014**, *16*, 1336-1343. (c) He, L.; Sharif, M.; Neumann, H.; Beller, M. and Wu, X. F. *Green Chem.* **2014**, *16*, 3763-3767. (d) Shen, C.; Man, N. Y. T.; Stewart, S. and Wu, X.-F. *Org. Biomol. Chem.* **2015**, *13*, 4422-4425. (e) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Langer, P.; Beller, M. and Wu, X.-F. *Angew. Chem., Int. Ed*. **2014**, *53*, 7579-7583. (f) He, L.; Li, H.; Neumann, H.; Beller, M. and Wu, X.-F. *Angew. Chem., Int. Ed.*, **2014**, *53*, 1420-1424. (g) Li, H.; Li, W.; Spannenberg, A.; Baumann, W.; Neumann, H.; Beller, M. and Wu, X.-F. *Chem.–Eur. J.* **2014**, *20*, 8541-8544. (h) Wu, X.-F.; Oschatz, S.; Block, A.; Spannenberg A. and Langer, P. *Org. Biomol. Chem.* **2014**, *12*, 1865-1870. (i) Chen, J.; Neumann, H.; Beller, M. and Wu, X.-F. *Org. Biomol. Chem.* **2014**, *12*, 5835-5838. (j) Wu, X.-F.; Oschatz, S.; Sharif, M.; Beller, M. and Langer, P. *Tetrahedron* **2014**, *70*, 23-29; (k) Mori, M.; Kobayashi, H.; Kimura, M. and Ban, Y. *Heterocycles* **1985**, *23*, 2803-2806.

(8) (a) Pereira, C. S. M.; Silva, V. M. T. M. and Rodrigues, A. E. *Green Chem*. **2011**, *13*, 2658-2071. (b) Sheldon, R. A. *Green Chem.* **2005**, *7*,

267-278. (c) Bennett, J. S.; Charles, K. L.; Miner, M. R.; Heuberger, C. F.; Spina, E. J.; Bartels, M. F. and Foreman, T. *Green Chem.* **2009**, *11*, 166-168. (d) Dandia, A.; Jain, A. K. and Laxkar, A. K. *Tetrahedron Lett.* **2013**, *54*, 3929-3932. (e) Ghosh, P. P.; Paul, S. and Das, A. R. *Tetrahedron Lett.* **2013**, *54*, 138-142.

(9) (a) Zhou, H.-F.; Li, Z.; Wang, Z.; Wang, T.; Xu, L. J.; He, Y.; Fan, Q.-H.; Pan, J.; Gu, L. and Chan, A. S. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 8464-8467. (b) Wang, Z.-J.; Zhou, H.-F.; Wang, T.-L.; He, Y.-M.; Fan, Q.-H. *Green Chem.* **2009**, *11*, 767-769. (c) Ding, Z.-Y.; Wang, T.; He, Y.-M.; Chen, F.; Zhou, H.-F.; Fan, Q.-H.; Guo, Q. and Chan, A. S. C. *Adv. Synth. Catal.* **2013**, *355*, 3727-3735. (d) Zhou, H.-F.; Fan, Q.-H.; Tang, W.-J.; Xu, L.-J.; He, Y.-M.; Deng, G.-J.; Zhao, L.-W.; Gu, L.-Q. and Chan, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 2172-2182. (e) Zhou, H.-F.; Fan, Q.-H.; Huang, Y.-Y.; Wu, L.; He, Y.-M.; Tang, W.-J.; Gu, L. Q. and Chan, A. S. C. *J. Mol. Catal. A: Chem.* **2007**, *275*, 47-53. (f) Pi, D.; Jiang, K.; Zhou, H.; Sui, Y.; Uozumi, Y. and Zou, K. *RSC. Adv.* **2014**, *4*, 57875-57844. (g) Jiang, K.; Pi, D.; Zhou, H.; Liu, S. and Zou, K. *Tetrahedron*, **2014**, *70*, 3056-3060. (h) Liu, S.; Jiang, K.; Pi, D.; Zhou, H.; Uozumi, Y. and Zou, K. *Chin. J. Org. Chem.* **2014**, *34*, 1369-1375.

(10) Roy, S.; Davydova, M. P.; Pal, R.; Gilmore, K.; Tolstikov, G. A.; Vasilevsky, S. F. and Alabugin, I. V. *J. Org. Chem.* **2011**, *76*, 7482-7490.

Chapter 2

Cu-Catalyzed Reduction of Azaarenes and Nitroaromatics with Diboronic Acid as Reductant

Danwei Pi, Haifeng Zhou, Yanmei Zhou, Qixing Liu, Renke He,

Guanshuo Shen, Yasuhiro Uozumi

Tetrahedron **2018***, 74,* 2121-2129

Introduction

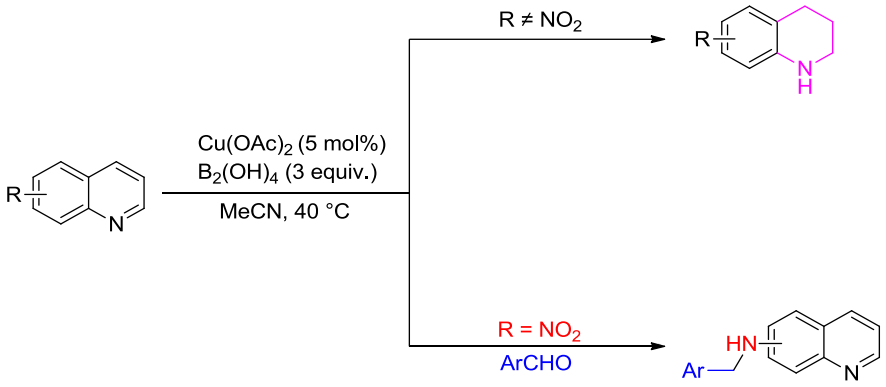
1,2,3,4-Tetrahydroquinolines and related *N*-heterocycles are important moieties in fine chemicals, pharmaceuticals, agrochemicals, dyes, fragrances, and hydrogen-storage materials.[1] The reduction of readily available quinolines using stoichiometric metal hydrides or reactive metals as classic reductants is a straightforward method for preparing such compounds.[2] In recent decades, various catalytic hydrogenations and transfer hydrogenations under homogeneous or heterogeneous conditions have also been developed.[3-5] Aromatic amines are important intermediates in the synthesis of many nitrogen-containing pharmaceuticals, agrochemicals, bioactive compounds, dyes, and polymers.[6] The reduction of nitro compounds is one of the common and simple routes to prepare amines. Since the discovery of Béchamp reduction, a classic process that generates much metallic waste,[7] numerous efforts have been focused on exploring new and efficient catalysts and reductants, as well as on developing simple and green procedures.[8] However, the reported methods have several drawbacks, such as a lack of chemoselectivity, the need to handle flammable hydrogen gas, the use of relatively expensive metal catalysts, harsh conditions. Given these facts, it is highly desirable to develop novel, efficient, and practical methods for preparing 1,2,3,4-tetrahydroquinolines and related compounds.

Diboron reagents were initially used as borylation agents for preparing

organoboron compounds.[9] In 2016, the diboronic acid [$B_2(OH)_4$]-mediated, Pd-catalyzed, transfer hydrogenation of unsaturated carbon-carbon bonds with water as a hydrogen donor was realized.[10] Subsequently, the Cu-dipinacolborane (B_2pin_2)-catalyzed chemoselective reduction of carbon-carbon double or triple bonds to C-C single bonds in *α,β*-unsaturated ketones was developed.[11] More recently, the reduction of aromatic nitro compounds to aromatic amines mediated by diboron reagents has also been reported.[12] Subsequently, Xuan and Song developed a Pd/B_2pin_2-catalyzed reduction of *N*-heteroaromatics with water as a hydrogen donor.[13] Moreover, a $B_2(OH)_4$-promoted reduction of *N*-heteroaromatics with water as both solvent and hydrogen donor under metal-free conditions has also achieved.[14] In addition, several reductive tandem reactions with diboron reagents have also been reported.[15] Lately, this author's group reported a palladium-catalyzed chemoselective reduction and reductive amination of nitroarenes with water as a hydrogen source mediated by diboronic acid.[12b] A one-pot synthesis of tetrahydroquinoxalines from readily available 2-amino(nitro)anilines and 1,2-dicarbonyl compounds mediated by diboronic acid with water as both a solvent and a hydrogen donor has also been reported by us.[14b] However, the noble metal palladium and excess amount of diboronic acid (8 equiv) were necessary in the above two cases. To continue this author group's interest in using diboron reagents as a mediator for transfer hydrogen, this author developed a Cu-catalyzed

reduction of azaarenes and nitro aromatic compounds with $B_2(OH)_4$ as a reductant under mild conditions. Most interestingly, the nitroazaarenes can be reduced exclusively to the corresponding amine, with the azaarene remaining intact (**Scheme 1**).

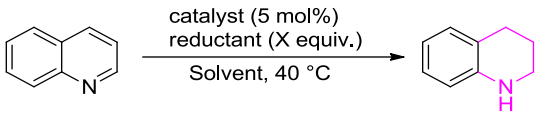
Scheme 1. Cu-catalyzed chemoselective reduction of azaarenes and nitro groups



Results and Discussion

Initially, this author selected the reduction of quinoline (**1a**) as a model reaction to optimize the reaction parameters. First, the reaction was performed with 3.0 equivalents of $B_2(OH)_4$ as reductant in acetonitrile at 40 °C for 24 h, but no reaction was observed (**Table 1**, entry 1).

Table 1. Optimization of the reaction conditions[a]



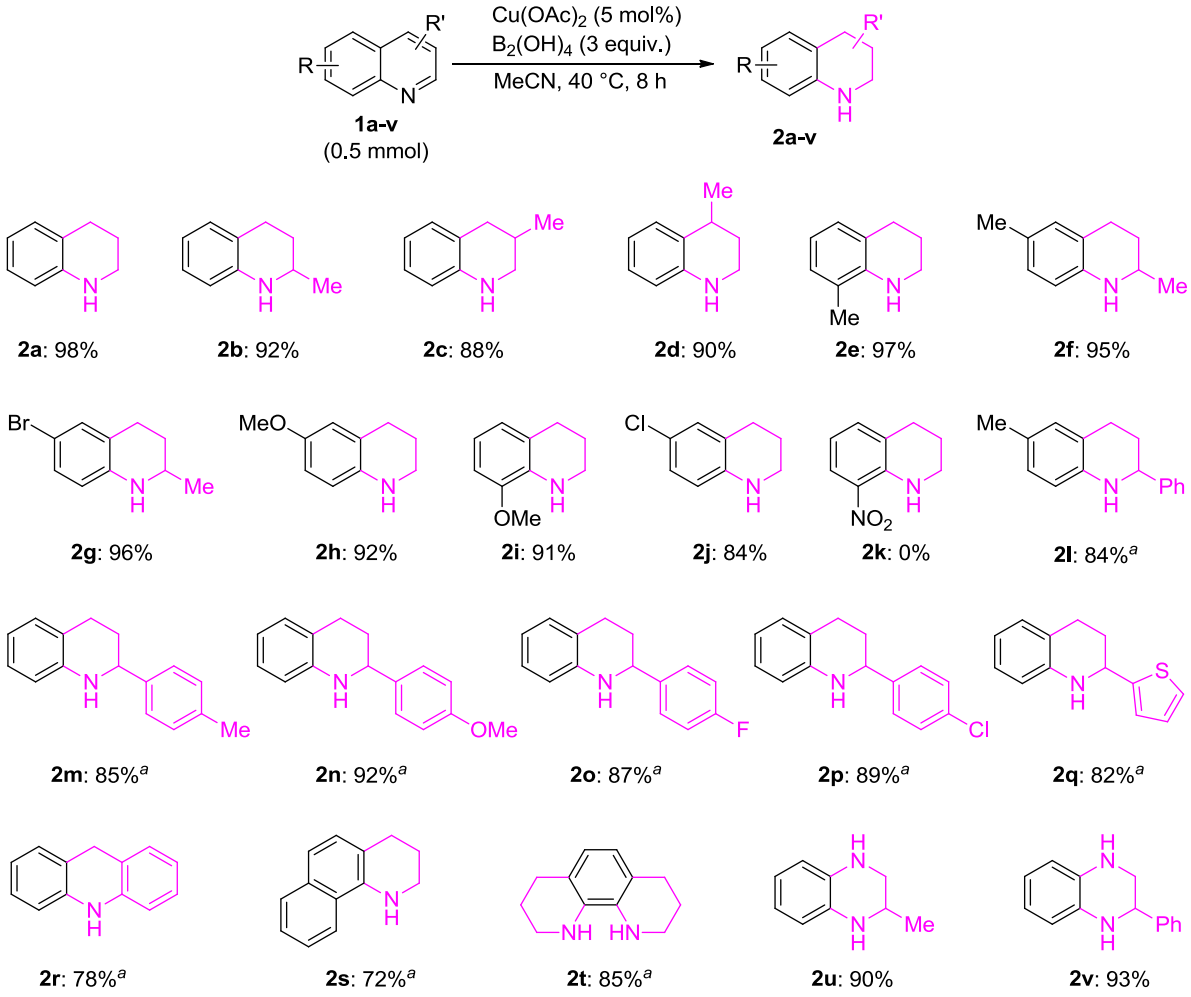
entry	catalyst	reductant (equiv.)	solvent	time (h)	yield (%)[b]
1	---	$B_2(OH)_4$ (3)	MeCN	24	0
2	Pd/C	$B_2(OH)_4$ (3)	MeCN	24	27
3	$Pd(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	32
4	$Fe(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	0
5	$Zn(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	0
6	AgOAc	$B_2(OH)_4$ (3)	MeCN	24	0
7	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	98
8	$Cu(OTf)_2$	$B_2(OH)_4$ (3)	MeCN	24	71
9	CuF_2	$B_2(OH)_4$ (3)	MeCN	24	9
10	$CuCl_2$	$B_2(OH)_4$ (3)	MeCN	24	33
11	$CuBr_2$	$B_2(OH)_4$ (3)	MeCN	24	29
12	CuCl	$B_2(OH)_4$ (3)	MeCN	24	75
13	CuI	$B_2(OH)_4$ (3)	MeCN	24	67
14[c]	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	24	61
15	$Cu(OAc)_2$	$B_2(OH)_4$ (2.5)	MeCN	24	92
16	$Cu(OAc)_2$	$NaBH_4$ (3)	MeCN	24	0
17	$Cu(OAc)_2$	$B(OH)_3$ (3)	MeCN	24	0
18	$Cu(OAc)_2$	$B_2(Pin)_2$ (3)	MeCN	24	0
19	$Cu(OAc)_2$	$B_2(cat)_2$ (3)	MeCN	24	0
20	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	8	98
21	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeCN	6	78
22	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	toluene	8	13
23	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	EtOAc	8	12
24	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	THF	8	45
25	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	CH_2Cl_2	8	7
26	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	DMF	8	60
27	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	MeOH	8	82
28	$Cu(OAc)_2$	$B_2(OH)_4$ (3)	H_2O	8	23

[a]Reaction conditions: quinoline (**1a**; 0.5 mmol), catalyst (5 mol %), reductant (3.0 equiv), solvent (2 mL), 40 °C. [b]Determined by GC analysis with an internal standard (mesitylene). [c]2 mol % $Cu(OAc)_2$ was used.

And then this author tested various metal catalysts [Pd/C, $Pd(OAc)_2$, $Fe(OAc)_2$, $Zn(OAc)_2$, AgOAc, and $Cu(OAc)_2$] (entries 2-7), and this author found that $Cu(OAc)_2$ gave 1,2,3,4-tetrahydroquinoline (**2a**) in 98% yield (entry 7). Other copper salts [$Cu(OTf)_2$, CuF_2, $CuCl_2$, $CuBr_2$, CuCl, and CuI] were also screened, but relatively lower yields were obtained (entries 8-13). Next, this author examined the effects of the catalyst loading and the amount of reductant. The yield of **2a** decreased to 61% when 2 mol % of $Cu(OAc)_2$ was used (entry 14). When the amount of $B_2(OH)_4$ was reduced to 2.5 equivalents, a 92% yield of **2a** was obtained (entry 15). Other boron reagents [$NaBH_4$, $B(OH)_3$, B_2pin_2, and $B_2(cat)_2$] were examined, but no reaction took place (entries 16-19). The yield of **2a** remained unchanged when the reaction time was reduced to 8 h (entry 20). Other aprotic solvents [toluene, EtOAc, tetrahydrofuran (THF), CH_2Cl_2, and *N*, *N*-dimethylformamide (DMF)] were screened, but moderate yields were obtained in each case (entries 22-26). The reaction also proceeded smoothly in methanol, giving an 82% yield (entry 27), whereas a lower yield was obtained in water (entry 28). Finally, 5 mol % $Cu(OAc)_2$, 3 equivalents of $B_2(OH)_4$, 2 mL of MeCN, 40 °C, and 8 h were selected as the optimal reaction conditions.

With the optimal reaction conditions in hand, this author investigated the scope of azaarene (**Scheme 2**).

Scheme 2. Scope of azaarenes

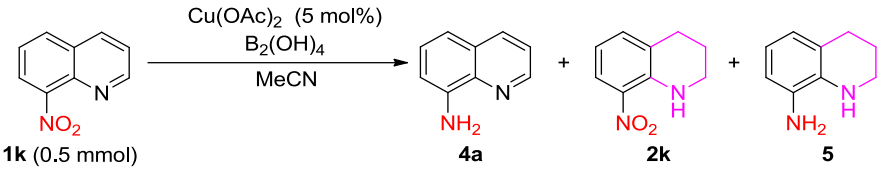


[a]80 °C, 12 h.

The reduction of electron-rich methyl-substituted quinolines **1b-g** and methoxy-substituted quinolines **1h-i** proceeded smoothly to give the corresponding products **2b-i** in 88-97% yield, whereas electron-deficient quinolines gave relatively lower yields. For example, 6-chloro-1,2,3,4-

tetrahydroquinoline (**2j**) was isolated in 84% yield. None of the desired product was obtained from 8-nitroquinoline (**1k**). The 2-arylquinolines **1l-p** also underwent this transformation, affording the corresponding products **2l-p** in 84-92% yield at 80 °C for 12 h. 2-(2-thienyl)quinoline (**1q**) was converted into the corresponding tetrahydroquinoline **2q** in 82% yield. Polycyclic heteroaromatics acridine (**1r**) and benzo[*h*]quinoline (**1s**) similarly gave the corresponding products **2r** and **2s** in 78% and 72% yield, respectively. In addition, both the pyridine rings of 1,10-phenanthroline (**1t**) were reduced to give 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (**2t**) in 85% yield. However, no reaction occurred when pyridine was used as a substrate. Furthermore, the quinoxalines **1u** and **1v** also underwent the reduction to give the corresponding tetrahydroquinoxalines **2u** and **2v** in 90% and 93% yield, respectively.

Table 2. Chemoselective reduction of 8-nitroquinoline[a]

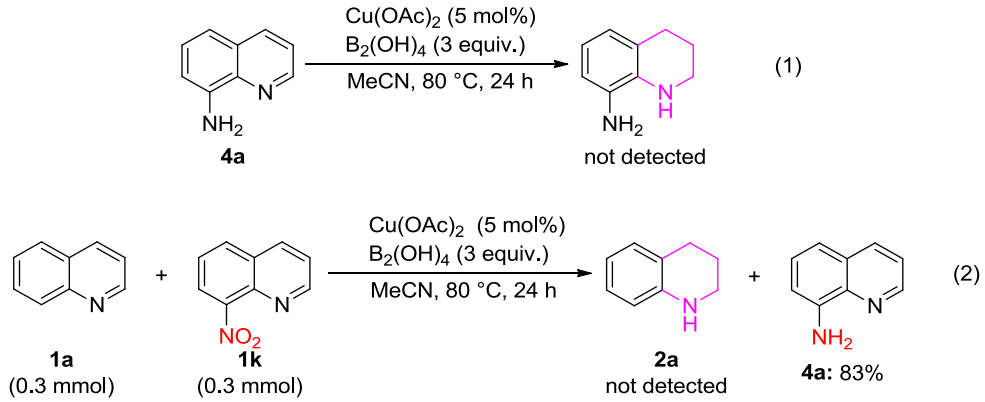


entry	$B_2(OH)_4$ (equiv.)	Temp (°C)	4a (%)	2k (%)	5 (%)
1	3	40	60	0	0
2	3	60	73	0	0
3	3	80	87	0	0
4	5	80	89	0	0
5	10	80	90	0	0
6[b]	5	80	0	0	78

[a]Reaction conditions: 8-nitroquinoline (**1k**; 0.5 mmol), $Cu(OAc)_2$ (5 mol %), $B_2(OH)_4$, MeCN (2 mL), 24 h. [b]In the absence of $Cu(OAc)_2$, water was used as solvent instead of MeCN.

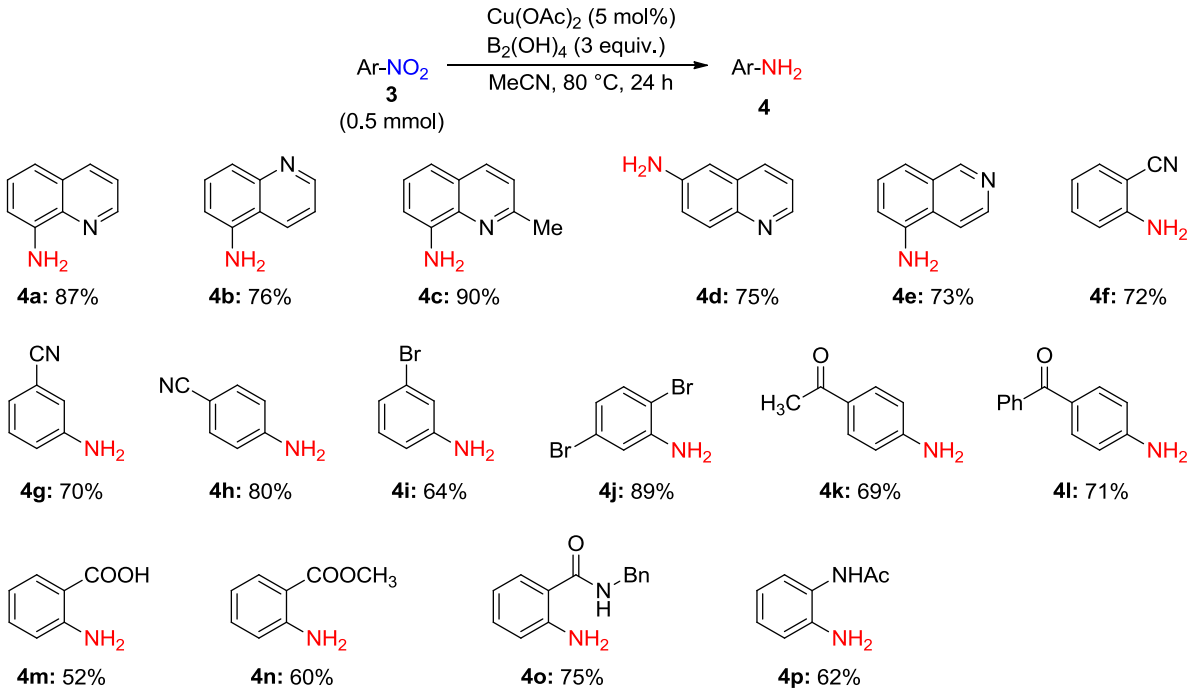
Surprisingly, when this author conducted the reduction of 8-nitroquinoline (**1k**) in the presence of 5 mol % of $Cu(OAc)_2$ with three equivalents of $B_2(OH)_4$ as reductant in MeCN at 40 °C for 24 h, the product **2k** and **5** were not detected. Instead, the nitro group of **1k** was reduced exclusively to give quinolin-8-amine (**4a**) in 60% yield (**Table 2**, entry 1). The product **2k** and **5** were still not observed even if raising the temperature and increasing the amount of $B_2(OH)_4$ (entries 2-5). Very interestingly, **1k** could be reduced to compound **5** in 78% yield in the absence of $Cu(OAc)_2$, without detecting selective hydrogenated products **4a** and **2k** (entry 6).

Scheme 3. Control experiments



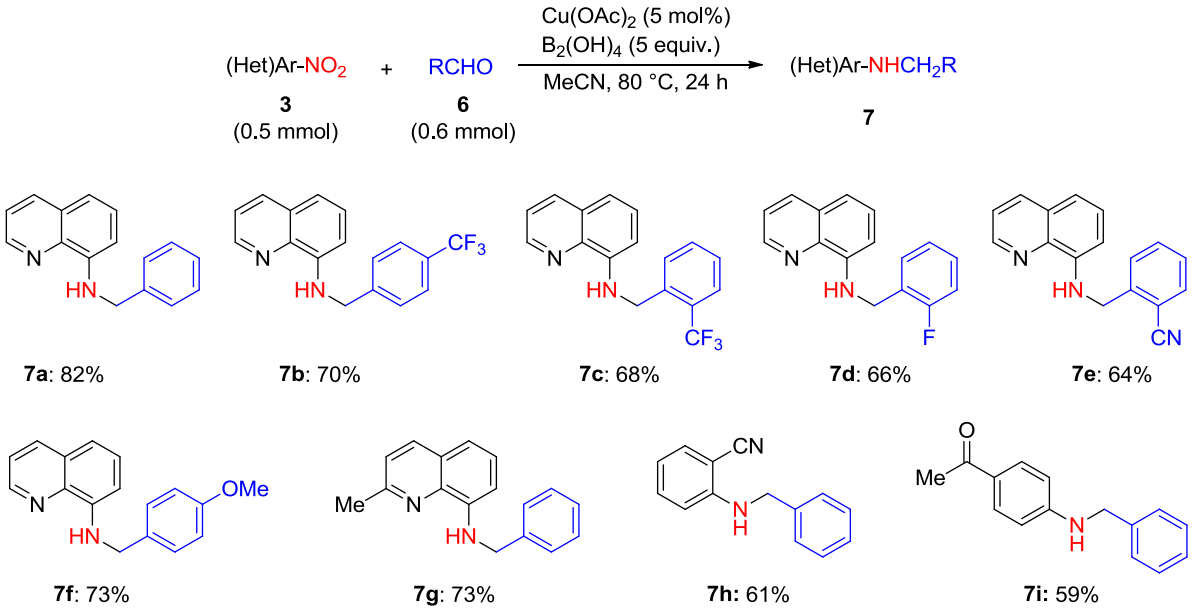
As shown in **Scheme 3**, several control experiments were conducted. When **4a** was used as a substrate under the optimized reaction conditions, no reaction occurred and the starting material remained intact. Moreover, when an equimolar mixture of quinoline (**1a**) and 8-nitroquinoline (**1k**) was subjected to the reaction, product **4a** was obtained in 83% yield, whereas 1,2,3,4-tetrahydroquinoline (**2a**) was not detected. This showed that the nitro group was reduced preferentially to the quinoline, and that nitro or amino compounds might poison Cu-catalyzed quinoline reduction.

Scheme 4. Scope of nitroaromatics



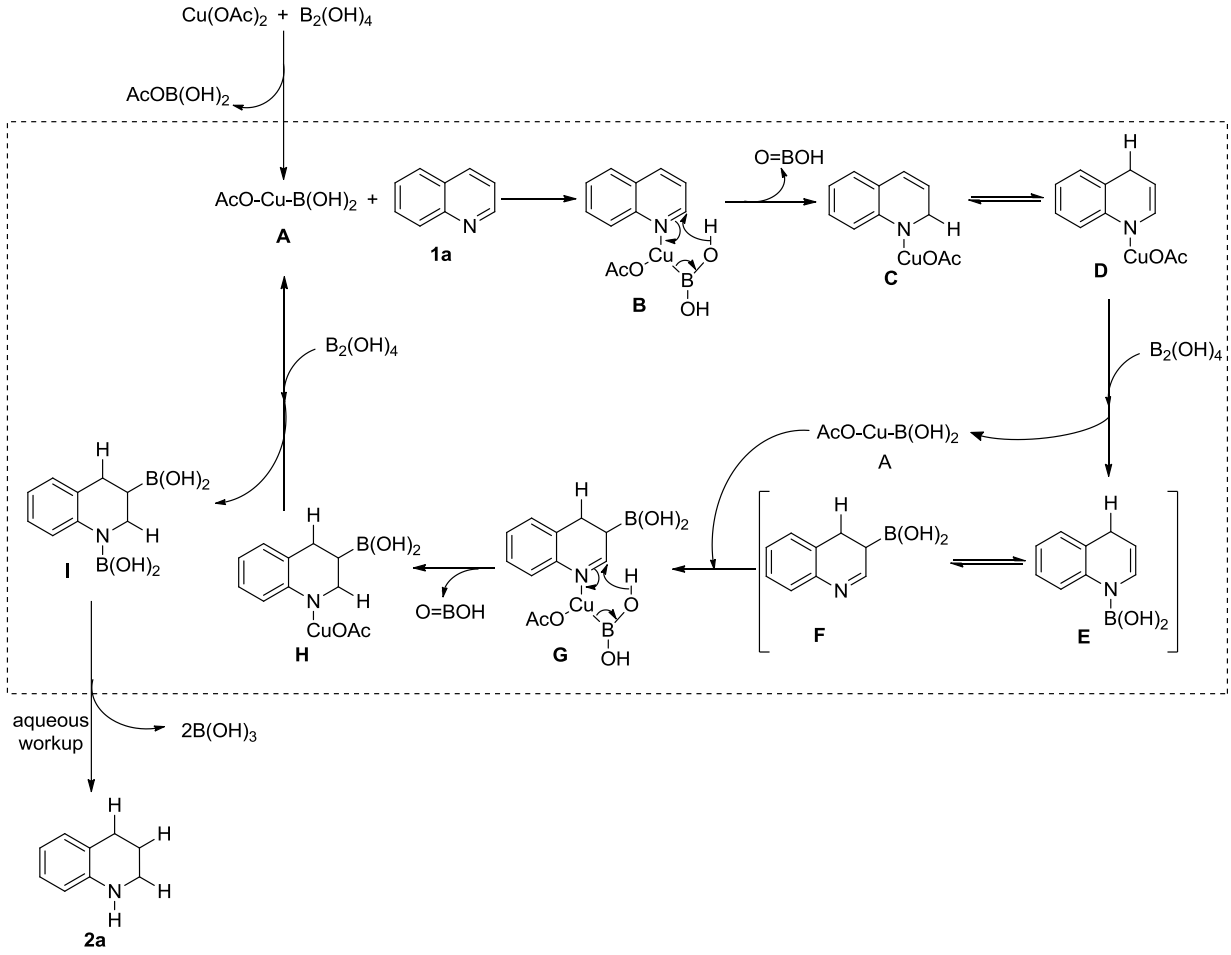
To further demonstrate the chemoselective reduction of nitro groups in the presence of *N*-heteroaromatics, this author examined the reduction of the nitroquinolines **3b-d** and 5-nitroisoquinoline (**3e**) (**Scheme 4**). The nitro groups were reduced exclusively to give corresponding amines **4b-e** in 73-90% yield. This author then evaluated other nitroarenes. The nitrobenzenes **3f-h** bearing a reducible cyano group at various positions were selectively reduced to the corresponding amines **4f-h** in 70-80% yield with the cyano group intact. The bromo(nitro)benzenes **3i** and **3j** were similarly reduced to afford amines **4i** and **4j**, respectively, without debromination. Furthermore, the nitrobenzenes **3k-p** containing carbonyl, carboxy, ester, or amide groups were converted into the corresponding amines **4k-p** in 52-75% yield.

Scheme 5. Scope of nitroaromatics



Inspired by a reported preparation of *N*-alkylanilines via one-pot reduction of the corresponding nitrobenzenes followed by reductive amination in the presence of $Pd/B_{10}H_{14}$[16] and this author group's previous work,[12b,14b] this author attempted the reductive amination of aldehydes with nitroarenes in the presence of the $Cu(OAc)_2/B_2(OH)_4$ system (**Scheme 5**). When 8-nitroquinoline was treated with various aromatic aldehydes **6a-f**, the corresponding secondary amines **7a-f** were obtained in 64-82% yield. 2-Methyl-8-nitroquinoline, 2-nitrobenzonitrile, and 4-nitroacetophenone were also subjected to this reductive amination with benzaldehyde (**6a**), giving the desired products **7g-i** in 59-73% yield.

Scheme 6. A proposed reaction pathway for the reduction of quinoline



In relation to the mechanism of the reduction of quinolines, this author proposes a plausible reaction pathway shown in **Scheme 6**.[13,14] Initially, transmetalation between $Cu(OAc)_2$ and $B_2(OH)_4$ forms the active catalytic species **A** in situ. Quinoline (**1a**) coordinates to **A** to give complex **B**, which eliminates metaboric acid (O=BOH) to afford intermediate **C**. This isomerizes to intermediate **D**, which, with the aid of $B_2(OH)_4$, is converted into enamine **E** with regeneration of the active catalytic species **A**. The imine **F** is formed by isomerization of enamine **E**. The C=N bond of imine

F is reduced by a similar catalytic cycle to give intermediate **I** with regeneration of the active catalytic species **A**. Finally, the tetrahydroquinoline (**2a**) is released through aqueous workup.

Conclusion

This author has developed a novel, ligand-free, copper-catalyzed, chemoselective reduction of azaarenes with diboronic acid as reductant in an aprotic solvent under mild conditions. It is interesting to note that the nitro group of nitroazaarenes was reduced exclusively to afford various amines. In addition, the reductive amination of aldehydes with nitroarenes to give secondary amines in a one-pot process was also achieved.

Experimental Section

General Methods. All reagents and solvents were purchased from commercial suppliers and used without further purification. Gas chromatography was performed with a FULI GC9790II gas chromatograph equipped with a 30 m capillary column. All products were isolated by column chromatography on silica gel (300-400 mesh) with petroleum ether (PE; bp 60-90 °C) and EtOAc as eluents. All compounds were characterized by means of ^{1}H NMR (400 MHz), and ^{13}C NMR (100 MHz) spectroscopy with a Bruker 400 MHz instrument. Melting points were determined on an X-4 apparatus.

Typical procedure for the synthesis of 1,2,3,4-tetrahydroquinoline (2a)

A 20mL Schlenk tube was charged with quinoline (1a; 65 mg, 0.5 mmol), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), $B_2(OH)_4$ (135 mg, 1.5 mmol), and MeCN (2.0 mL). The mixture was stirred at 40 °C for 8 h until the reaction was completed (TLC), then cooled to room temperature and concentrated under reduced pressure. Water (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography with petroleum ether/ethyl acetate (8:1) as an eluent to give a brown liquid (**2a**: 65 mg, 98%yield).

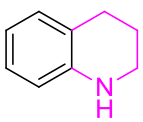
Typical procedure for the synthesis of 8-Aminoquinoline (4a)

A 20mL Schlenk tube was charged with 8-nitroquinoline (**1k**; 87 mg, 0.5 mmol), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), $B_2(OH)_4$ (135 mg, 1.5 mmol), and MeCN (2.0 mL). The mixture was stirred at 80 °C for 24 h, then cooled to room temperature and concentrated under reduced pressure. Similar workup to **2a** gave a brown solid (**4a**: 63 mg, 87% yield).

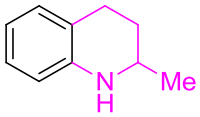
Typical procedure for the synthesis of *N*-Benzylquinolin-8-amine (7a)

A 20mL Schlenk tube was charged with 8-nitroquinoline (**1k**; 87 mg, 0.5 mmol), benzaldehyde (**6a**; 64 mg, 0.6 mmol), $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), $B_2(OH)_4$ (225 mg, 2.5 mmol), and MeCN (3.0 mL). The mixturewas stirred at 80 °C for 24 h until the reaction was completed (TLC), then cooled to room temperature and concentrated under reduced pressure. Similar workup to **2a** gave a yellow solid (**7a**: 96 mg, 82% yield).

1,2,3,4-Tetrahydroquinoline (2a).[4i] Brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94-1.99 (m, 2H, CH_2), 2.79 (t, J = 6.4 Hz, 2H, CH_2), 3.32 (t, J = 5.6 Hz, 2H, CH_2), 6.49 (d, J = 7.6 Hz, 1H, Ar-H), 6.61-6.65 (m, 1H, Ar-H), 6.97-7.01(m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.22, 27.02, 42.03, 114.25, 116.98, 121.50, 126.78, 129.58, 144.83 ppm.

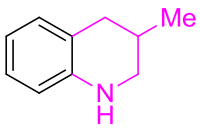


2-Methyl-1,2,3,4-tetrahydroquinoline (2b).[4i] Colorless liquid; ^{1}H NMR



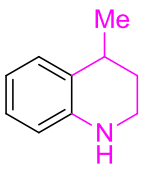
(400 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.0 Hz, 3H, CH_3), 1.65-1.72 (m, 1H), 1.97-2.03 (m, 1H), 2.77-2.95 (m, 2H, CH_2), 3.44-3.49 (m, 1H, CH), 3.67 (s, br, 1H), 6.54 (d, J = 8.0 Hz, 1H, Ar-H), 6.68-6.72 (m, 1H, Ar-H), 7.03-7.07 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.75, 26.74, 30.25, 47.26, 114.15, 117.08, 121.20, 126.82, 129.40, 144.91 ppm.

3-Methyl-1,2,3,4-tetrahydroquinoline (2c).[4i] Brown liquid; ^{1}H NMR



(400 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.4 Hz, 3H, CH_3), 2.11-2.15 (m, 1H), 2.51 (dd, J_1 =16.0 Hz, J_2 =10.4 Hz, 1H), 2.83 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H), 2.87 (dd, J_1 = 4.8 Hz, J_2 = 2.0 Hz, 1H), 2.96 (dd, J_1 = 10.8 Hz, J_2 = 9.6 Hz, 1H), 3.31-3.35 (m, 1H), 6.55 (d, J = 8.0 Hz, 1H, Ar-H), 6.66-6.70 (m, 1H, Ar-H), 7.01-7.06 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.01, 27.24, 35.53, 48.90, 113.94, 116.98, 121.17, 126.75, 129.58, 144.34 ppm.

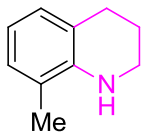
4-Methyl-1,2,3,4-tetrahydroquinoline (2d).[4i] Brown liquid; ^{1}H NMR



(400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.8 Hz, 3H, CH_3), 1.73-1.77 (m, 1H), 2.02-2.07 (m, 1H), 2.96-2.99 (m, 1H, CH_3), 3.31-3.41 (m, 2H, CH_2), 6.54 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, Ar-H), 6.68-6.72 (m, 1H, Ar-H), 7.01-7.05 (m, 1H, Ar-H), 7.13 (d, J = 7.6 Hz,

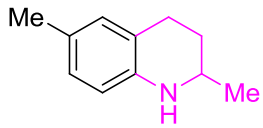
1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.74, 29.90, 30.27, 39.04, 114.22, 116.99, 126.65, 126.78, 128.51, 144.30 ppm.

8-Methyl-1,2,3,4-tetrahydroquinoline (2e).[4i] Brown liquid; ^{1}H NMR



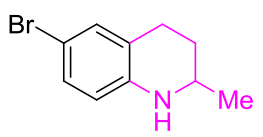
(400 MHz, $CDCl_3$): δ = 2.00-2.06 (m, 2H), 2.17 (s, 3H, CH_3), 2.88 (t, J = 6.4 Hz, 2H), 3.46 (t, J = 5.6 Hz, 2H), 6.65 (t, J = 7.2 Hz, 1H), 6.95 (dd, J_1 = 10.0 Hz, J_2 = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.21, 22.23, 27.36, 42.41, 116.46, 120.92, 121.24, 127.44, 127.91, 142.76 ppm.

2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (2f).[4i] Yellow liquid; ^{1}H NMR



(400 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.0 Hz, 3H, CH_3), 1.62-1.68 (m, 1H), 1.96-2.01 (m, 1H), 2.28 (s, 3H, Ar-CH_3), 2.74-2.89 (m, 2H), 3.39-3.45 (m, 2H), 6.48 (d, J = 8.4 Hz, 1H, Ar-H), 6.85-6.87 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.49, 22.66, 26.65, 30.40, 47.37, 114.34, 121.31, 126.34, 127.27, 129.89, 142.48 ppm.

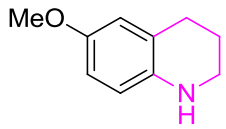
6-Bromo-2-methyl-1,2,3,4-tetrahydroquinoline (2g).[4i] Colorless oil; ^{1}H



NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, J = 6.0 Hz, 3H, CH_3), 1.57-1.62 (m, 1H), 1.93-1.98 (m, 1H), 2.74-2.90 (m, 2H), 3.39-3.44 (m, 1H), 6.38 (d, J = 8.4 Hz, 1H, Ar-H), 7.06-7.12 (m,

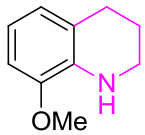
2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.53, 26.47, 29.65, 47.12, 108.28, 115.42, 123.16, 129.35, 131.70, 143.80 ppm.

6-Methoxy-1,2,3,4-tetrahydroquinoline (2h).[4j] Colorless oil; ^{1}H NMR



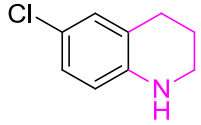
(400 MHz, $CDCl_3$): δ = 1.90-1.96 (m, 2H, CH_2), 2.74-2.77 (m, 2H, CH_2), 3.24-3.27 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 6.45 (d, J = 8.4 Hz, 1H, Ar-H), 6.56-6.61 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.47, 27.02, 42.38, 55.84, 112.91, 114.89, 115.63, 122.93, 138.90, 151.84 ppm

8-Methoxy-1,2,3,4-tetrahydroquinoline (2i).[18] Colorless oil; ^{1}H NMR



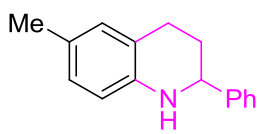
(400 MHz, $CDCl_3$): δ = 1.98-2.04 (m, 2H, CH_2), 2.83 (t, J = 6.4 Hz, 2H, CH_2), 3.37-3.40 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.63-6.68 (m, 3H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.08, 26.67, 41.55, 55.43, 107.42, 115.94, 121.60, 121.73, 134.31, 146.41 ppm.

6-Chloro-1,2,3,4-tetrahydroquinoline (2j).[4j] Brown liquid; ^{1}H NMR



(400 MHz, $CDCl_3$): δ = 1.93-1.99 (m, 2H, CH_2), 2.76 (t, J = 6.4 Hz, 2H, CH_2), 3.32 (t, J = 5.6 Hz, 2H, CH_2), 6.43 (d, J = 8.4 Hz, 1H, Ar-H), 6.93-6.96 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.74, 26.86, 41.88, 115.21, 121.35, 122.99, 126.53, 129.06, 143.12 ppm.

2-Phenyl-1,2,3,4-tetrahydroquinoline (2l).[4i] Brown liquid; ^{1}H NMR (400

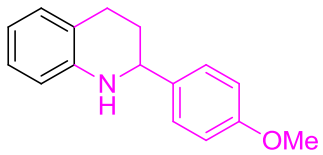


MHz, $CDCl_3$): δ = 2.09-2.15 (m, 1H), 2.21-2.25 (m, 1H), 2.82-2.88 (m, 1H), 2.99-3.03 (m, 1H), 4.13 (br, 1H), 4.53 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H, CH_2), 6.64 (d, J = 7.6 Hz, 1H, Ar-H), 6.75-6.79 (m, 1H, Ar-H), 7.11-7.14 (m, 2H, Ar-H), 7.40-7.52 (m, 5H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.48, 31.09, 56.33, 114.09, 117.25, 120.96, 126.66, 127.01, 127.55, 128.68, 129.41, 144.83, 144.92 ppm.

2-(*p*-Tolyl)-1,2,3,4-tetrahydroquinoline (2m).[18] Yellow liquid; ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 2.04-2.10 (m, 1H), 2.12-2.17 (m, 1H), 2.43 (s, 3H, CH_3), 2.79-2.84 (m, 1H), 2.96-3.00 (m, 1H), 4.47 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H, CH), 6.58-6.61 (m, 1H, Ar-H), 6.70-6.74 (m, 1H, Ar-H), 7.06-7.10 (m, 2H, Ar-H), 7.24 (d, J = 8.0 Hz, 2H, Ar-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.16, 26.54, 31.08, 56.07, 114.00, 117.13, 120.93, 126.51, 126.92, 129.29, 129.33, 137.13, 141.89, 144.86 ppm.

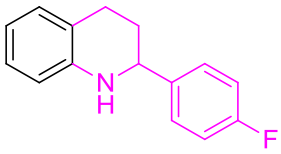
2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (2n).[17a] Pale yellow



oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02-2.04 (m, 1H), 2.10-2.13 (m, 1H), 2.77-2.82 (m, 1H), 2.93-2.97 (m, 1H), 3.86 (s, 3H, OCH_3), 4.43 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H,

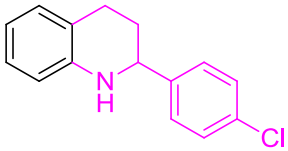
CH), 6.58 (d, J = 0.8 Hz, 1H, Ar-H), 6.67-6.71 (m, 1H, Ar-H), 6.92-6.95 (m, 2H, Ar-H), 7.03-7.06 (m, 2H, Ar-H), 7.34-7.37 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.58, 31.12, 55.35, 55.75, 113.94, 113.98, 117.13, 120.90, 126.88, 127.65, 129.31, 136.91, 144.85, 158.98 ppm.

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (2o).[17] Colorless oil; ^{1}H



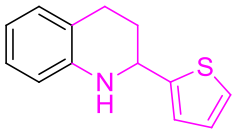
NMR (400 MHz, $CDCl_3$): δ = 1.99-2.06 (m, 1H), 2.11-2.17 (m, 1H), 2.75-2.82 (m, 1H), 2.94-3.02 (m, 1H), 4.07 (br, 1H), 4.48 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H, CH), 6.60 (d, J = 8.0 Hz, 1H, Ar-H), 6.72 (t, J = 7.2 Hz, 1H, Ar-H), 7.05-7.11 (m, 4H, Ar-H), 7.39-7.41 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.34, 31.18, 55.64, 114.09, 115.27, 115.48, 117.39, 120.85, 126.98, 128.07, 128.15, 129.36, 140.53, 144.59, 160.93, 163.37 ppm.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoline (2p).[17] Pale yellow oil;



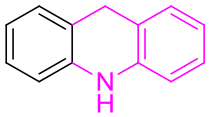
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99-2.05 (m, 1H), 2.12-2.17 (m, 1H), 2.75-2.80 (m, 1H), 2.93-2.97 (m, 1H), 4.07 (br, 1H), 4.48 (dd, J_1 = 9.2 Hz, J_2 = 3.6 Hz, 1H, CH), 6.60 (d, J = 7.6 Hz, 1H, Ar-H), 6.70-6.74 (m, 1H, Ar-H), 7.05-7.09 (m, 2H, Ar-H), 7.30-7.50 (m, 4H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.17, 31.02, 55.63, 144.01, 144.11, 117.45, 120.83, 126.58, 126.94, 127.01, 127.47, 127.94, 128.61, 128.73, 129.36, 133.05, 143.39, 144.45 ppm.

2-(Thiophen-2-yl)-1,2,3,4-tetrahydroquinoline (2q).[17] Viscous oil; ^{1}H



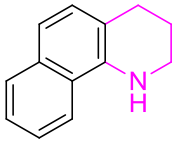
NMR (400 MHz, $CDCl_3$): δ = 2.07-2.12 (m, 1H), 2.19-2.22 (m, 1H), 2.78-2.84 (m, 1H), 2.93-2.97 (m, 1H), 4.10 (s, 1H), 4.63 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H, Ar-H), 6.70-6.74 (m, 1H, Ar-H), 7.05-7.09 (m, 2H, Ar-H), 7.16-7.17 (m, 1H, Ar-H), 7.26-7.27 (m,1H, Ar-H), 7.36-7.37 (m,1H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.24, 30.28, 52.14, 114.15, 117.38, 120.81, 120.98, 126.14, 126.17, 126.95, 129.38, 144.44, 146.14 ppm.

9,10-Dihydroacridine (2r).[4i] Yellow solid, mp 152-155 °C; ^{1}H NMR (400



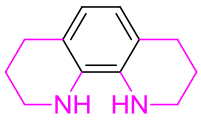
MHz, $CDCl_3$): δ = 4.10 (s, 2H), 6.01 (br, 1H), 6.71 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 2H), 6.88 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 2H), 7.11-7.16 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.41, 113.45, 120.05, 120.65, 127.02, 128.62, 140.12 ppm.

1,2,3,4-Tetrahydrobenzo[h]quinoline (2s).[4j] Yellow oil; ^{1}H NMR (400



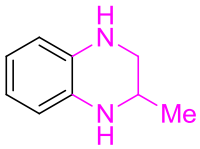
MHz, $CDCl_3$): δ = 2.07-2.12 (m, 2H), 2.98 (t, J = 6.0 Hz, 2H), 3.54 (t, J = 5.2 Hz, 2H), 7.17-7.25 (m, 2H), 7.44-7.46 (m, 2H), 7.73-7.76 (m, 1H), 7.79-7.81 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.16, 27.49, 42.46, 115.87, 116.98, 119.46, 123.27, 124.79, 124.97, 128.57, 128.63, 133.05, 139.02 ppm.

1,2,3,4,7,8,9,10-Octahydro-1,10-phenanthroline (2t).[12b] Yellow solid,



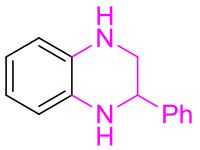
mp 69-71 °C; 1H NMR (400 MHz, CDCl3): δ = 1.90-1.95 (m, 4H), 2.76-2.79 (m, 4H), 3.34 (s, 4H), 6.50 (s, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.52, 26.93, 42.65, 119.19, 120.55, 132.86 ppm.

2-Methyl-1,2,3,4-tetrahydroquinoxaline (2u).[13] Yellow solid, mp 88-

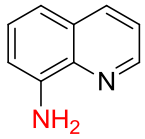


90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, J = 6.4 Hz, 3H, CH_3), 3.09 (dd, J_1 = 10.8 Hz, J_2 = 8.4 Hz, 1 H), 3.36 (dd, J_1 = 10.8 Hz, J_2 = 2.8 Hz, 1H), 3.52-3.58 (m, 3H), 6.54-6.57 (m, 2H, Ar-H), 6.63-6.66 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.96, 45.74, 48.28, 114.48, 114.53, 118.72, 133.26, 133.63 ppm.

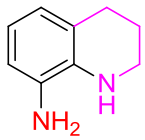
2-Phenyl-1,2,3,4-tetrahydroquinoxaline (2v).[14b] Brown liquid; ^{1}H NMR



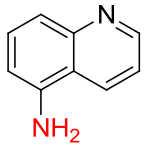
(400 MHz, $CDCl_3$): δ = 3.35-3.40 (m, 1H), 3.51 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 4.53 (dd, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 6.61-6.64 (m, 2H), 6.67-6.70 (m, 2H), 7.36-7.45 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.16, 54.76, 114.48, 114.82, 118.82, 119.03, 127.01, 127.92, 127.94, 128.67, 132.71, 134.19, 141.84 ppm.

Quinolin-8-amine (4a).[12b] Brown solid, mp 62-65 °C; ^{1}H NMR (400 MHz, 

$CDCl_3$): δ = 5.03 (s, br, 2H), 6.98 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.20 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.36-7.42 (m, 2H), 8.11 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.81 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.08, 116.09, 121.38, 127.40, 128.87, 136.04, 138.44, 143.95, 147.48 ppm.

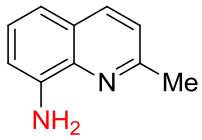
1,2,3,4-Tetrahydroquinolin-8-amine (5).[14a] Brown oil; ^{1}H NMR (400 

MHz, $CDCl_3$): δ = 6.55-6.48 (m, 3H), 3.27 (t, J = 5.2 Hz, 2H), 2.93 (brs, 3H), 2.72 (t, J = 6.4 Hz, 2H), 1.89-1.83 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.63, 27.26, 42.81, 114.31, 118.28, 121.37, 123.51, 134.09, 134.13 ppm.

Quinolin-5-amine (4b).[12b] Brown solid, mp 106-109 °C; ^{1}H NMR (400 

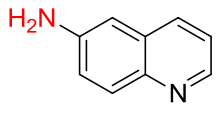
MHz, $CDCl_3$): δ = 4.26 (s, br, 2H), 6.86 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.39 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 7.53-7.62 (m, 2H), 8.22 (d, J = 8.4 Hz, 1H), 8.92 (dd, J_1 = 4.4 Hz, J_2 = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.07, 118.73, 119.65, 120.22, 129.55, 130.05, 142.24, 149.11, 150.30 ppm.

2-Methylquinolin-8-amine (4c).[12b] Brown solid, mp 56-58 °C; ^{1}H NMR



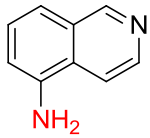
(400 MHz, $CDCl_3$): δ = 2.75 (s, 3H), 5.00 (s, br, 2H), 6.95 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.15 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.27-7.32 (m, 2H), 7.99 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.27, 102.89, 110.16, 115.93, 122.18, 126.33, 126.89, 136.11, 143.38, 156.20 ppm.

Quinolin-6-amine (4d).[12a] Grey solid, mp 117-119 °C; ^{1}H NMR (400 MHz,



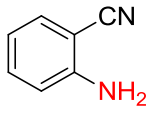
$CDCl_3$): δ = 4.00 (s, br, 2H), 6.94 (d, J = 9.2 Hz, 1H), 7.15-7.22 (m, 1H), 7.27-7.32 (m, 1H), 7.90-7.96 (m, 2H), 8.65-8.70 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.46, 121.43, 121.59, 129.77, 130.59, 133.82, 143.45, 144.60, 146.90 ppm.

Isoquinolin-5-amine (4e).[12b] Brown solid, mp 127-129 °C; ^{1}H NMR (400



MHz, $CDCl_3$): δ = 4.25 (s, br, 2H), 6.99 (t, J = 4.4 Hz, 1H), 7.45 (d, J = 4.8 Hz, 2H), 7.62 (d, J = 6.0 Hz, 1H), 8.53 (d, J = 6.0 Hz, 1H), 9.23 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.14, 114.10, 118.06, 126.01, 127.82, 129.41, 141.28, 142.01, 152.97 ppm.

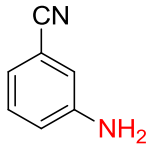
2-Aminobenzonitrile (4f).[12b] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$):



δ = 4.46 (s, br, 2H), 6.75-6.79 (m, 2H), 7.34-7.42 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.00, 115.20, 117.70,

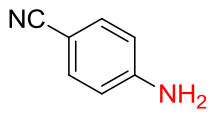
118.02, 132.39, 134.06, 149.67 ppm.

3-Aminobenzonitrile (4g).[12a] Yellow solid, mp 50-52 °C; ^{1}H NMR (400



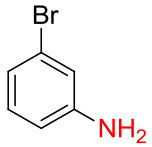
MHz, $CDCl_3$): δ = 3.91 (s, br, 2H), 6.89-6.94 (m, 2H), 7.04-7.07 (m, 1H), 7.26 (t, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.96, 117.46, 118.89, 119.21, 122.05, 130.08, 146.98 ppm.

4-Aminobenzonitrile (4h).[12b] Yellow solid, mp 83-85 °C; ^{1}H NMR (400



MHz, $CDCl_3$): δ = 4.20 (s, br, 2H), 6.68 (d, J = 8.8 Hz, 2H), 7.45 (dd, J_1 = 8.4 Hz, J_2 = 3.6 Hz, 2H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 100.11, 114.46, 120.23, 133.85, 150.47 ppm.

3-Bromoaniline (4i).[12b] White solid, mp 29-31 °C; ^{1}H NMR (400 MHz,



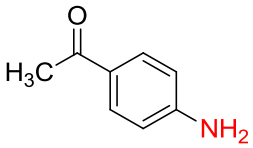
$CDCl_3$): δ = 3.75 (s, br, 2H), 6.61-6.64 (m, 1H), 6.87-6.92 (m, 2H), 7.04 (t, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.65, 117.84, 121.39, 123.07, 130.64, 147.81 ppm.

2,5-Dibromoaniline (4j).[12b] White solid, mp 53-55 °C; ^{1}H NMR (400

MHz, $CDCl_3$): δ = 4.18 (s, br, 2H), 6.77 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.77, 118.12, 121.75, 122.17,

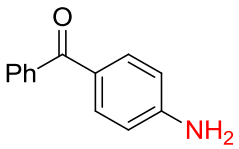
133.64, 145.30 ppm.

1-(4-Aminophenyl)ethanone (4k).[12b] Yellow solid, mp 104-106 °C; ^{1}H



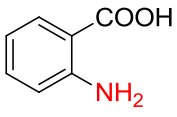
NMR (400 MHz, $CDCl_3$): δ = 2.54 (s, 3H), 4.18 (s, br, 2H), 6.69 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 2H), 7.85 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.14, 113.74, 127.87, 130.84, 151.14, 196.55 ppm.

(4-Aminophenyl)(phenyl)methanone (4l).[12b] Yellow solid, mp 122-



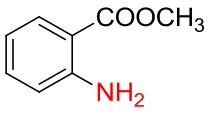
124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 (s, br, 2H), 6.70-6.73 (m, 2H), 7.47-7.51 (m, 2H), 7.56-7.60 (m, 1H), 7.75-7.77 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.66, 127.46, 128.11, 129.56, 131.45, 132.98, 138.88, 150.93, 195.35 ppm.

2-Aminobenzoic acid (4m).[12b] White solid, mp 178-180 °C; ^{1}H NMR (400



MHz, $CDCl_3$): δ = 6.72 (d, J = 6.8 Hz, 2H), 7.34-7.38 (m, 1H), 7.98 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.59, 116.50, 116.83, 132.17, 135.15, 151.14, 173.63 ppm.

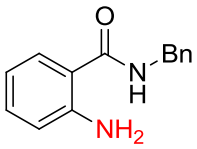
Methyl-2-aminobenzoate (4n).[12b] Colorless oil; ^{1}H NMR (400 MHz,



$CDCl_3$): δ = 3.91 (s, 3H), 5.76 (s, br, 2H), 6.66-6.71 (m, 2H), 7.28-7.33 (m, 1H), 7.90 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz,

1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.57, 110.76, 116.31, 116.71, 131.25, 134.14, 150.46, 168.63 ppm.

2-Amino-*N*-benzylbenzamide (4o).[12b] White solid, mp 117-118 °C; ^{1}H

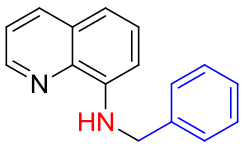


NMR (400 MHz, $CDCl_3$): δ = 4.65 (d, J = 5.6 Hz, 2H), 5.60 (s, br, 2H), 6.38 (s, br, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 7.23-7.27 (m, 1H), 7.34-7.40 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.76, 115.80, 116.64, 117.40, 127.11, 127.61, 127.85, 128.83, 132.45, 138.28, 148.87, 169.17 ppm.

***N*-(2-Aminophenyl)acetamide (4p)**.[12b] Colorless oil; ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 2.18 (s, 3H), 3.91 (s, br, 2H), 6.80-6.83 (m, 2H), 7.07-7.11 (m, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.52 (s, br, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.68, 118.16, 119.54, 124.24, 125.51, 127.36, 140.96, 169.06 ppm.

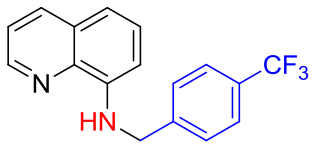
***N*-Benzylquinolin-8-amine (7a)**.[12b] Yellow solid, mp 40-42 °C; ^{1}H NMR



(400 MHz, $CDCl_3$): δ = 4.62 (d, J = 5.2 Hz, 2H), 6.66 (s, br, 1H), 6.70 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.30-7.44 (m, 5H), 7.49-7.51 (m, 2H), 8.12 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.77 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.73, 105.16, 114.19, 121.47, 127.17,

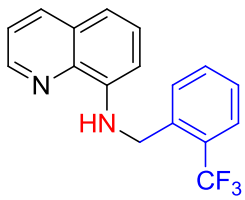
127.45, 127.80, 128.66, 136.07, 138.24, 139.25, 144.58, 146.97 ppm.

***N*-(4-(Trifluoromethyl)benzyl)quinolin-8-amine (7b)**.[12b] Yellow solid,



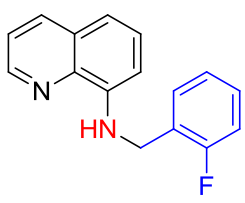
mp 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, J = 6.0 Hz, 2H), 6.60 (d, J = 7.6 Hz, 1H), 6.76 (s, br, 1H), 7.14 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.45 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 7.57-7.65 (m, 4H), 8.13 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 8.80 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.26, 105.30, 114.70, 121.60, 122.91, 125.60 (q, J_F = 3.7 Hz) 127.55 (d, J_F = 27.7 Hz), 128.67, 129.56, 136.16, 138.20, 143.57, 144.16, 147.14 ppm.

***N*-(2-(trifluoromethyl)benzyl)quinolin-8-amine (7c)**.[12b] Yellow solid,



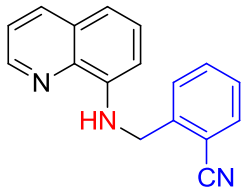
mp 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (d, J = 6.0 Hz, 2H), 6.56 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 6.78 (t, J = 5.6 Hz, 1H), 7.12 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.51-7.33 (m, 4H), 7.73 (dd, J_1 = 16.4 Hz, J_2 = 7.6 Hz, 2H), 8.13 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 8.80 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.89 (d, J_F = 3.1 Hz), 105.22, 114.57, 121.55, 123.31, 126.02 (t, J_F = 5.9 Hz), 126.95, 127.71(d, J_F = 8.0 Hz), 127.97, 128.23, 128.67, 132.19, 136.13, 137.95, 138.21, 144.10, 147.11.

***N*-(2-Fluorobenzyl)quinolin-8-amine (7d)**.[12b] Yellow oil; ^{1}H NMR (400



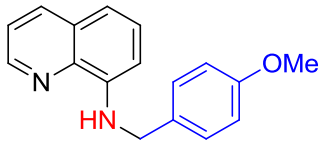
MHz, $CDCl_3$): δ = 4.69 (d, J = 6.0 Hz, 2H), 6.65 (s, br, 1H), 6.71 (dd, J_1 = 7.2 Hz, J_2 = 0.4 Hz, 1H), 7.10-7.15 (m, 3H), 7.28-7.30 (m, 1H), 7.37-7.49 (m, 3H), 8.12 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.8 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.12 (d, J_F = 4.7 Hz), 105.12, 114.43, 115.33 (d, J_F = 21.1 Hz), 121.50, 124.22 (d, J_F = 3.5 Hz), 126.12 (d, J_F =14.6 Hz), 127.77, 128.71 (d, J_F = 8.0 Hz), 129.23 (d, J_F = 4.4 Hz), 136.10, 138.26, 144.31, 147.05, 159.76, 162.21 ppm.

2-((Quinolin-8-ylamino)methyl)benzonitrile (7e).[12b] Yellow solid, mp



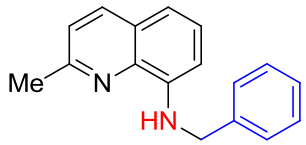
112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.86 (d, J = 6.4 Hz, 2H), 6.59-6.83 (m, 1H), 6.85 (s, br, 1H), 7.14 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.34-7.41 (m, 2H), 7.45 (q, J = 4.4 Hz, 1H), 7.53-7.57 (m, 1H), 7.63-7.65 (m, 1H), 7.74 (dd, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 8.13 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.80 (dd, J_1 = 4.4 Hz, J_2 = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.77, 105.35, 111.23, 114.99, 117.51, 121.64, 127.59, 127.65, 127.83, 128.65, 133.04, 133.16, 136.16, 138.20, 143.33, 143.81, 147.22 ppm.

***N*-(4-Methoxybenzyl)quinolin-8-amine (7f)**.[12b] Brown solid, mp 71-



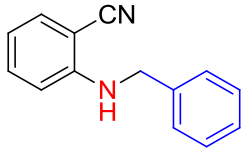
73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H), 4.53 (d, J = 5.2 Hz, 2H), 6.56 (s, br, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.92-6.95 (m, 2H), 7.10 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.37-7.43 (m, 4H), 8.11 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.76 (dd, J_1 = 4.0 Hz, J_2 = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.20, 55.34, 105.09, 114.03, 114.08, 121.44, 127.80, 128.65, 128.75, 131.21, 136.05, 138.23, 144.61, 146.93, 158.8 ppm.

***N*-Benzyl-2-methylquinolin-8-amine (7g)**.[12b] Yellow solid, mp 60-62 °C;



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (s, 3H), 4.61 (d, J = 4.8 Hz, 2H), 6.69 (s, br, 1H), 7.06 (d, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.28-7.38 (m, 4H), 7.40-7.42 (m, 2H), 7.48-7.50 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.22, 47.73, 114.05, 105.23, 122.18, 126.69, 127.06, 127.39, 128.60, 136.16, 137.50, 139.55, 144.13, 155.74 ppm.

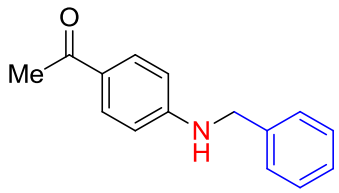
2-(Benzylamino)benzonitrile (7h).[12b] Yellow solid, mp 118-120 °C; ^{1}H



NMR (400 MHz, $CDCl_3$): δ = 4.48 (d, J = 5.6 Hz, 2H), 5.08 (s, br, 1H), 6.68 (d, J = 8.8 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 7.30-7.41 (m, 6H), 7.46 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl3): δ = 47.48, 95.90, 111.07, 116.90, 117.97,

127.21, 127.69, 128.91, 132.80, 134.34, 137.75, 150.09 ppm.

1-(4-(Benzylamino)phenyl)ethanone (7i).[12b] Yellow solid, mp 84-86 °C;



^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H), 4.45 (d, J = 5.6 Hz, 2H), 4.66 (s, br, 1H), 6.64 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 7.30-7.42 (m, 5H), 7.86 (d, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.09, 47.63, 111.63, 127.41, 127.63, 128.61, 128.86, 130.85, 138.24, 151.95, 196.47 ppm.

References

(1) (a) Sridharan, V.; Suryavanshi P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157-7259. (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron.* **1996**, *52*, 15031-15070. (c) Scott, J. D; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669-16730. (d) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444-463. (e) Crabtree, R. H. *Energy Environ. Sci.* **2008**, *1*, 134-138.

(2) (a) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395-404. (b) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc. Perkin Trans.* **2001**, 955-977.

(3) Some selected reviews, see: (a) Bianchini, C.; Barbaro, P.; Macchi, M.; Meli, A.; Vizza. F. *Helvetica Chimica Acta*. **2001**, *84*, 2895-2923. (b) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171-4175. (c) Kuwano, R. *Heterocycles*. **2008**, *76*, 909-922. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557-2590.

(4) Selected examples of organometallic hydrogenation and transfer hydrogenation of quinolines, see (a) Alvanipour, A.; Kispert, L. D. *J. Mol. Catal.* **1988**, *48*, 277-283. (b) Baiczewski, P.; Joule, J. A. *Synth. Commun*. **1990**, *20*, 2815-2819. (c) Lu, S.-M; Han, X.-W; Zhou, Y.-G. *J. Organomet. Chem.* **2007**, *692*, 3065-3089. (d) Zhu, G; Pang, K.; Parkin, G. *J. Am. Chem. Soc.* **2008**, 130, 1564-1565. (e) Dobereiner, G. E.; Nova, A.; Schley, N. D.; Hazari, N.; Miller, S. J.; Eisenstein, O.;

Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, 133, 7547-7562. (f) Tao, L.; Zhang, Q.; Li, S. S.; Liu, X.; Liu, Y. M.; Cao, Y. *Adv. Synth. Catal.* **2015**, *357*, 753-760. (g) Zhang, L.; Wang, X. Y.; Xue, Y.; Zeng, X. J.; Chen, H.; Li, R. X.; Wang, S. L. *Catal. Sci. Technol.* **2014**, *4*, 1939-1948. (h) Niu, M. M.; Wang, Y. H.; Chen, P.; Du, D. J.; Jiang, J. Y.; Jin, Z. L. *Catal. Sci. Technol.* **2015**, *5*, 4746-4749. (i) Talwar, D.; Li, H. Y.; Durham, E.; Xiao, J. *Chem. Eur. J.* **2015**, *21*, 5370-5379. (j) Chen, F.; Surkus, A. E.; He, L.; Pohl, M. M.; Radnik, J.; Topf, C.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2015**, *137*, 11718-11724.

(5) Selected examples of organocatalytic transfer hydrogenation of quinolines, see: (a) Rueping, M.; Theissmann, T.; Antonchick, A. P. *Synlett.* **2006**, *7*, 1071-1074. (b) Bruckmann, A.; Pena, M. A.; Bolm, C. *Synlett.* **2008**, 6, 900-902. (c) Geier, S. J.; Chase, P. A.; Stephan, D. W. *Chem. Commun.* **2010**, *46*, 4884-4886. (d) Rueping, M.; Antonchick, A. R.; Theissmann, T. *Angew. Chem.* **2006**, *118*, 3765-3768. (e) Rueping, M.; Antonchick, A.P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683-3686. (f) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759-762. (g) Chatterjee, I.; Oestreich, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 1965-1968.

(6) (a) Dowing, R. S.; Kunkeler, P. J.; Bekkum, H. V. *Catal. Today.* **1997**, *37*, 121-136. (b) Ono, N. *Synthesis*. **2001**, *16*, 2528. (c) Gunanathan, C.; Milstein, D. *Angew Chem. Int. Ed.* **2008**, *47*, 8661-8664. (d) Kantam,

M. L.; Chakravarti, R.; Pal, U.; Sreedhar, B.; Bhargava, S. *Adv. Synth. Catal.***2008**, *350*, 822-827. (e) Liu, S.; Wang, Y.; Jiang, J.; Jin, Z. *Green Chem.* **2009**, *11*, 1397-1400. (f) Birch, A. M.; Groombridge, S.; Law, R.; Leach, A. G.; Mee, C. D.; Schramm, C. *J. Med. Chem.* **2012**, *55*, 3923-3933. (g) Vishnoi, S.; Agrawal, V.; Kasana, V. K. *J. Agric. Food Chem.* **2009**, *57*, 3261-3265. (h) Tafesh, A. M.; Weiguny, J. *Chem Rev.* **1996**, *96*, 2035-2052. (i) Pandarus, V.; Ciriminna, R.; Beland, F.; Pagliaro, M. *Adv. Synth. Catal.* **2011**, *353*, 1306-1316. (j) Mikami, Y.; Noujima, A.; Mitsudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Lett.* 2010, 39, 223-225. (k) Cárdenas-Lizana, F.; Gómez-Quero, S.; Keane, M. A. *Catal Commun.* **2008**, *9*, 475-481.

(7) Béchamp, A. J. *Ann. Chim. Phys.* **1854**, *42*, 186.

(8) For a review on the advancement of methodologies for reduction of nitroarenes, see, Kadam, H. K.; Tilve, S. G. *RSC Adv.* **2015**, *5*, 83391-83407. and references cited therein.

(9) (a) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091-9161. (b) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc*. **2010**, 132, 17701-17703. (c) Molander, G. A.; Cavalcanti, L. N.; García-García, C. J. *J. Org. Chem.* **2013**, *78*, 6427-6439. (d) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M.; Dreher, S. D; Tudge, M. T. *J. Am. Chem. Soc.* **2012**, *134*, 11667-11673. (e) Chen, K.; Zhang, S.; He, P.; Li, P. *Chem. Sci*. **2016**, *7*, 3676-

3680. (f) Zhang, L.; Jiao, L. *J. Am. Chem. Soc*. **2017**, 139, 607-610.\

(10) (a) Cummings, S. P.; Le, T.-N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B.J. *J. Am. Chem. Soc.* **2016**, 138, 6107-6110. (b) Ojha, D. P.; Gadde, K.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5062-5065.

(11) (a) Zhou, X.-F.; Sun, Y.-Y.; Wu, Y.-D.; Dai, J.-J.; Xu, J.; Huang, Y. *Tetrahedron*. **2016**, *72*, 5691-5698. (b) Ding, W.; Song, Q. *Org. Chem. Front.* **2016**, *3*, 14-18.

(12) (a) Lu, H.; Geng, Z.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Org. Lett.* **2016**, *18*, 2774-2776. (b) Zhou, Y.; Zhou, H.; Liu, S.; Pi, D.; Shen, G. *Tetrahedron.* **2017**, 73, 3898-3904.

(13) Xuan, Q.; Song, Q. *Org. Lett.* **2016**, 18, 4250-4253.

(14) (a) Xia, Y. T.; Sun, X. T.; Zhang, L.; Luo, K.; Wu, L. *Chem. Eur. J.* **2016**, *22*, 17151-17155. (b) Liu, S.; Zhou, Y.; Sui, Y.; Liu, H.; Zhou H. *Org. Chem. Front.* **2017**, *4*, 2175-2178.

(15) (a) Yang, K.; Zhou, F.; Kuang, Z.; Gao, G.; Driver, G. T.; Song, Q. *Org. Lett.* **2016**, *18*, 4088-4091. (b) Ke, M.; Song, Q. *J. Org. Chem.* **2016**, *81*, 3654-3664. (c) Ke, M.; Song, Q. *Adv. Synth. Catal*. **2017**, *359*, 384-389. (d) Ke, M.; Song, Q. *Chem. Commun.* **2017**, *53*, 2222-2225. (e) Xuan, Q.; Kong, W.; Song, Q. *J. Org. Chem.* **2017**, *82*, 7602-7607. (f) Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 3987-3991.

(16) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C.-O. M.; Yoon, C. M. *Chem.*

Commun. **2000**, 32, 1857-1858.

(17) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878-9891.

(18) Pi, D.; Zhou, H.; Cui, P.; He, R.; Sui, Y. *ChemistrySelect*. **2017**, *2*, 3976-3979.

Chapter 3

Aqueous Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex under Batch and Continuous-Flow Conditions

Guanshuo Shen, Takao Osako, Makoto Nagaosa, Yasuhiro Uozumi,

J. Org. Chem. **2018**, *83*, 7380-7387

Introduction

The development of green, sustainable catalytic organic transformations is an important challenge in current organic chemistry.[1] A key strategy for achieving green, sustainable organic transformations is to reduce the use of hazardous and nonsustainable organic solvents produced from petroleum feedstocks. Water is an ideal solvent because it is ecofriendly, cheap, nontoxic, and abundant.[1,2] Moreover, enzymatic reactions in nature occur efficiently in aqueous media. Despite the great benefits of water as a solvent, organic transformations in water tend to suffer from low reactivity as a result of the low solubility of the organic substrates and catalysts. To overcome this difficulty, various methods have been developed for conducting catalytic organic reactions in water. As part of this author group's continuing efforts in this field of research, this author's group has previously developed various transition-metal catalysts immobilized on amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin, and this author's group has also applied them in a wide variety of organic transformations in water under heterogeneous conditions.[3] In addition to the high recyclability of the immobilized catalysts, the amphiphilic part of PS-PEG provides a reaction environment for the organic substrates in water to that realizes the efficient green, sustainable organic transformations.

The asymmetric rhodium-catalyzed 1,4-addition of organometallic-

reagents to enones is widely used as an efficient and important C-C bond-forming process, providing chiral β-substituted carbonyl compounds that are useful as chiral building blocks in organic synthesis.[4] After the first report of an asymmetric 1,4-addition of arylboronic acids to enones catalyzed by rhodium(I)/BINAP,[5] various excellent asymmetric transition-metal catalysts with chiral ligands have been developed to achieve highly enantioselective 1,4-addition. In particular, chiral diene ligands have recently attracted much attention and they have been recognized as novel chiral ligands especially in rhodium- and iridium-catalyzed asymmetric reactions, providing catalytic activity and selectivity[6,7] that are superior to those of common chiral phosphine ligands.[8,9] However, the asymmetric transition-metal-catalyzed transformations using chiral dienes are generally performed in organic solvents under homogeneous conditions. The conversion of the asymmetric reactions involving chiral diene catalysts into green sustainable processes in water remains an immature technique.[10,11]

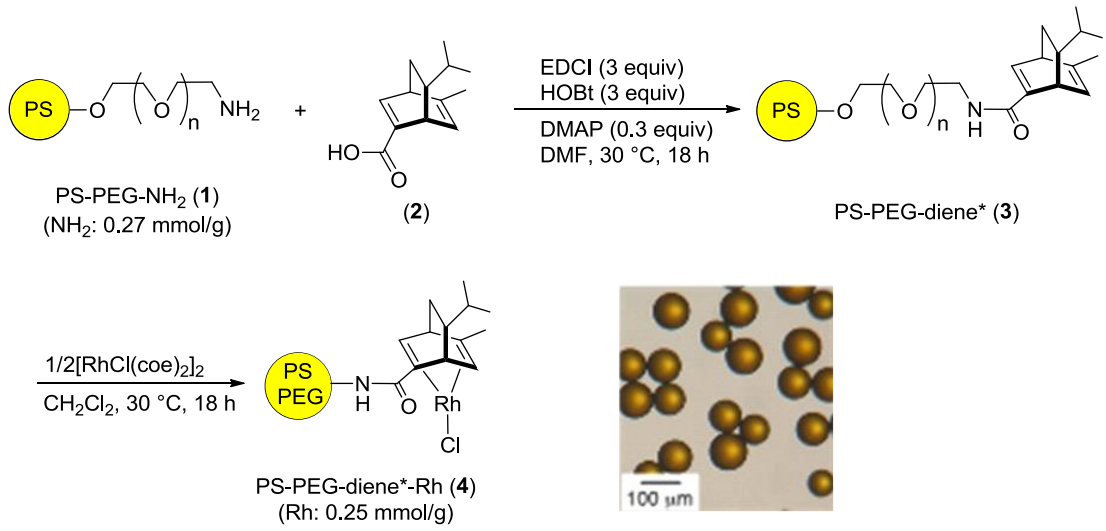
Herein, this author has developed a rhodium−chiral diene complex immobilized on amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin and its use in the 1,4-addition of arylboronic acids to enones in water under heterogeneous conditions. The immobilized rhodium-chiral diene complex efficiently promoted the asymmetric 1,4- addition of arylboronic acids to enones in water at 50 °C to give the corresponding β-substituted

carbonyl compounds in good-to-excellent yields with excellent enantioselectivity as well as with high recyclability of the catalyst. Moreover, the immobilized rhodium-chiral diene complex was successfully applied to a continuous-flow asymmetric 1,4-addition reaction, showing a high productivity (11.7 g) of the desired *β*-substituted carbonyl compound with a high turnover number (TON = 1073) and excellent enantioselectivity (93% ee) over 12 h.

Results and Discussion

The rhodium-chiral diene complex immobilized on amphiphilic PS−PEG resin **4** was prepared according to **Scheme 1**.

Scheme 1. Preparation of PS-PEG-diene*-Rh (4)

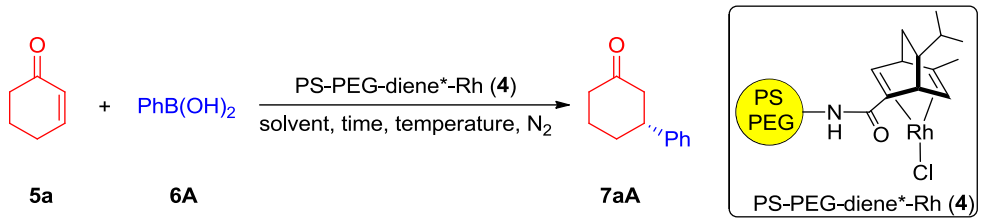


Treatment of amino-functionalized PS-PEG **1** with (1*R*,4*R*,7*R*)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (**2**)[7e] in

the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 3.0 equiv), 1-hydroxybenzotriazole (HOBt; 3.0 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 0.3 equiv) in DMF at 30 °C for 18 h gave PS-PEG-supported chiral diene (PS-PEG-diene*, **3**). Complexation of **3** with chlorobis(cyclooctene)rhodium(I) dimer ($[RhCl(coe)_2]_2$) in CH_2Cl_2 at 30 °C for 18 h afforded brown polymer beads of PS-PEG supported rhodium-chiral diene complex (PS-PEG-diene*-Rh, **4**). ICP analysis revealed that this had a rhodium content of 0.25 mmol/gr.

Initially, this author screened the reaction conditions for the asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) in the presence of PS-PEG-diene*-Rh (**4**) (**Table 1**).

Table 1. Optimization of conditions for the asymmetric 1,4-addition[a]



5a 6A 7aA

entry	cat. loading (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	2.5	H_2O	50	5	>99 (94)	95
2	2.5	H_2O	40	5	86 (61)	95
3	2.5	H_2O	30	5	40 (30)	94
4	2.5	H_2O	25	5	25 (13)	94
5[d]	2.5	H_2O	40	5	40 (34)	95
6	1.3	H_2O	50	5	87 (68)	95
7	0.65	H_2O	50	5	73 (55)	94
8	2.5	toluene- H_2O (9:1)	50	5	57 (48)	95
9	2.5	toluene- H_2O (9:1)	50	5	17 (15)	96
10	2.5	toluene- H_2O (9:1)	50	5	0	
11	2.5	toluene- H_2O (9:1)	50	5	0	
12	2.5	toluene- H_2O (9:1)	50	5	0	
13	2.5	H_2O	50	1	(47)	95
14	2.5	H_2O	50	2	(77)	95
15	2.5	H_2O	50	3	(91)	95
16	2.5	H_2O	50	4	(91)	95

[a]Reaction conditions: enone **5a** (0.3 mmol), $PhB(OH)_2$ (**6A**; 0.45 mmol), PS-PEG-diene*-Rh (**4**; 0.65-2.5 mol %), solvent (1 mL), 25-50 °C, 1-5 h. [b]Determined by ^1H NMR with an internal standard (CH_3NO_2). The isolated

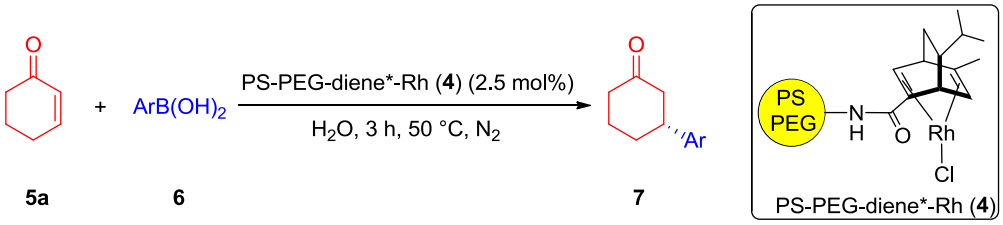
yields are shown in parentheses. [c]Determined by HPLC on a chiral stationary column (DAICEL CHIRALCEL AD-H). The absolute configuration of **7aA** was determined to be *R* on the basis of its optical rotation. [d]The reaction was performed in air.

The reaction of **5a** with **6A** (1.5 equiv) in the presence of **4** (2.5 mol % Rh) in H_2O at 50 °C was completed in 5 h, giving (*R*)-3-phenylcyclohexanone (**7aA**) in 94% isolated yield and 95% ee (Table 1, entry 1). Notably, no additives such as bases were necessary for the author's standard conditions, whereas conventional Rh-catalyzed 1,4-addition reactions in organic solvents require the presence of a base. Decreasing the reaction temperature resulted in an incomplete reaction (entries 2-4), although the enantioselectivity was retained. When the reaction was performed at 40 °C under air, the isolated yield of **7aA** dropped to 34%, suggesting that the catalytic activity decreases under air (entry 5). Reducing the catalyst loading affected the yield of **7aA** (entries 6 and 7). Interestingly, PS-PEG-diene*-Rh (**4**) showed poor activity in organic solvents (toluene, MeOH, dioxane, THF, or DMF; entries 8-12).[12] These results clearly suggest that water is the best solvent for catalysis by the amphiphilic PS-PEG supported rhodium-chiral diene catalysis. It is also noteworthy that the enantioselectivity for the 1,4-addition in water using PS-PEG-diene*-Rh (**4**) was higher than its homogeneous counterpart

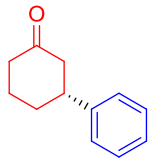
reported so far which was performed in dioxane-water (10:1) (7aA, 86% ee; using a combination of $[RhCl\text{-}(C_2H_4)_2]_2$ (3 mol % Rh) and the methyl ester of **2** (3.3 mol %) at 20 °C),[7e] presumably because of the steric effect of the C2-carboxamide group and water-based improvement of the reactivity. To optimize the reaction time, the completion of the 1,4-addition at 50 °C was investigated at 1, 2, 3, and 4 h (entries 13-16). The reaction was completed in 3 h, giving **7aA** in 91% isolated yield with 95% ee (entry 15).

With the optimized conditions in hand, this author investigated the substrate scope of arylboronic acids **6** in the asymmetric 1,4-addition to cyclohex-2-en-1-one (**5a**) in water (**Scheme 2**).

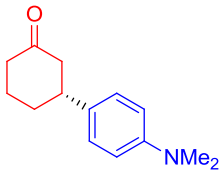
Scheme 2. Scope of the arylboronic acids[a]



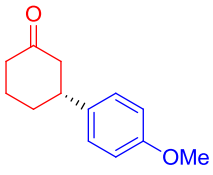
5a **6** **7**



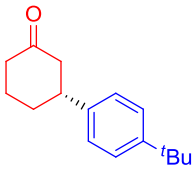
7aA
91% yield, 95% ee



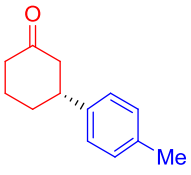
7aB
87% yield, 92% ee[b]



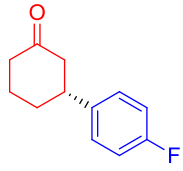
7aC
99% yield, 94% ee



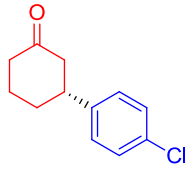
7aD
68% yield, 91% ee[c]



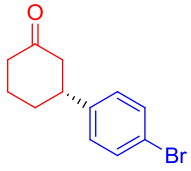
7aE
80% yield, 94% ee



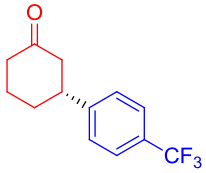
7aF
91% yield, 96% ee



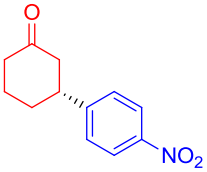
7aG
99% yield, 96% ee



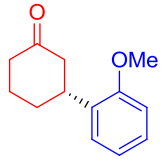
7aH
91% yield, 96% ee



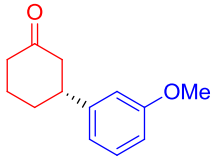
7aI
96% yield, 98% ee



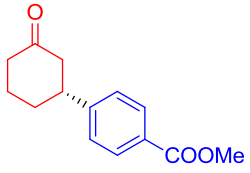
7aJ
90% yield, 94% ee[c]



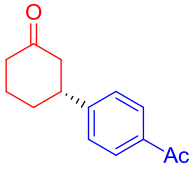
7aK
99% yield, 87% ee



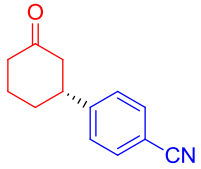
7aL
81% yield, 95% ee



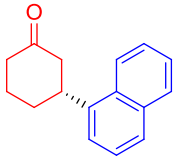
7aM
81% yield, 96% ee



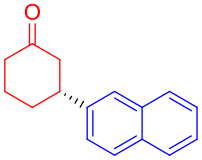
7aN
99% yield, 95% ee[c]



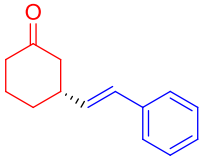
7aO
96% yield, 97% ee[d]



7aP
92% yield, 84% ee



7aQ
94% yield, 95% ee



7aR
64% yield, 91% ee

[a]Reaction conditions: enone **5a** (0.3 mmol), arylboronic acid **6** (0.45 mmol), PS-PEG-diene*-Rh (**4**; 2.5 mol % Rh), H_2O (1 mL), 50 °C, 3 h. Isolated yields are shown. The ee values were determined by HPLC on a chiral stationary column. The absolute configuration of products **7** were assigned on the basis of their optical rotation. [b]The reaction was performed for 5 h.

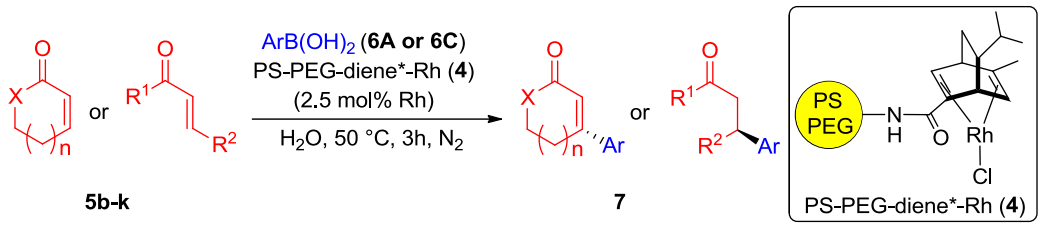
[c]The reaction was performed for 6 h. [d]The reaction was performed in the presence of KOH (50 mol %) for 4 h.

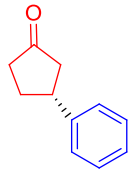
Phenylboronic acids **6B-E** bearing electron-donating groups at the *para* position underwent asymmetric 1,4-addition to **5a** in water at 50 °C under N_2 to give the corresponding *β*-substituted cyclohexanones **7aB-aE** in 68-99% yield and 91-94% ee, although the reactions of **6B** and **6D** required longer reaction times (5 and 6 h, respectively). Various (*p*-halophenyl) boronic acids also reacted to afford the products **7aF-aH** in excellent yields and with excellent enantioselectivity. The reaction of phenylboronic acids bearing the electron-withdrawing substituents CF_3 and NO_2 proceeded smoothly to afford the corresponding cyclohexanones **7aI** and **7aJ** in 96% and 90% yield and with 98% ee and 94% ee, respectively. The presence of *o*- or *m*-methoxy groups on the phenylboronic acids (**6K** and **6H**) did not affect the asymmetric reaction. Other functionalities, such as ester and ketone groups, were also tolerated, and the products **7aM** and **7aN** were obtained in excellent yields and with excellent enantioselectivity. The reaction of (4-cyanophenyl)boronic acid (**6O**) proceeded slowly under the optimized conditions, but the addition of 50 mol % of KOH promoted the reaction to give **7aO** in 96% yield with 97% ee.[13] The 1,4-addition of 1- and 2-naphthylboronic acids (**6P** and **6Q**, respectively) or [(*E*)-2-phenylvinyl]boronic acid (**6R**) also proceeded to afford the corresponding

adducts **7aP-aR** in 64-94% yield and 84-95% ee.

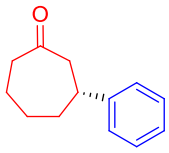
Next, this author investigated the scope of the enones in the asymmetric 1,4-addition in water catalyzed by PS-PEG-diene*-Rh (**4**) (**Scheme 3**).

Scheme 3. Scope of Enones[a]

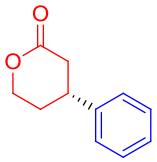




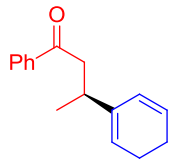
7bA
87% yield, 95% ee[b]



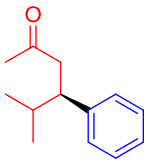
7cA
59% yield, 89% ee[b]



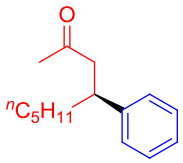
7dA
41% yield, 75% ee[b]



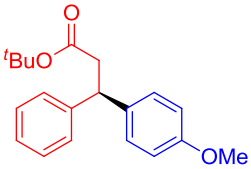
7eA
82% yield, 94% ee



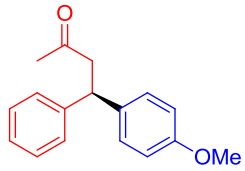
7fA
74% yield, 96% ee[b]



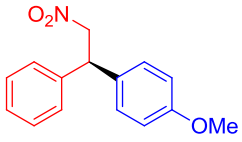
7gA
66% yield, 97% ee



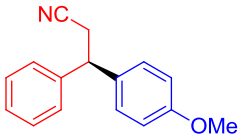
7hC
58% yield, 97% ee[c]



7iC
77% yield, 94% ee[d]



7jC
52% yield, 56% ee[b]

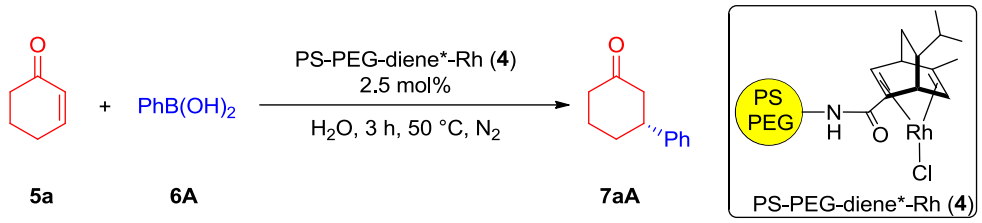


7kC
12% yield, 51% ee[b]

[a]Reaction conditions: enone **5** (0.3 mmol), arylboronic acid **6** (0.45 mmol), PS-PEG-diene*-Rh (**4**; 2.5 mol % Rh), H_2O (1 mL), 50 °C, 3 h. Isolated yields are shown. The ee values were determined by HPLC on a chiral stationary column. The absolute configurations of products 7 were assigned based on the basis of their optical rotations. [b]The reaction was performed for 6 h. [c]The reaction was performed in the presence of KOH (50 mol %) for 12 h. [d]The reaction was performed for 7 h.

Cyclopent-2-en-1-one (**5b**) on reaction for 6 h gave **7bA** in 87% yield with 95% ee. In the reaction of the 7-membered cyclic enone **5c**, the yield of the product **7cA** decreased to 59% yield, but a high enantioselectivity was retained. The reaction of 5,6-dihydro-2*H*-pyran-2-one (**5d**) proceeded for 6 h to afford the adduct **7dA** in moderate yield (41%) and moderate enantioselectivity (75% ee). Linear *E*-enones **5e-i** also underwent asymmetric 1,4-addition in water catalyzed by PS-PEG-diene*-Rh (**4**) to give the corresponding products **7eA-7iC** in 58-82% yield and excellent enantioselectivity (94-97% ee), whereas addition of 50 mol % of KOH was required to promote formation of **7hC**.[13] *β*-Nitrostyrene **5j** was also tolerated in the reaction, giving adduct **7jC** in moderate yield (52%) and moderate enantioselectivty (56% ee).[14] The reactivity of cinnamonitrile was poor; only a 12% of the adduct **7kC** was obtained, with moderate enantioselectivity.[15] The moderate enantioselectivity in the 1,4-addition of nitro- and cyanoolefins is probably due to coordination of the corresponding functional groups to the chiral rhodium center. The PS-PEG-diene*-Rh (**4**) displayed good recyclability (**Table 2**).

Table 2. Recycling experiment of PS-PEG-diene*-Rh (4) in the asymmetric 1,4-addition of 6A to 5a[a]



5a 6A 7aA

run	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
yield[b] (%)	91	92	92	89	92	94	92	93	90	91	91
ee[c] (%)	95	95	94	94	94	94	94	93	93	92	92

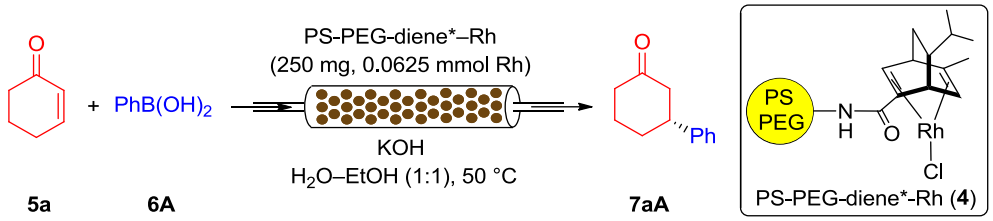
[a]Reaction conditions: enone **5a** (0.3 mmol), $PhB(OH)_2$ (**6A**; 0.45 mmol), PS-PEG-diene*-Rh (**4**; 2.5 mol % Rh), H_2O (1 mL), 50 °C, 3 h. [b]Isolated yields. [c]Determined by HPLC on a chiral stationary column (Daicel CHIRALCEL AD-H).

After completion of the asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) under the optimized conditions, ethyl acetate was added. Under an inert atmosphere, the catalyst was then separated from the reaction mixture by simple filtration, washed with ethyl acetate, and dried in vacuo before being reused in subsequent runs. The catalyst was successfully reused 10 times without loss of its catalytic activity or enantioselectivty. The 11th reaction run still gave (*R*)-3-phenylcyclohexanone **7aA** in 91% yield and 92% ee. ICP analysis of the recovered catalyst after the 11th run showed 29.2% of the rhodium content

was leached from the initial catalyst. In fact, after the 11th reaction run, the activity of the catalyst gradually decreased.

The success of the asymmetric 1,4-addition reaction under batch conditions prompted us to apply the PS-PEG-diene*-Rh (**4**) in a continuous-flow reaction. Continuous-flow organic reactions provide remarkable advantages in terms of improved safety, high efficiency, precise control of reaction conditions, and simple scale-up.[16] Consequently, switching to the continuous-flow reactions to realize further efficient, practical, and green sustainable transformations has become an important recent challenge in organic chemistry. The continuous-flow asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) catalyzed by PS-PEG-diene*-Rh (**4**) was carried out in a flow reactor (**Table 3**).

Table 3. Optimization for the continuous-flow asymmetric 1,4-addition[a]



entry	**5a** (mM)	KOH (mM)	flow rate (mL/min)	contact time (s)	conv[b] (%)
1	25		1.0	29	0
2	25	25	1.0	29	>99
3	25	25	2.0	15	>99
4	50	50	2.0	15	>99
5	50	50	3.0	10	97 (79[c], 96[d])

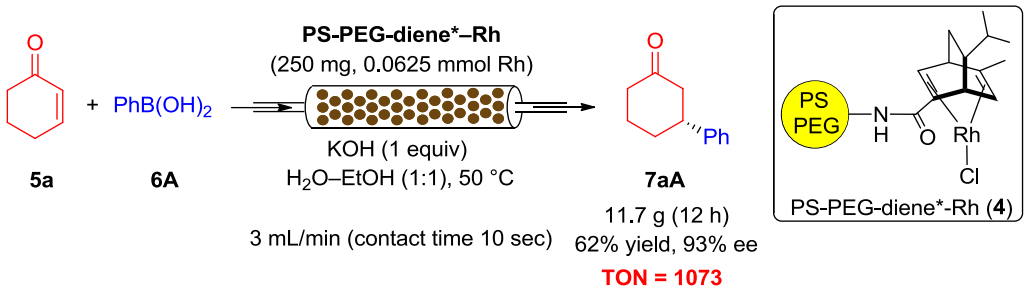
[a]Reaction conditions: 1:1 (v/v) H_2O-EtOH solution containing cyclohex-2-en-1-one (**5a**, 25 or 50 mM), $PhB(OH)_2$ (**6A**, 1.5 equiv), and KOH (0 or 1 equiv) was introduced into a flow reactor equipped with a cartridge of PS-PEG-diene*-Rh **4** (250 mg, 0.0625 mmol Rh) at 50 °C at a flow rate of 1.0−3.0 mL/min. [b]Determined by GC-MS. [c]Isolated yield. [d]Enantiomeric excess as determined by HPLC on a chiral stationary column (DAICEL CHIRALCEL AD-H).

A solution of **5a** (25 mM) and **6A** (37.5 mM, 1.5 equiv) in a 1:1 mixture of H_2O and EtOH[17] was introduced into the reactor at a flow rate of 1.0 mL/min and passed through a catalyst cartridge (internal diameter: 4 mm; length: 70 mm), charged with PS-PEG-diene*-Rh (**4**; 250 mg, 0.0625

mmol Rh) at 50 °C. The contact time of the solution with the catalyst was 29 s. However, no reaction occurred in this case (entry 1). The addition of 1 equiv of KOH (25 mM) significantly promoted the reaction, which was complete within 29 s (entry 2).[13] When the flow rate was increased to 2.0 mL/min (contact time: 15 s), full conversion of the substrates was observed (entry 3). Increasing the concentration of the substrate solution to 50 mM did not affect the conversion (entry 4). Further increasing the flow rate to 3 mL/min (contact time: 10 s) in the flow reaction using 50 mM solution still maintained a high activity (97% conversion).[18] The desired (*R*)-3-phenylcyclohexan-1-one (**7aA**) was obtained in 79% isolated yield with 96% ee (entry 5).

Long-term continuous-flow asymmetric 1,4-addition catalyzed by PS-PEG-diene*-Rh (**4**) was conducted under the optimized flow conditions [**5a** (50 mM), **6A** (75 mM), and KOH (50 mM) in H_2O-EtOH (1:1), 50 °C, flow rate = 3.0 mL/min, contact time 10 s] (**Scheme 4**).

Scheme 4. Long-Term continuous-flow asymmetric 1,4-addition



The continuous-flow asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) for 12 h produced 11.7 g of (*R*)-3-phenylcyclohexanone (**7aA**; total yield: 62%) with excellent enantioselectivity (93% ee). The total TON of the catalyst reached 1073 for 12 h.

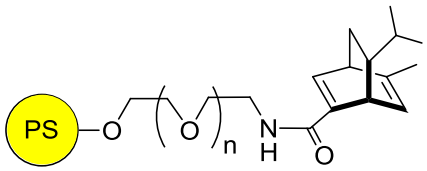
Conclusion

In conclusion, this author has developed a rhodium-chiral diene complex immobilized on amphiphilic polystyrene-poly-(ethylene glycol) (PS-PEG) resin that efficiently catalyzes the asymmetric 1,4-addition of various arylboronic acids to cyclic or linear enones in water under batch conditions to give the corresponding *β*-arylated carbonyl compounds in excellent yields and with enantioselectivity. The catalyst was readily recovered by simple filtration and reused 10 times without loss of its catalytic activity or enantioselectivity. Moreover, the immobilized rhodium-chiral diene complex was successfully applied in a continuous-flow reaction. In a flow reactor containing the immobilized rhodium-chiral diene complex, the asymmetric 1,4-addition at 50 °C was completed in 10 s at 50 °C with retention of high enantioselectivity. Long-term continuous-flow asymmetric 1,4-addition readily accomplished a 10-g-scale synthesis of the desired adduct with high enantioselectivity.

Experimental Section

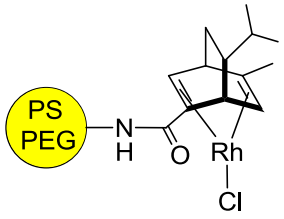
General Methods. All chemicals were commercially available and were used without further purification unless otherwise mentioned. PS-PEG-amino resin (TentaGel S NH_2; average diameter 0.90 mm, 1% divinylbenzene cross-linked, loading value of amino residue 0.2-0.3 mmol/g) was purchased from Rapp Polymere. Water was deionized with a Millipore system to Milli-Q grade. NMR spectra were recorded at 25 °C on a JEOL JNM-ECS400 spectrometer (396 MHz for ^{1}H, 100 MHz for $^{13}C\{^{1}H\}$) or a JEOL JNM-AL400 spectrometer (100 MHz for ^{13}C). Chemical shifts for ^{1}H NMR are reported in δ ppm referenced to an internal tetramethylsilane (TMS) as a standard or to the solvent peak. Chemical shifts for ^{13}C NMR are given relative to the solvent peak as an internal standard. HPLC analysis was performed on a JASCO HPLC system equipped with CD-2095plus, MD-2015plus, RI-930, UV-1570, PU-1580, and DG-2080−53. GC analysis was carried out on a Hewlett-Packard 4890 system. GC−MS data were collected with an Agilent 6890 GC/5973N MS detector or a JEOL AccuTOF GC JMS-T100GC equipped with Agilent 6890N GC. Optical rotations were recorded on a JASCO P-1020 polarimeter. ICP analysis was performed on a LEEMAN LABORATORIES Profile plus plasma spectrometer. The continuous-flow reaction was carried out in an X-Cube reactor system (ThalesNano Nanotechnology Inc., Budapest) with no gas mode.

Preparation of PS-PEG-Diene* (3). A mixture of (1*R*,4*R*,7*R*)-7-



isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid[7e] (0.21 g, 1.0 mmol), PS-PEG-NH_2 (**1**) (2.6 g, 0.7 mmol), EDCI·HCl (0.58 g, 3.0 mmol), HOBt·H_2O (0.46 g, 3.0 mmol), and DMAP (0.037 g, 0.3 mmol) in DMF (20 mL) was shaken at 30 °C for 18 h until the reaction was complete as demonstrated by a Kaiser test.[19] The resulting PS-PEG-diene* was collected by filtration, washed with DMF (5 × 12 mL) and EtOAc (5 × 12 mL), and dried under vacuum for 24 h to give white beads: 2.5 g (91%); $^{13}C\{^1H\}$ SR-MAS NMR (100 MHz, $CDCl_3$) δ 164.3, 143.2, 142.3, 136.5, 126.4, 122.9, 111.0, 69.1, 46.3, 42.1, 38.3, 37.9, 32.4, 30.5, 20.6, 20.1, 17.6.

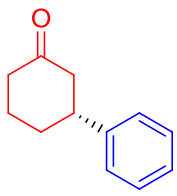
Preparation of PS-PEG-Diene*-Rh (4). A mixture of PS-PEG-diene* (**3**;



0.78 g, 0.2 mmol) and $[RhCl(coe)_2]_2$ (0.090 g, 0.125 mmol) in CH_2Cl_2 (8 mL) was shaken at 30 °C for 18 h under N_2. The resulting PS-PEG-diene*-Rh was collected by filtration, washed with dichloromethane (5 × 8 mL), and dried under vacuum for 15 h to give brown beads: 0.79 g (97%); $^{13}C\{^1H\}$ SR-MAS NMR (100 MHz, $CDCl_3$) δ 168.1, 144.0, 126.7, 105.8, 104.5, 69.1, 54.2, 50.0, 46.2, 44.5, 42.8, 38.2, 29.4, 19.5. ICP analysis; 0.25 mmol Rh/g.

Asymmetric 1,4-Addition of Arylboronic Acids 6 to Enones 5 with PS-PEG-diene*-Rh 4. General Procedure. PS-PEG-diene*-Rh (**4**) (30.0 mg, 0.0075 mmol) and arylboronic acid **6** (0.45 mmol) were charged to a vial under an inert atmosphere. After addition of degassed H_2O (1 mL) and enone **5** (0.3 mmol), the mixture was shaken at 50 °C for 3 h. After being cooled to room temperature, the resulting mixture was filtered using a Bond Elut reservoir. The polymer catalyst was washed with ethyl acetate (5 × 3 mL). The filtrates were combined and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography with *n*-hexane and ethyl acetate to afford the corresponding *β*-arylated carbonyl adducts **7**.

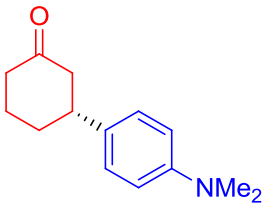
(*R*)-3-Phenylcyclohexanone (7aA).[5a,7a,e] The product was isolated by



silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (47.6 mg, 91% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 19.4 °C) δ 7.34 (t, J = 7.5 Hz, 2H), 7.26-7.22 (m, 3H), 3.01 (tt, J = 11.9 and 3.6 Hz, 1H), 2.63-2.34 (m, 4H), 2.18-2.08 (m, 2H), 1.91-1.76 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 211.1, 144.3, 128.7, 126.7, 126.5, 48.9, 44.7, 41.2, 32,7, 25.5; MS (GC-EI, *m*/*z*) 174.2 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 13.76 min for minor isomer, t_R = 15.58 min for major isomer];

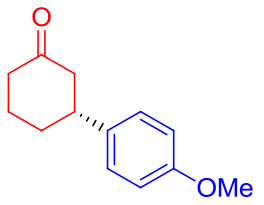
$[\alpha]^{22}_{D}$ +20.6 (*c* 1.6, $CHCl_3$).

(*R*)-3-[4-(Dimethylamino)phenyl]cyclohexanone (7aB).[20] The product



was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (56.7 mg, 87% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.6 °C) δ 7.10 (dt, *J* = 8.7 and 3.2 Hz, 2H), 6.71 (dt, *J* = 9.1 and 3.2 Hz, 2H), 2.96-2.89 (m and s, 7H), 2.59-2.35 (m, 4H), 2.15-2.03 (m, 2H), 1.82-1.72 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.0 °C) δ 211.6, 149.4, 132.4, 127.1, 112.8, 49.3, 43.9, 41.2, 40.7, 33.0, 25.5; HRMS (GC-TOF-EI, *m*/*z*) calcd for $C_{14}H_{19}NO$ (M) 217.1467, found 217.1455; 92% ee [HPLC conditions: two Chiralcel OD-H columns, hexane/*i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 49.43 min for major isomer, t_R = 68.67 min for minor isomer]; $[\alpha]^{23}_{D}$ +19.9 (*c* 2.7, $CHCl_3$).

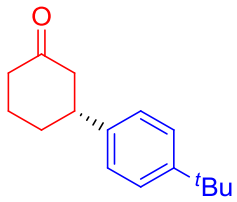
(*R*)-3-(4-Methoxyphenyl)cyclohexanone (7aC).[5c,7a,e] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.33) as a colorless oil (60.7 mg, 99% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 7.14 (dt, *J* = 8.7 and 3.2 Hz, 2H), 6.87 (dt, *J* = 8.7 and 3.2 Hz, 2H), 3.79 (s, 3H), 2.96 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59-2.36 (m, 4H), 2.16-2.04 (m, 2H), 1.83-1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$,

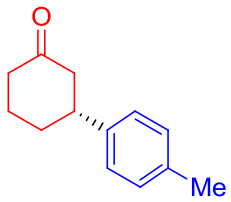
20.3 °C) δ 211.2, 158.2, 136.5, 127.4, 113.9, 55.2, 49.2, 43.9, 41.1, 32.9, 25.4; MS (GC-EI, *m*/*z*) 204.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 100:1, flow rate 0.6 mL/min, wavelength = 249 nm, t_R = 18.56 min for minor isomer, t_R = 19.35 min for major isomer]; $[\alpha]^{24}_D$ +17.7 (*c* 1.8, $CHCl_3$).

(*R*)-3-(4-tert-Butylphenyl)cyclohexanone (7aD).[8a] The product was



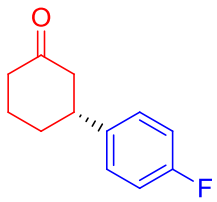
isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.58) as a white solid (47.0 mg, 68% yield): mp 39-40 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.0 °C) δ 7.35 (dt, *J* = 8.3 and 2.0 Hz, 2H), 7.16 (dt, *J* = 7.9 and 1.6 Hz, 2H), 2.98 (tt, *J* = 11.5 and 3.9 Hz, 1H), 2.61-2.37 (m, 4H), 2.17-2.06 (m, 2H), 1.86-1.75 (m, 2H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.3 °C) δ 211.3, 149.5, 141.3, 126.2, 125.5, 49.0, 44.2, 41.2, 34.4, 32,8, 31.3, 25.6; MS (GC-EI, *m*/*z*) 230.2 (M); 91% ee [HPLC conditions: Chiralcel OJ-H column, hexane/*i*PrOH = 97:3, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 16.65 min for minor isomer, t_R = 18.55 min for major isomer]; $[\alpha]^{24}_D$ +13.6 (*c* 0.6, $CHCl_3$).

(*R*)-3-(4-Methylphenyl)cyclohexanone (7aE).[7a,8a] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (45.2 mg, 80% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.15-7.10 (m, 4H), 2.96 (tt, J = 11.9 and 4.3 Hz, 1H), 2.59-2.34 (m, 4H), 2.33 (s, 3H), 2.16-2.04 (m, 2H), 1.85-1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 211.2, 141.4, 136.2, 129.3, 126.4, 49.0, 44.3, 41.1, 32.8, 25.5, 21.0; MS (GC-EI, *m*/*z*) 188.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 97:3, flow rate 0.6 mL/min, wavelength = 249 nm, t_R = 11.46 min for minor isomer, t_R = 12.49 min for major isomer]; $[\alpha]^{24}_D$ +10.1 (*c* 2.05, $CHCl_3$).

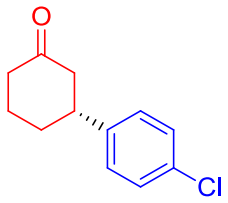
(*R*)-3-(4-Fluorophenyl)cyclohexanone (7aF).[7a,8a] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (52.5 mg, 91% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.21-7.16 (m, 2H), 7.05-6.99 (m, 2H), 3.00 (tt, J = 11.9 and 3.6 Hz, 1H), 2.60-2.37 (m, 4H), 2.17-2.06 (m, 2H), 1.88-1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.1 °C) δ 210.7, 161.5 (d, J = 245 Hz), 140.0 (d, J = 2.9 Hz), 127.9 (d, J = 7.7 Hz), 115.4 (d, J = 21 Hz), 49.0, 43.9, 41.1, 32,8, 25.3; MS (GC-EI, *m*/*z*) 192.2 (M); 96% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength =

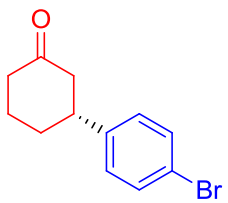
249 nm, t_R = 12.61 min for minor isomer, t_R = 14.68 min for major isomer]; $[\alpha]^{23}_D$ +11.3 (*c* 1.7, $CHCl_3$).

(*R*)-3-(4-Chlorophenyl)cyclohexanone (7aG).[8a] The product was isolated



by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (62.0 mg, 99% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 19.8 °C) δ 7.29 (dt, *J* = 8.7 and 1.9 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 2.99 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59-2.33 (m, 4H), 2.18-2.05 (m, 2H), 1.87-1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 21.5 °C) δ 210.5, 142.7, 132.3, 128.7, 127.9, 48.7, 44.0, 41.1, 32.6, 25.3; MS (GC-EI, *m*/*z*) 208.2 (M); 96% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 98:2, flow rate 0.8 mL/min, wavelength = 249 nm, t_R = 12.98 min for minor isomer, t_R = 13.84 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (*c* 1.2, $CHCl_3$).

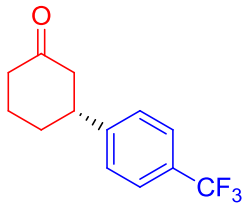
(*R*)-3-(4-Bromophenyl)cyclohexanone (7aH).[8b] The product was isolated



by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (69.1 mg, 91% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.98 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59-2.33 (m, 4H), 2.17-2.05 (m, 2H), 1.87-1.71 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.8 °C) δ 210.5, 143.2, 131.7, 128.3, 120.3, 48.7, 44.1,

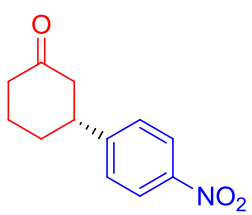
41.1, 32, 6, 25.3; MS (GC-EI, *m*/*z*) 252.1 (M); 96% ee [HPLC conditions: Chiralcel OJ-H column, hexane/*i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 33.88 min for minor isomer, t_R = 37.04 min for major isomer]; $[\alpha]^{23}_D$ +6.8 (*c* 1.2, $CHCl_3$).

(*R*)-3-[4-(Trifluoromethyl)phenyl]cyclohexanone (7aI).[7a] The product



was isolated by silica gel column chromatography (nhexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (69.8 mg, 96% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 21.1 °C) δ 7.59 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 3.09 (tt, J = 11.5 and 4.0 Hz, 1H), 2.63-2.36 (m, 4H), 2.21-2.08 (m, 2H), 1.93-1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.8 °C): δ 210.2, 148.2, 129.0 (q, J = 32.4 Hz), 127.0, 125.7 (q, J = 3.8 Hz), 124.1 (d, J = 271.8 Hz), 48.5, 44.5, 41.1, 32,5, 25.4; MS (GC-EI, m/z) 242.2 (M); 98% ee [HPLC conditions: two Chiralcel OD-H columns, hexane/*i*PrOH = 97:3, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 20.19 min for major isomer, t_R = 21.68 min for minor isomer]; $[\alpha]^{22}_D$ +11.4 (*c* 3.4, $CHCl_3$).

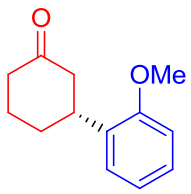
(*R*)-3-(4-Nitrophenyl)cyclohexanone (7aJ).[21] The product was isolated



by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (59.2 mg, 90% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.9 °C) δ 8.20 (d,

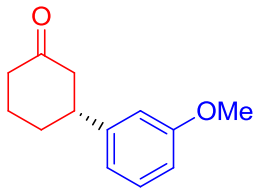
J = 7.9 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 3.15 (tt, J = 11.5 and 4.0 Hz, 1H), 2.64-2.37 (m, 4H), 2.22-2.11 (m, 2H), 1.95-1.77 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 21.1 °C) δ 209.6, 151.5, 146.8, 127.5, 124.0, 48.2, 44.4, 41.0, 32.3, 25.3; HRMS (GC-TOF-EI, m/z) calcd for $C_{12}H_{13}NO_3$ (M) 219.0895, found 219.0900; 94% ee [HPLC conditions: Chiralcel AS-H column, hexane/*i*PrOH = 9:1, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 38.07 min for minor isomer, t_R = 43.19 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (c 0.7, $CHCl_3$).

(*R*)-3-(2-Methoxyphenyl)cyclohexanone (7aK).[8a] The product was



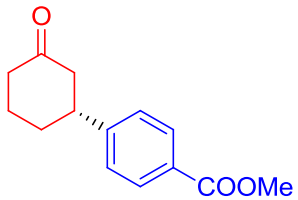
isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.41) as a colorless oil (60.7 mg, 99% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.6 °C) δ 7.22 (dd, J = 7.5 and 2.0 Hz, 1H), 7.19 (td, J = 7.9 and 1.6 Hz, 1H), 6.94 (td, J = 7.5 and 1.6 Hz, 1H), 6.87 (dd, J = 8.3 and 0.8 Hz, 1H), 3.81 (s, 3H), 3.41 (tt, J = 11.9 and 4.0 Hz, 1H), 2.60-2.36 (m, 4H), 2.14-2.00 (m, 2H), 1.92-1.71 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 20.6 °C) δ 211.7, 156.6, 132.4, 127.5, 126.5, 120.6, 110.5, 55.2, 47.5, 41.3, 37.9, 30.9, 25.5; MS (GC-EI, m/z) 204.1 (M); 87% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 97:3, flow rate 0.7 mL/min, wavelength = 249 nm, t_R = 12.68 min for minor isomer, t_R = 13.81 min for major isomer]; $[\alpha]^{24}_D$ +36.4 (c 0.97, $CHCl_3$).

(*R*)-3-(3-Methoxyphenyl)cyclohexanone (7aL).[5a,7a] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.33) as a colorless oil (49.6 mg, 81% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.25 (td, J = 7.5 and 0.8 Hz, 1H), 6.83-6.76 (m, 3H), 3.81 (s, 3H), 2.97 (tt, J = 11.9 and 4.4 Hz, 1H), 2.62-2.37 (m, 4H), 2.18-2.07 (m, 2H), 1.87-1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.6 °C): δ 211.0, 159.8, 146.0, 129.7, 118.9, 112.7, 111.6, 55.2, 48.9, 44.7, 41.2, 32.6, 25.5; MS (GC-EI, *m*/*z*) 204.2 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane/ *i*PrOH = 90:10, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 14.92 min for major isomer, t_R = 15.74 min for minior isomer]; $[\alpha]^{25}_D$ +15.1 (*c* 1.1, $CHCl_3$).

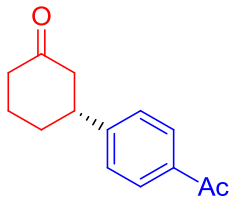
(*R*)-Methyl-4-(3-oxocyclohexyl)benzoate (7aM).[11] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (56.4 mg, 81% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.0 °C) δ 8.00 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.91 (s, 3H), 3.08 (tt, J = 11.9 and 3.9 Hz, 1H), 2.63-2.35 (m, 4H), 2.20-2.05 (m, 2H), 1.93-1.70 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.4 °C) δ 210.4, 166.8, 149.4, 130.0, 128.6, 126.6, 52.1, 48.4, 44.6, 41.1, 32,4, 25.4; MS (GC-EI, *m*/*z*) 232.1 (M); 96% ee [HPLC conditions: Chiralcel OJ-H

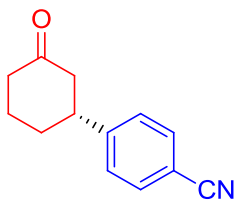
column, hexane/*i*PrOH = 97:3, flow rate 0.8 mL/min, wavelength = 249 nm, t_R = 90.63 min for minor isomer, t_R = 96.09 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (*c* 0.9, $CHCl_3$).

(*R*)-3-(4-Acetylphenyl)cyclohexanone (7aN).[8c] The product was isolated



by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.16) as a colorless oil (64.2 mg, 99% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 7.94 (dt, *J* = 8.7 and 2.0 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.09 (tt, *J* = 11.5 and 3.6 Hz, 1H), 2.63-2.40 (m, 7H), 2.21-2.08 (m, 2H), 1.91-1.77 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 210.3, 197.6, 149.6, 135.7, 128.8, 126.8, 48.4, 44.6, 41.1, 32.4, 26.6, 25.4; MS (GC-EI, *m*/*z*) 216.1 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 34.32 min for major isomer, t_R = 40.32 min for minor isomer]; $[\alpha]^{23}_D$ +14.7 (*c* 2.1, $CHCl_3$).

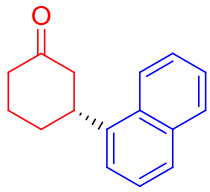
(*R*)-3-(4-Cyanophenyl)cyclohexanone (7aO).[22] The product was isolated



by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.19) as a colorless oil (57.4 mg, 96% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.4 °C) δ 7.65 (dt, *J* = 8.7 and 2.0 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 3.10 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.63-2.39 (m, 4H), 2.21-2.09 (m, 2H), 1.90-1.78 (m, 2H); ^{13}C{^{1}H}

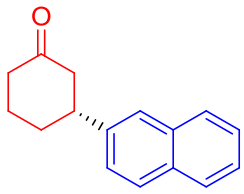
NMR (100 MHz, $CDCl_3$, 20.3 °C) δ 209.8, 149.5, 132.5, 127.4, 118.7, 110.6, 48.1, 44.5, 40.9, 32.2, 25.2; HRMS (GC-TOF-EI, *m*/*z*) calcd for $C_{13}H_{13}NO$ (M) 199.0997, found 199.0982; 97% ee [HPLC conditions: Chiralcel OJ-H column, hexane/*i*PrOH = 97:3, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 66.62 min for minor isomer, t_R = 70.05 min for major isomer]; $[\alpha]^{23}_D$ +1.8 (*c* 0.9, $CHCl_3$).

(*R*)-3-(1-Naphthyl)cyclohexanone (7aP).[8a] The product was isolated by



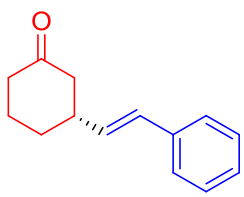
silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.45) as a white solid (82.9 mg, 92% yield): mp 69-71 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 7.54-7.37 (m, 4H), 3.84 (tt, *J* = 11.5 and 4.0 Hz, 1H), 2.78-2.40 (m, 4H), 2.24-2.15 (m, 2H), 2.04−1.87 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, 19.9 °C) δ 211.3, 140.0, 133.9, 130.8, 129.0, 127.2, 126.2, 125.6, 125.5, 122.6, 122.4, 48.5, 41.4, 39.3, 32.2, 25.5; MS (GC-EI, *m*/*z*) 224.2 (M); 84% ee [HPLC conditions: Chiralcel AS-H column, hexane/*i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 12.62 min for major isomer, t_R = 21.23 min for minor isomer]; $[\alpha]^{24}_D$ +53.2 (*c* 1.4, $CHCl_3$).

(*R*)-3-(2-Naphthyl)cyclohexanone (7aQ).[7a,8a] The product was isolated



by silica gel column chromatography (n-hexane/ethyl acetate = 5:1, R_f = 0.43) as a white solid (84.7 mg, 94% yield): mp 69-71 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 19.9 °C) δ 7.82-7.79 (m, 3H), 7.64 (s, 1H), 7.50-7.46 (m, 2H), 7.36 (dd, J = 7.9 and 1.6 Hz, 1H), 3.17 (tt, J = 11.1 and 7.5 Hz, 1H), 2.69-2.60 (m, 2H), 2.51-2.37 (m, 2H), 2.21-2.14 (m, 2H), 2.00-1.78 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.6 °C) δ 211.0, 141.7, 133.5, 132.3, 128.3, 127.6, 127.6, 126.2, 125.6, 125.3, 124.7, 48.8, 44.8, 41.2, 32.7, 25.5; MS (GC-EI, *m*/*z*) 224.1 (M); 95% ee [HPLC conditions: Chiralcel AS-H column, hexane/*i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 22.49 min for major isomer, t_R = 31.89 min for minor isomer]; $[\alpha]^{23}_D$ +47.3 (*c* 1.4, $CHCl_3$).

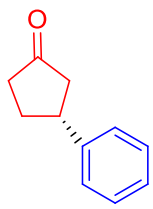
(*R*)-3-[(1*E*)-2-Phenylethenyl]cyclohexanone (7aR).[5b,7e] The product was



isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.49) as a colorless oil (53.1 mg, 64% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.36-7.20 (m, 5H), 6.39 (dd, J = 15.8 and 0.8 Hz, 1H), 6.16 (dd, J = 15.8 and 7.1, 1H), 2.69-2.66 (m, 1H), 2.56-2.50 (m, 1H), 2.44-2.37 (m, 1H), 2.36-2.28 (m, 2H), 2.11-2.07 (m, 1H), 2.05-1.99 (m, 1H), 1.78-1.68 (m 1H), 1.67-1.58 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.0 °C) δ

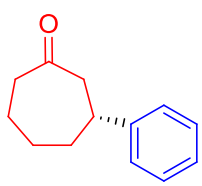
210.9, 137.1, 132.9, 129.1, 128.6, 127.4, 126.1, 47.4, 41.9, 41.3, 31.4, 25.0; MS (GC-EI, *m*/*z*) 200.2 (M); 91% ee [HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 17.49 min for minor isomer, t_R = 19.55 min for major isomer]; $[\alpha]^{25}_D$ −7.1 (*c* 1.0, $CHCl_3$).

(*R*)-3-Phenylcyclopentanone (7bA).[7a,8a] The product was isolated by



silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (41.8 mg, 87% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 19.6 °C) δ 7.35 (t, *J* = 6.7 Hz, 2H), 7.27-7.26 (m, 3H), 3.43 (tt, *J* = 11.1 and 4.0 Hz, 1H), 2.67 (dd, *J* = 18.2 and 7.9 Hz, 1H), 2.51-2.26 (m, 4H), 2.05-1.94 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.5 °C) δ 218.5, 143.0, 128.7, 126.7, 45.8, 42.2, 38.9, 31.2; MS (GC-EI, *m*/*z*) 160.2 (M); 95% ee [HPLC conditions: two Chiralcel AS-H columns, hexane/*i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 83.69 min for major isomer, t_R = 97.96 min for minor isomer]; $[\alpha]^{23}_D$ +47.3 (*c* 1.01, $CHCl_3$).

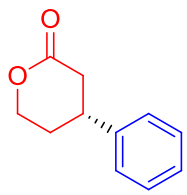
(*R*)-3-Phenylcycloheptanone (7cA).[7a,8a] The product was isolated by



silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.55) as a colorless oil (33.3 mg, 59% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.8 °C) δ 7.31 (tt, *J* = 7.5 and 1.6

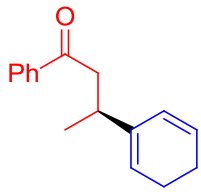
Hz, 2H), 7.23-7.17 (m, 3H), 2.98-2.90 (m, 2H), 2.67-2.58 (m, 3H), 2.12-1.98 (m, 3H), 1.77-1.69 (m, 2H), 1.52-1.48 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 20.7 °C) δ 213.6, 146.9, 128.6, 126.4, 126.3, 51.2, 43.9, 42.7, 39.2, 29,2, 24.2; MS (GC-EI, *m*/*z*) 188.1 (M); 89% ee [HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 16.95 min for minor isomer, t_R = 18.20 min for major isomer]; $[\alpha]^{25}_D$ +49.8 (*c* 0.6, $CHCl_3$).

(*R*)-4-Phenyltetrahydro-2H-pyran-2-one (7dA).[8a] The product was

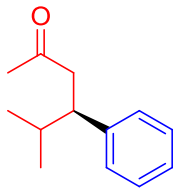


isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.19) as a colorless oil (21.7 mg, 41% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 22.0 °C) δ 7.37 (tt, *J* = 7.9 and 1.6 Hz, 2H), 7.28 (tt, *J* = 7.1 and 1.6 Hz, 1H), 7.21 (dt, *J* = 7.1 and 1.6 Hz, 2H), 4.54-4.49 (m, 1H), 4.40 (td, *J* = 11.0 and 3.6 Hz, 1H), 3.25 (tt, *J* = 10.3 and 5.1 Hz, 1H), 2.93 (ddd, *J* = 17.0, 5.9, and 1.2m, 1H), 2.64 (dd, *J* = 17.8 and 10.3 Hz, 1H), 2.21-2.15 (m, 1H), 2.10-2.00 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 22.1 °C) δ 170.6, 142.7, 128.9, 127.1, 126.4, 68.6, 37.4, 37.3, 30.2; MS (GC-EI, *m*/*z*) 176.1 (M); 75% ee [HPLC conditions: Chiralcel AS-H column, hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 18.53 min for major isomer, t_R = 23.74 min for minor isomer]; $[\alpha]^{23}_D$ −0.9 (*c* 0.4, $CHCl_3$).

(*S*)-1,3-Diphenylbutan-1-one (7eA).[10a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (55.2 mg, 82% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 22.0 °C) δ 7.92 (dt, J = 6.7 and 1.2 Hz, 2H), 7.54 (tt, J = 7.9 and 1.6 Hz, 1H), 7.44 (t, J = 7.9 Hz, 2H), 7.32-7.28 (m, 4H), 7.22-7.17 (m, 1H), 3.50 (sext, J = 7.10 Hz, 1H), 3.30 (dd, J = 17.0 and 5.9 Hz, 1H), 3.18 (dd, J = 17.0 and 8.3 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 22.0 °C) δ 199.0, 146.5, 137.1, 132.9, 128.5, 128.5, 128.0, 126.8, 126.2, 47.0, 35.5, 21.8; MS (GC-EI, *m*/*z*) 224.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 18.49 min for major isomer, t_R = 23.53 min for minor isomer]; $[\alpha]^{23}_D$ +13.6 (*c* 1.1, $CHCl_3$).

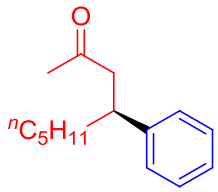


(*R*)-5-Methyl-4-phenylhexan-2-one (7fA).[5a,7a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.69) as a colorless oil (42.2 mg, 74% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.27 (t, J = 6.7 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 2.92 (q, J = 5.9 Hz, 1H), 2.80-2.78 (m, 2H), 1.97 (s, 3H), 1.83 (sext, J = 7.1 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.74 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 208.4, 143.2, 128.2, 128.1, 126.2, 48.0, 47.6, 33.3, 30.6, 20.7,

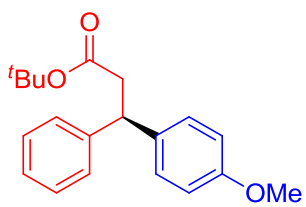


20.3; MS (GC-EI, *m*/*z*) 190.2 (M); 96% ee [HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH = 95:5, flow rate 0.7 mL/min, wavelength = 249 nm, t_R = 7.57 min for major isomer, t_R = 8.36 min for minor isomer]; $[\alpha]^{24}_D$ +27.2 (*c* 0.9, $CHCl_3$).

(*S*)-4-Phenylnonan-2-one (7gA).[5a,7e] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.69) as a colorless oil (43.2 mg, 66% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.2 °C) δ 7.28 (t, *J* = 7.1 Hz, 2H), 7.18 (t, *J* = 8.9 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 2H), 3.11 (quint, *J* = 7.5 Hz, 1H), 2.71 (dd, *J* = 7.1 and 1.6 Hz, 2H), 2.01 (s, 3H), 1.64-1.52 (m, 2H), 1.23-1.07 (m, 6H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.2 °C) δ 208.1, 144.6, 128.4, 127.4, 126.3, 50.9, 41.3, 36.4, 31.7, 30.7, 27.0, 22.5, 14.0; MS (GC-EI, *m*/*z*) 218.2 (M); 97% ee [HPLC conditions: two Chiralcel OD-H columns, hexane/*i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 29.23 min for major isomer, t_R = 31.72 min for minor isomer]; $[\alpha]^{24}_D$ +19.8 (*c* 1.2, $CHCl_3$).

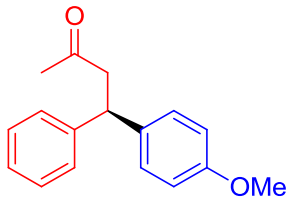


(*R*)-*tert*-Butyl 3-(4-Methoxyphenyl)-3-phenylpropanoate (7hC).[7d] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.72) as a white solid (54.4 mg, 58% yield): mp 67-



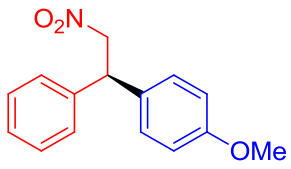
68 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.8 °C) δ 7.28-7.14 (m, 7H), 6.81 (dt, J = 8.3 and 2.0 Hz, 2H), 4.43 (t, J = 8.3 Hz, 1H), 3.76 (s, 3H), 2.92 (d, J = 7.9 Hz, 2H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.2 °C): δ 171.2, 158.1, 143.9, 135.7, 128.7, 128.4, 127.6, 126.3, 113.8, 80.4, 55.2, 46.6, 42.2, 27.8; MS (GC-EI, m/z) 312.2 (M); 97% ee [HPLC conditions: Chiralcel OJ-H column, hexane/*i*PrOH = 97:3, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 38.22 min for major isomer, t_R = 49.85 min for minor isomer]; $[\alpha]^{24}_D$ −0.9 (c 2.2, $CHCl_3$).

(*R*)-4-(4-Methoxyphenyl)-4-phenylbutan-2-one (7iC).[7c] The product



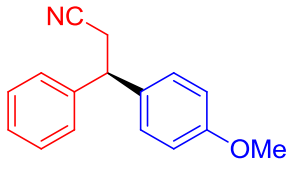
was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.40) as a colorless oil (58.8 mg, 77% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 19.9 °C) δ 7.28-7.12 (m, 7H), 6.80 (dt, J = 9.1 and 2.0 Hz, 2H), 4.53 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 3.14 (d, J = 7.1 Hz, 2H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.9 °C) δ 207.1, 158.0, 144.1, 135.9, 128.6, 128.5, 127.5, 126.3, 113.9, 55.1, 49.8, 45.2, 30.6; MS (GC-EI, m/z) 254.2 (M); 94% ee [HPLC conditions: Chiralcel OJ-H column, hexane/*i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 114.88 min for minor isomer, t_R = 120.98 min for major isomer]; $[\alpha]^{24}_D$ +0.64 (c 1.7, $CHCl_3$).

(*R*)-1-Methoxy-4-(2-nitro-1-phenylethyl)benzene (7jC).[7g] The product



was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.46) as a colorless oil (40.1 mg, 52% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.34-7.21 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.95 (d, J = 7.9 Hz, 2H), 4.86 (t, J = 7.9 Hz, 1H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.4 °C) δ 158.9, 139.5, 131.2, 129.0, 128.7, 127.5, 127.5, 114.4, 79.4, 55.2, 48.2; MS (GC-EI, *m*/*z*) 257.1 (M); 56% ee [HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 77.36 min for minor isomer, t_R = 86.66 min for major isomer]; $[\alpha]^{23}_D$ +6.4 (*c* 1.0, $CHCl_3$).

(*R*)-3-(4-Methoxyphenyl)-3-phenylpropanenitrile (7kC).[7f] The product



was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (8.5 mg, 12% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.33 (tt, J = 7.5 and 1.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.15 (dt, J = 8.7 and 2.0 Hz, 2H), 6.86 (dt, J = 8.7 and 2.0 Hz, 2H), 4.33 (t, J = 7.5 Hz, 1H), 3.7 (s, 3H), 3.00 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.1 °C) δ 158.7, 141.5, 133.3, 128.8, 128.6, 127.4, 127.3, 118.5, 114.2, 55.2, 46.3, 24.4; MS (GC-EI, *m*/*z*) 237.2 (M); 51% ee [HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH = 8:2, flow rate 0.5 mL/min,

wavelength = 210 nm, t_R = 41.55 min for minor isomer, t_R = 46.68 min for major isomer]; $[\alpha]^{23}_D$ −6.4 (*c* 0.7, $CHCl_3$).

Recycling Experiment for Asymmetric 1,4-Addition of Phenylboronic Acid (6a) to Cyclohex-2-en-1-one (5a) with PS-PEG-Diene*-Rh (4). PS-PEG-Diene*-Rh (**4**) (100 mg, 0.025 mmol) and phenylboronic acid **6A** (183 mg, 1.5 mmol) were charged to a vial under inert atmosphere. After addition of degassed H_2O (3 mL) and cyclohex-2-en-1-one **5a** (96.1 mg, 1.0 mmol), the mixture was shaken at 50 °C for 3 h. After being cooled to room temperature, the resulting mixture was filtered under an inert atmosphere using a Bond Elut reservoir. The recovered catalyst was washed with ethyl acetate (5 × 3 mL), dried under vacuum, and reused in a subsequent reaction.

Continuous-Flow Reaction of Asymmetric 1,4-Addition of Phenylboronic Acid (6a) to Cyclohex-2-en-1-one (5a) with PS-PEG-Diene*-Rh (4). A solution of cyclohex-2-en-1-one (**5a**; 50 mM), phenylboronic acid (**6A**; 75 mM, 1.5 equiv), and KOH (50 mM, 1 equiv) in a 1:1 (v/v) mixture of H_2O and EtOH was introduced at a flow rate of 3.0 mL/min (contact time: 10 s) into an X-Cube reactor system fitted with a catalyst cartridge (ϕ 4.0 × 70 mm) containing PS-PEG-diene*-Rh (**4**) (250 mg, 0.0625 mmol Rh) (reaction volume in the cartridge of **4**: 0.48

mL). The flow reaction was carried out at 50 °C for 12 h. The resulting solution (2160 mL) was extracted three times with EtOAc, and the organic layers were combined and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford **7aA** (11.7 g, 62%, 93% ee).

References

(1) (a) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267-278. (b) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301-312. (c) Jessop, P. G. *Green Chem.* **2011**, *13*, 1391-1398 and references cited therein.

(2) (a) Dixneuf, P. H.; Cadierno, V. *Metal-Catalyzed Reactions in Water*; Wiley-VCH: Weinheim, 2013. (b) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725-748. (c) Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, *41*, 1415-1427 and references cited therein.

(3) For selected examples of studies on PS-PEG-supported transition-metal complex catalysts from the authors' group, see: (a) Uozumi, Y. *Top. Curr. Chem.* **2004**, *242*, 77-112. (b) Uozumi, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1183-1195. (c) Osako, T.; Torii, K.; Hirata, S.; Uozumi, Y. *ACS Catal.* **2017**, *7*, 7371-7377 and references cited therein.

(4) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829-2844. (b) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093-2105. (c) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95-119. (d) Heravi, M. M.; Dehghani, M.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2016**, *27*, 513-588 and references cited therein.

(5) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579-5580. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479-8482. (c) Takaya, Y.;

Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957-6961.

(6) Selected reviews: (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482-4502. (b) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett*. **2011**, 1345-1356. (c) Feng, X.; Du, H. Asian *J. Org. Chem.* **2012**, *1*, 204-213 and references cited therein.

(7) Selected examples: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508-11509. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628-1629. (c) Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 3213-3214. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821-3824. (e) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387-4389. (f) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589-592. (g) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172-175.

(8) Recent examples for chiral phosphine ligands in Rh-catalyzed 1,4 addition: (a) Lang, F.; Li, D.; Chen, J. M.; Chen, J.; Li, L. C.; Cun, L. F.; Zhu, J.; Deng, J. G.; Liao, J. *Adv. Synth. Catal.* **2010**, *352*, 843-846. (b) Berhal, F.; Esseiva, O.; Martin, C.-H.; Tone, H.; Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 2806-2809. (c) Falkowski, J. M.; Sawano, T.; Zhang, T.; Tsun, G.; Chen, Y.; Lockard, J. V.; Lin, W. *J. Am. Chem. Soc.* **2014**, *136*, 5213-5216.

(9) Hayashi and co-workers previously reported preparation of an amphiphilic resin (PS-PEG)-supported BINAP ligand and its use for rhodium-catalyzed asymmetric 1,4-addition in water: Otomaru, Y.; Senda, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3357-3359.

(10) Kobayashi and co-workers reported development of heterogeneous polymer-supported chiral rhodium nanoparticles and their application to asymmetric 1,4-addition in organic solvents: (a) Yasukawa, T.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 16963-16966. (b) Miyamura, H.; Nishino, K.; Yasukawa, T.; Kobayashi, S. *Chem. Sci.* **2017**, *8*, 8362-8372 and references cited therein.

(11) Cui and co-workers also reported chiral porous organic frameworks for the heterogeneous asymmetric 1,4-addition in 1,4-dioxane: Dong, J.; Liu, Y.; Cui, Y. *Chem. Commun.* **2014**, *50*, 14949-14952.

(12) Similar poor activity of a PS-PEG-supported palladium catalyst in organic solvents was reported: (a) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919-2920. (b) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2004**, *6*, 281-283.

(13) Addition of KOH enhances the catalytic activity due to formation of a more active rhodium−hydroxyl species, which significantly promotes the rhodium-catalyzed 1,4-addition; Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052-5058.

(14) (a) Li, R.; Wen, Z.; Wu, N. *Org. Biomol. Chem.* **2016**, *14*, 11080-11084.

(b) Fang, J.-H.; Jian, J.-H.; Chang, H.-C.; Kuo, T.-S.; Lee, W.-Z.; Wu, P.-Y.; Wu, H.-L. *Chem. - Eur. J.* **2017**, *23*, 1830-1838. See also ref 10b.

(15) Dziechciejewski, W. J.; Weber, R.; Sowada, O.; Boysen, M. M. K. *Org. Lett.* **2015**, *17*, 4132-4135. See also ref 7f.

(16) Recent typical reviews for flow chemistry: (a) Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327-360. (b) Kobayashi, S. *Chem. - Asian J.* **2016**, *11*, 425-436. (c) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796-11893. For our recent contribution to flow chemistry, see ref 3c.

(17) Because of the insolubility of the organic substrates in pure water, this author used a 1:1 mixture of H_2O and EtOH containing the substrates (25-50 mM) for the flow reaction.

(18) In general, a substrate in a solution can be converted with an excess amount of heterogeneous catalyst packed in a cartridge under flow conditions. Thus, a rapid full conversion was observed in the author's flow reaction.

(19) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595-598.

(20) Identification of the racemic product was reported: Hu, X.; Martin, D.; Melaimi, M.; Bertrand, D. *J. Am. Chem. Soc.* **2014**, *136*, 13594-13597. The absolute configuration was tentatively assigned on the basis of the mechanistic similarity of the asymmetric induction.

(21) Identification of the racemic product was reported; Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 17747-17750. The absolute configuration was tentatively assigned on the basis of the mechanistic similarity of the asymmetric induction.

(22) Ma, H.-C.; Kan, J.-L.; Chen, G.-J.; Chen, C.-X.; Dong, Y.-B. *Chem. Mater.* **2017**, *29*, 6518-6524.

Chapter 4

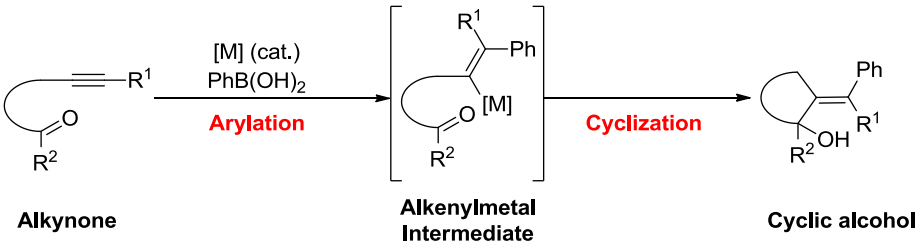
Asymmetric Arylative Cyclization of Alkynones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex in Water

Guanshuo Shen, Yasuhiro Uozumi, Unpublished

Introduction

Transition metal catalyzed tandem reactions have been proved to be an efficient and atom-economic method for the preparation of cyclic compounds from alkynones. The process involved intermolecular carbometallation of organometal species onto the C-C triple bond, following the intramolecular cyclization of the newly generated alkenylmetal intermediate onto the carbonyl group, and finally the protonolysis with water to release the allylic alcohol product (**Scheme 1**).

Scheme 1. Transition metal catalyzed arylative cyclization

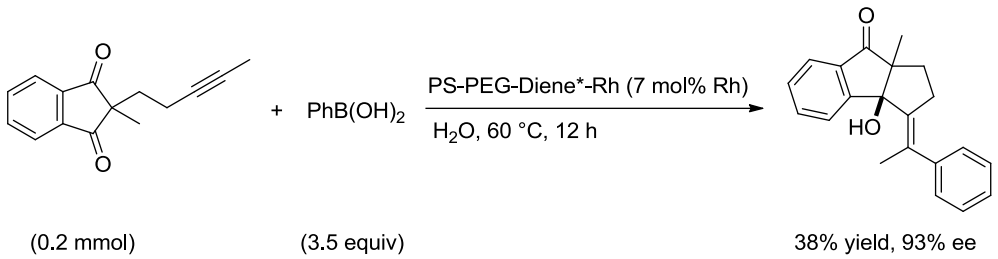


The research groups of Hayashi[1], Murakami[2], and Lam[3] *et al* have contributed greatly to this field. Although these elegant protocols have emerged, however, in the transition metal, especially rhodium or iridium, catalyzed the tandem reaction of alkyne substituted cyclic-diketone to prepare the useful bicyclic molecules[4], the racemic and ring expansion product or 1,4-migration product was always observed. Moreover, these reactions are generally performed in organic solvents under homogeneous conditions. The conversion of the asymmetric arylative cyclization of

alkynones to produce polycycle products into the green sustainable process in water remains underexplored. In addition, previously, this author has developed a rhodium-chiral diene complex immobilized on an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin (PS-PEG-diene*-Rh) and its use in the asymmetric 1,4-addition of arylboronic acids to enones in water under heterogeneous conditions.[5]

Herein, this author examined the asymmetric arylative cyclization of alkynones with arylboronic acids in water under heterogeneous conditions. Based on this author's initial results, the immobilized rhodium-chiral diene complex promoted the asymmetric arylative cyclization of 2-methyl-2-(pent-3-yn-1-yl)-1*H*-indene-1,3(2*H*)-dione with phenylboronic in water to give the corresponding bicyclic chiral alcohol in excellent enantioselectivity with a moderate yield. Further improvement of the yield of the desired product is ongoing (**Scheme 2**).

Scheme 2. PS-PEG-diene*-Rh catalyzed asymmetric arylative cyclization in water

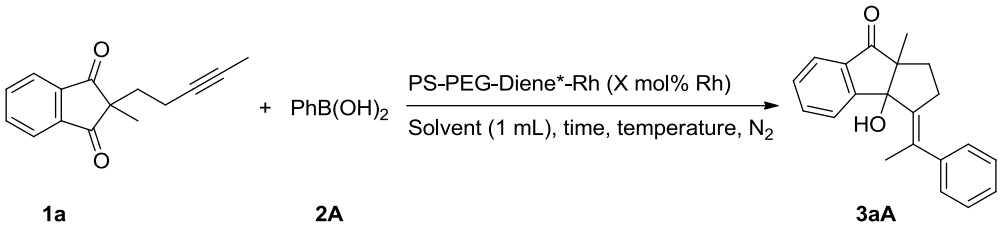


Results and Discussion

Initially, this author screened the reaction conditions for the asymmetric arylative cyclization of alkynone (**1a**) with phenylboronic acid (**2A**) in the presence of PS-PEG-diene*-Rh (**Table 1**). The reaction of **1a** with **2A** (3.5 equiv) in the presence of PS-PEG-diene*-Rh (2.5 mol % Rh) in H_2O at 60 °C for 12 h, giving (*E*)-3a-hydroxy-8a-methyl-3-(1-phenylethylidene)-1,3,3a,8a-tetrahydrocyclopenta[*a*]inden-8(2*H*)-one (**3aA**) in 38% isolated yield and 93% ee (Table 1, entry 1). Elevating the reaction temperature to 75 °C afforded the product in 31% isolated yield (entry 2). The reaction temperature can be decreased to 40 °C, yielding product in 37% isolated yield and 93% ee (entries 2-4). Further decrease the reaction temperature to 30 °C resulted in lower yield (entry 5), although the enantioselectivity was retained. Reducing the catalyst loading to 3 mol% did not affect the yield of **3aA**, while 1.5 mol% of catalyst loading afforded **3aA** in 17% isolated yield and slightly lower ee (entries 6 and 7). Interestingly, decreasing the amount of phenylboronic acid **2A** to 1.5 equivalent, the product **3aA** was obtained in 33% yield, suggesting that the ratio of substrate did not significantly affect the reaction (entry 8). Notably, in all cases the dimerization product was obtained, this probably the main reason for the lower yield of this reaction. To suppress the dimerization side-reaction, this author performed the reaction in 5 mL of H_2O at 40 °C for 16 h, however, this method not worked, still dimerization product was

obtained (entry 9). Next, switching the pure water solvent to *tert*-butanol and mix solvents of ethanol-H_2O (3:1), the reaction did not occur (entries 10 and 11). When mix solvents of methanol-H_2O (1:10) were used, the reaction proceeded but without improvement of the yield (entry 12). These results clearly suggest that water is essential for this reaction. In entry 13, the substrate **1a** dissolved in methanol was added dropwise via 6 h, unfortunately, this method can not suppress the dimerization either.

Table 1. Optimization of conditions for the asymmetric arylative cyclization[a]



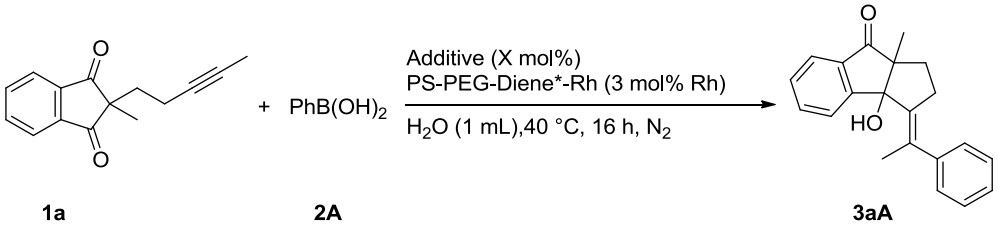
1a 2A 3aA

entry	cat. loading (mol %)	solvent	temp (°C)	time (h)	isolated yield (%)	ee (%)
1	7	H_2O	60	12	38	93
2	7	H_2O	75	12	31	93
3	7	H_2O	50	12	38	93
4	7	H_2O	40	12	37	93
5	7	H_2O	30	12	25	92
6	3	H_2O	40	12	36	93
7	1.5	H_2O	40	12	17	91
8[b]	3	H_2O	40	16	33	93
9	3	H_2O (5 mL)	40	16	38	91
10	3	^{t}BuOH	40	16	---	---
11	3	EtOH-H_2O (3/1)	40	16	---	---
12	3	MeOH-H_2O (1/10)	40	16	31	94
13[c]	3	MeOH-H_2O (1/10)	40	16	22	94

[a]Reaction conditions: alkynone **1a** (0.2 mmol), $PhB(OH)_2$ (**2A**; 0.7 mmol), PS-PEG-diene*-Rh (1.5-7 mol %), solvent (1 mL), 30-75 °C, 12-16 h. [b]0.3 mmol $PhB(OH)_2$ was used. [c]Alkynone **1a** was dissolved in methanol and then added dropwise via 6 hours.

To further improve the yield of the desired product, the effect of the additive was checked, the results were shown in **table 2**. The reaction of **1a** with **2A** in the presence of 1.5 equivalent of KF, the desired product **3aA** was obtained in 22% isolated yield and 77% ee (**table 2**, entry 1). When K_2CO_3 was used as an additive, no reaction has been occurred (entry 2). Other additives such as Cs_2CO_3, K_3PO_4, K_3PO_4, KOH, NaOAc were used, generally gave lower yield and ee of the product **3aA** (entries 3-6). These results suggest that the above-mentioned additives are not suitable for this asymmetric arylative cyclization.

Table 2. Additive effect[a]



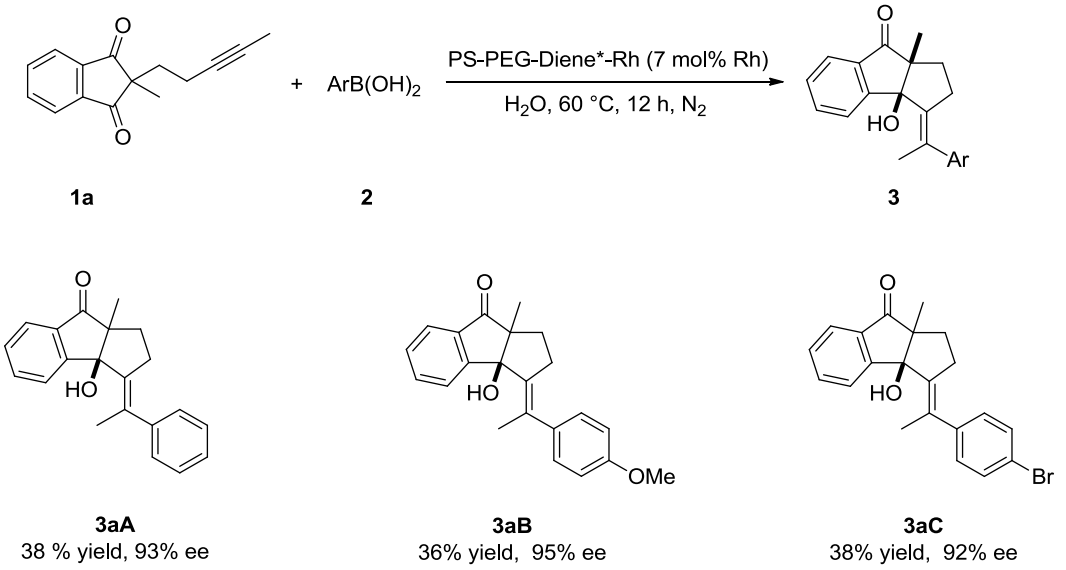
1a **2A** **3aA**

entry	solvent	temp (°C)	additive	Conv.[b] (%)	isolated yield (%)	ee (%)
1	H_2O	40	KF (150 mol%)	50	22	77
2	H_2O	40	K_2CO_3 (50 mol%)	3	--	--
3	H_2O	40	C_2CO_3 (50 mol%)	24	10	68
4	H_2O	40	K_3PO_4 (50 mol%)	31	11	68
5	H_2O	40	KOH (50 mol%)	24	11	71
6	H_2O	40	NaOAc (200 mol%)	22	12	82

[a]Reaction conditions: alkynone **1a** (0.2 mmol), $PhB(OH)_2$ (**2A**; 0.3 mmol), PS-PEG-diene*-Rh (3 mol %), H_2O (1 mL), 40 °C, 16 h. [b]GC-MS

Before further improvement the yield of the desired product, selected arylboronic acids **2** were examined for the current asymmetric arylative cyclization (**Scheme 3**). 4-Methoxyphenylboronic acid **2B** underwent the asymmetric arylative cyclization with alkynone **1a** in water at 60 °C under N_2 to give the desired product **3aB** in 36% yield and 95% ee. The 4-bromophenylboronic acid also reacted to afford the product **3aC** in 38% yield and 92% ee. It should be emphasized that all of these products have been previously unknown. Further improvement of the yield and confirm the absolute configuration of the desired products are ongoing.

Scheme 3. Scope of the arylboronic acid[a]



[a]Reaction conditions: alkynone **1a** (0.2 mmol), $ArB(OH)_2$ (**2**; 0.7 mmol), PS-PEG-diene*-Rh (7 mol %), H_2O (1 mL), 60 °C, 12 h. The ee values were determined by HPLC on a chiral stationary column. The absolute configuration of products **2** were unclear at this stage.

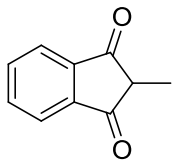
Conclusion

In conclusion, the rhodium-chiral diene complex immobilized on an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin catalyzed asymmetric arylative cyclization of alkynones in water was developed. In the reaction of 2-methyl-2-(pent-3-yn-1-yl)-1*H*-indene-1,3(2*H*)-dione with arylboronic acids to give the corresponding allylic alcohol products in 36-38% yield and 92-95% ee. Further improvement of the yield of the desired product is ongoing.

Experimental Section

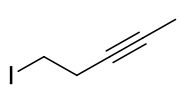
General Methods. All chemicals were commercially available and were used without further purification unless otherwise mentioned. PS-PEG-amino resin (TentaGel S NH_2; average diameter 0.90 mm, 1% divinylbenzene cross-linked, loading value of amino residue 0.2-0.3 mmol/g) was purchased from Rapp Polymere. Water was deionized with a Millipore system to Milli-Q grade. NMR spectra were recorded at 25 °C on a JEOL JNM-ECS400 spectrometer (396 MHz for ^{1}H, 100 MHz for $^{13}C\{^{1}H\}$) or a JEOL JNM-AL400 spectrometer (100 MHz for ^{13}C). Chemical shifts for ^{1}H NMR are reported in δ ppm referenced to an internal tetramethylsilane (TMS) as a standard or to the solvent peak. Chemical shifts for ^{13}C NMR are given relative to the solvent peak as an internal standard. HPLC analysis was performed on a JASCO HPLC system equipped with CD-2095plus, MD-2015plus, RI-930, UV-1570, PU-1580, and DG-2080−53. GC analysis was carried out on a Hewlett-Packard 4890 system. GC-MS data were collected with an Agilent 6890 GC/5973N MS detector or a JEOL AccuTOF GC JMS-T100GC equipped with Agilent 6890N GC. Optical rotations were recorded on a JASCO P-1020 polarimeter. ICP analysis was performed on a LEEMAN LABORATORIES Profile plus plasma spectrometer. The continuous-flow reaction was carried out in an X-Cube reactor system (ThalesNano Nanotechnology Inc., Budapest) with no gas mode.

Preparation of 2-Methyl-1*H*-indene-1,3(2*H*)-dione



The 2-methyl-1*H*-indene-1,3(2*H*)-dione was prepared according to the known procedures[5]. In an inert atmosphere, a three-neck flask was charged with a stir bar, sodium hydride on oil (6.0 g, 50-72 wt%, 125-180 mmol), dry toluene (75 mL). The resulting mixture was stirred at room temperature for 10 min. Then a solution of pentan-3-one (10.25 g, 119 mmol) and dimethyl phthalate (25.0 g, 128.5 mmol) in dry toluene (50 mL) was added slowly. After stirring for additional 10 min, the resulted solution was heated at reflux for 16 h. After cooling down to room temperature, the residue was filtered, washed with toluene (3×25 mL), dried under vacuum and dissolved in water. The aqueous layer was acidified dropwise with 35% HCl. The residue was filtered and dried under vacuum to give light orange solid: 12.96 g (68%); ^{1}H NMR (396 MHz, $CDCl_3$, 20.8°C) δ 7.99 (dd, J = 5.2 and 2.8 Hz, 2H), 7.85 (dd, J = 5.2 and 2.8 Hz, 2H), 3.06 (q, J = 8.0 Hz, 1H), 1.42 (d, J = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 21.2 °C) δ 210.0, 141.9, 135.6, 123.2, 48.7, 10.4; MS (GC-EI, m/z) 160.2 (M).

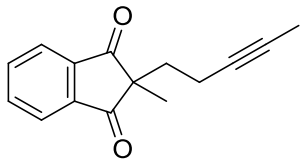
Preparation of 5-Iodopent-2-yne



The 5-iodopent-2-yne was prepared according to the known procedure[6]. A three-neck flask containing a stirring bar was charged with Et_2O/MeCN (200 mL, 2/1), 3-pentyn-1-ol (1.68 g, 20 mmol).

The resulting mixture was stirred at 0 °C. Afterwards, PPh_3 (7.87 g, 30.0 mmol), imidazole (2.04 g, 30.0 mmol) and I_2 (7.61 g, 30.0 mmol) were added carefully. The reaction mixture was warmed to 30 °C and stirred for 2 h. Pentane (50 mL) was added, the resulting suspension was filtered and washed with pentane/Et_2O (30 mL, 30/1). The filtrates were combined and carefully evaporated. The resulting crude material was purified by silica gel column chromatography with pentane to afford the highly volatile title compound as a colorless oil (2.52 g, 65%).

Preparation of 2-Methyl-2-(pent-3-yn-1-yl)-1*H*-indene-1,3(2*H*)-dione

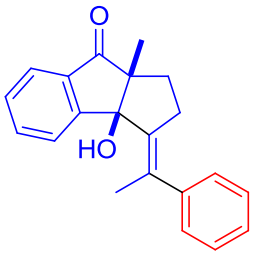


In an inert atmosphere, a three-neck flask was charged with a stir bar, 2-methyl-1*H*-indene-1,3(2*H*)-dione (3.20 g, 20 mmol), 18-crown-6 (5.29 g, 20 mmol), dry DMF (75 mL). The resulting mixture was stirred at room temperature for 30 min. Then potassium *tert*-butoxide solution 1.0 M in THF (20 mL, 20 mmol) was added in several portions. Next, 5-iodopent-2-yne (5.82 g, 30 mmol) was added with a syringe pump for 50 min. The resulting mixture was heated at 35 °C and stirred for 20 h. The reaction mixture was quenched with water (250 mL) and extracted with ethyl acetate (100 mL × 3). The combined filtrates were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography with *n*-hexane and ethyl

acetate to afford the title compound as a colorless oil (2.67 g, 59%). ^{1}H NMR (396 MHz, $CDCl_3$, 20.8°C) δ 7.99 (dd, *J* = 6.0 and 2.4 Hz, 2H), 7.85 (dd, *J* = 6.0 and 2.4 Hz, 2H), 2.09 (td, *J* = 4.8 and 1.6 Hz, 2H), 2.04-2.06 (m, 2H), 1.48 (t, *J* = 2.0 Hz, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 203.8, 141.3, 135.6, 123.2, 78.2, 78.2, 53.4, 34.2, 20.8, 15.0, 3.2.

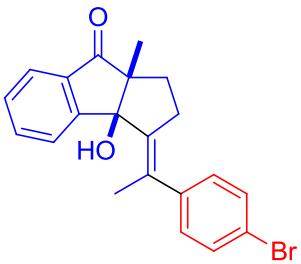
PS-PEG-diene*-Rh catalyzed asymmetric arylative cyclization of alkynone 1 with arylboronic acids 2. General procedure. PS-PEG-diene*-Rh (56.0 mg, 0.014 mmol) and arylboronic acid **2** (0.7 mmol) were charged to a vial under an inert atmosphere. After addition of degassed H_2O (1 mL) and alkynone **1** (0.2 mmol), the mixture was shaken at 60 °C for 12 h. After being cooled to room temperature, the resulting mixture was filtered using a Bond Elut reservoir. The polymer catalyst was washed with ethyl acetate (5 × 3 mL). The filtrates were combined and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography with *n*-hexane and ethyl acetate to afford the corresponding allylic alcohols **3**.

(*E*)-3a-Hydroxy-8a-methyl-3-(1-phenylethylidene)-1,3,3a,8a-tetrahydrocyclopenta[a]inden-8(2*H*)-one



The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.41) as a colorless oil (23.1 mg, 38% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 21.3 °C) δ 7.60-7.62 (m, 1H), 7.37-7.43 (m, 3H), 7.27-7.31 (m, 2H), 7.18 (dt, J = 6.0 and 1.6 Hz, 2H), 6.28 (dt, J = 8.0 and 1.6 Hz, 1H), 2.63 (dd, J = 16.8 and 8.4 Hz, 1H), 2.44 (s, 1H), 2.37 (ddd, J = 12.8, 7.6 and 0.8 Hz, 1H), 2.10−2.12 (m, 1H), 1.90 (d, J = 1.6 Hz, 1H), 1.71 (ddd, J = 20.8, 8.0 and 2.4 Hz, 1H), 1.11 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.0 °C) δ 208.7, 155.2, 142.9, 140.9, 135.0, 134.3, 134.1, 128.9, 128.4, 128.3, 127.2, 125.1, 122.8, 86.2, 65.0, 31.7, 30.1, 25.0, 18.7; HRMS (GC-TOF-EI, *m*/*z*) calcd for $C_{21}H_{20}O_2$ (M) 304.1463, found 304.1459; 93% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 90:10, flow rate 0.3 mL/min, wavelength = 254 nm, t_R = 16.59 min for major isomer, t_R = 18.85 min for minor isomer].

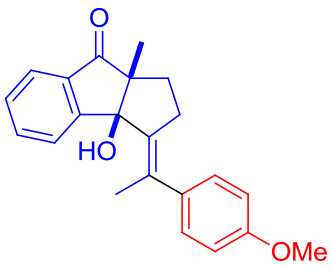
(*E*)-3-(1-(4-Bromophenyl)ethylidene)-3a-hydroxy-8a-methyl-1,3,3a,8a-tetrahydrocyclopenta[a]inden-8(2*H*)-one



The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.43) as a white solid (29.1 mg, 38% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 21.3 °C) 7.61-7.63 (m, 1H), 7.52

(dt, J = 8.8 and 2.0 Hz, 2H), 7.32 (dt, J = 6.0 and 3.2 Hz, 2H), 7.07 (dt, J = 8.8 and 2.0 Hz, 2H), 6.34-6.36 (m, 1H), 2.61 (dd, J = 16.8 and 7.6 Hz, 1H), 2.36 (ddd, J = 12.8, 8.0 and 1.2 Hz, 1H), 2.16 (s, 1H), 2.04-2.14 (m, 1H), 1.87 (d, J = 1.2 Hz, 1H), 1.71 (dd, J = 16.8 and 4.8 Hz, 1H), 1.11 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 20.7 °C) δ 208.4, 154.8, 141.9, 141.4, 134.5, 134.1, 131.1, 130.9, 128.6, 125.0, 123.0, 120.9, 86.4, 65.1, 31.5, 30.2, 24.9, 18.6; HRMS (TOF-ESI, m/z) calcd for $C_{21}H_{19}BrO_2$ (M) 382.0568, found 382.0568; 92% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 90:10, flow rate 0.3 mL/min, wavelength = 254 nm, t_R = 18.82 min for major isomer, t_R = 20.63 min for minor isomer].

(*E*)-3a-Hydroxy-3-(1-(4-methoxyphenyl)ethylidene)-8a-methyl-1,3,3a,8a-tetrahydrocyclopenta[a]inden-8(2*H*)-one



The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.33) as a colorless oil (24.1 mg, 36% yield): ^{1}H NMR (396 MHz, $CDCl_3$, 21.6 °C) δ 7.61-7.63 (m, 1H), 7.29-7.34 (m, 2H), 7.12 (dt, J = 8.4 and 2.8 Hz, 2H), 6.95 (dt, J = 8.8 and 2.4 Hz, 2H), 6.39-7.41 (m, 1H), 3.88 (s, 3H), 2.60 (dd, J = 17.2 and 8.0 Hz, 1H), 2.41 (s, 1H), 2.35 (ddd, J = 12.4, 8.0 and 1.2 Hz, 1H), 2.07−2.10 (m, 1H), 1.87 (d, J = 1.2 Hz, 1H), 1.72 (ddd, J = 20.8, 8.0 and 4.4 Hz, 1H), 1.12 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$, 20.7 °C) δ 208.8, 158.8, 155.4, 141.0, 135.1, 134.6, 134.4, 134.1, 130.0, 128.4, 125.2,

122.9, 113.7, 86.2, 64.8, 55.3, 31.9, 30.2, 25.2, 18.6; HRMS (ESI-TOF, *m*/*z*) calcd for $C_{22}H_{22}O_3$ $(M+Na)^+$ 357.1467, found 357.1463; 95% ee [HPLC conditions: Chiralcel AD-H column, hexane/*i*PrOH = 90:10, flow rate 0.3 mL/min, wavelength = 254 nm, t_R = 20.85 min for major isomer, t_R = 25.71 min for minor isomer].

References

(1) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K. and Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54-55.

(2) (a) Miura, T.; Shimada, M. and Murakami, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 7598-7600. (b) Miura, T.; Shimada, M. and Murakami, M. *Tetrahedron* **2007**, *63*, 6131-6140.

(3) Partridge, B. M.; González, J. S. and Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 6523-6527.

(4) (a) Filippini, M.-H. and Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27-76. (b)Butkus, E. *Synlett* **2001**, 1827-1835. (c) Presset, M.; Coquerel, Y. and Rodriguez, J. *Chem. Rev.* **2013**, *113*, 525-595.

(5) (a) Mosher, W. A.; Soeder, R. W. *J. Org. Chem.* **1971**, *36*, 1561-1563. (b) Kistemaker, J. C. M.; Štacko, P.; Roke, D.; Wolters, A. T.; Heideman, G. H.; Chang, M.-C.; Meulen, P. V. D.; Visser, J. V.; Otten, E.; Feringa, B. L. *J. Am. Chem. Soc.* **2017**, *139*, 9650-9661.

(6) Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Fürstner, A. *Chem. Eur. J.* **2016**, *22*, 8484-8507.

Conclusion

Chapter 1: This author has developed an efficient, metal- and oxidant-free green approach for the synthesis of 2-substituted 4(3*H*)-quinazolinones. Various 2-aryl-, 2-alkyl-, and 2-(4-oxoalkyl)-quinazolinones were readily prepared by successive condensation of 2-aminobenzamides with a wide range of acyclic or cyclic 1,3-diketones, intramolecular nucleophile addition, and selective C-C bond cleavage, catalyzed by natural camphorsulfonic acid in an aqueous ethyl lactate solution (33 examples, 35-98% yield). This author also proposed a plausible reaction pathway for this reaction.

Chapter 2: A ligand-free copper-catalyzed reduction of azaarenes with diboronic acid as reductant in an aprotic solvent under mild conditions has been developed. This author found that copper catalyzed the reduction of azaarenes with diboronic acid as a reductant in acetonitrile under mild conditions to give the corresponding tetrahydroquinolines in up to 98% yield. Most interestingly, the nitroazaarenes could be reduced exclusively to give the corresponding amines without touching the azaarene moieties. Furthermore, the reductive amination of aromatic nitro compounds and aromatic aldehydes has also been realized. A series of hydrogenated azaarenes and secondary amines were obtained with good functional group tolerance. Reductive amination of aromatic nitro compounds and aromatic aldehydes with diboronic acid were also reported.

Chapter 3: This author reported the development of a rhodium-chiral diene complex immobilized on an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin (PS-PEG-diene*-Rh) and its use in the asymmetric 1,4-addition of arylboronic acids to enones (a.k.a. Miyaura-Michael addition) in water under heterogenous conditions. PS-PEG-diene*-Rh efficiently catalyzed the asymmetric 1,4-addition of various arylboronic acids to cyclic or linear enones in water under batch conditions to give the corresponding β-arylated carbonyl compounds in excellent yields and with excellent enantioselectivity (up to 99% yield, up to 98% ee). The catalyst displayed excellent recyclability. Thus, the supported catalyst was readily recovered by simple filtration from the resulting reaction mixture and reused 10 times without loss of its catalytic activity and enantioselectivity (fresh 91% yield, 95% ee; 10th reuse 91% yield, 92% ee). This author also applied PS-PEG-diene*-Rh for the continuous-flow reaction. In a flow reactor containing a cartridge of the immobilized rhodium-chiral diene complex, the continuous-flow asymmetric 1,4-addition of phenylbronic acid to cyclohex-2-en-one at 50 °C was completed within 10 seconds. The long-term continuous-flow reaction for 12 h provided 11.7 g of (*R*)-3-phenylcyclohexanone with 93% enantioselectivity. The total TON of the catalysts reached 1073.

Chapter 4: In order to extend the catalytic utility of PS-PEG-diene*-Rh, this author examined the asymmetric arylative cyclization of alkynones in water. This author prepared 2-methyl-2-(pent-3-yn-1-yl)-1*H*-indene-1,3(2*H*)-dione as an alkynone substrate which underwent asymmetric arylative cyclization with phenylboronic acid in the presence of PS-PEG-diene*-Rh in water to give 38% yield of (*E*)-3a-hydroxy-8a-methyl-3-(1-phenylethylidene)-1,3,3a,8a-tetrahydrocyclopenta[*a*]inden-8(2*H*)-one with 93% ee. Further improvement of the yield of the desired product is ongoing.

Acknowledgement

I would like to express my deepest appreciation to my supervisor, professor Yasuhiro Uozumi for giving me the precious opportunity to join the research group, giving me the chance to venture into the world of amphiphilic resin-supported homochiral diene rhodium complex catalyzed asymmetric reactions in water and for his patience and support during these years.

Also, I would like to thank professor Masahiro Hiramoto, professor Maki Minakawa, professor Norie Momiyama and professor Toshiyasu Suzuki for reviewing my thesis. Furthermore, I would like to express my sincere gratitude to professor Haifeng Zhou, professor Toshiaki Mase, assistant professors Dr. Takao Osako and Dr. Go Hamasaka, who have given me a lot of help during my study. The profit that I gained from their profound knowledge, remarkable expertise and intellectual ingenuity will be of everlasting significance to my future life and career.

I would like to extend my gratitude to all former and present members in professor Uozumi's Laboratory for their helpful discussions during the seminar, the coffee breaks and for creating a great work atmosphere in the laboratory. Dr. Makoto Nagaosa, Dr. Shiguang Pan, Dr. David Roy, Dr. Anggi Eka Putra, Dr. Kim Kiseong, Dr. Shuichi Hirata, Dr. Yuya Sigiyama, Dr. Shuo Yan, Mr. Shun Ichii, Ms. Ryoko Niimi and Mr. Kazuki Tani helps

me a lot in my doctoral course. I am also very thankful to Ms. Kaoru Torii and Ms. Aya Tazawa for teaching me how to use NMR, HPLC, GC, and measure optical rotations.

Many thanks to the people in professor Zhou's group, I have a very happy life there and it was my dream start place. I also wish to thank the people who have participated in my hobbies outside of the laboratory, with special mention to Shingo Kojima for some interesting moments during the futsal in Okazaki.

Finally, I would like to express my heartfelt thanks to my family, relatives, and friends for their continuing dedicated support and considerable encouragement.

List of Publications

1. Brønsted Acid-Catalyzed Selective C-C Bond Cleavage of 1,3-Diketones: A Facile Synthesis of 4(3*H*)-Quinazolinones in Aqueous Ethyl Lactate

   Guanshuo Shen, Haifeng Zhou, Peng Du, Sensheng Liu, Kun Zou and Yasuhiro Uozumi, *RSC Adv.* **2015**, *5*, 85646-85651

2. Cu-Catalyzed Reduction of Azaarenes and Nitroaromatics with Diboronic Acid as Reductant

   Danwei Pi, Haifeng Zhou, Yanmei Zhou, Qixing Liu, Renke He, Guanshuo Shen, Yasuhiro Uozumi, *Tetrahedron* **2018**, *74*, 2121-2129

3. Aqueous Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex under Batch and Continuous-Flow Conditions

   Guanshuo Shen, Takao Osako, Makoto Nagaosa, and Yasuhiro Uozumi, *J. Org. Chem.* **2018**, *83*, 7380-7387

List of Presentations

1. Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Homochiral Diene Rhodium Complex in Water

   Guanshuo Shen, Takao Osako, Makoto Nagaosa, Yasuhiro Uozumi, The 98th CSJ Annual Meeting, Nihon University (Tokyo), Mar. 2018, 2H6-13

2. Aqueous Asymmetric 1,4-Addition Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex

   Guanshuo Shen, Takao Osako, Makoto Nagaosa, Yasuhiro Uozumi, The Japanese Society for Process Chemistry, Funabori (Tokyo), Jul. 2018, 1P-33

3. Aqueous Asymmetric 1,4-Addition with a Chiral Diene Rhodium Catalyst Immobilized on an Amphiphilic Resin

   Guanshuo Shen, Takao Osako, Makoto Nagaosa, Yasuhiro Uozumi, The 65th Organometallic Chemistry, Doshisha University (Kyoto), Sep. 2018, P2-68