How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202213074
International Edition: doi.org/10.1002/anie.202213074
German Edition: doi.org/10.1002/ange.202213074

Hydroamination

Skeleton-Reorganizing Coupling Reactions of Cycloheptatriene and Cycloalkenones with Amines

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Abstract: Skeletal reorganization reactions have emerged as an intriguing tool for converting readily available compounds into complicated molecules inaccessible by traditional methods. Herein, we report a unique skeleton-reorganizing coupling reaction of cycloheptatriene and cycloalkenones with amines. In the presence of Rh/acid catalysis, cycloheptatriene can selectively couple with anilines to deliver fused 1,2-dihydroquinoline products. Mechanistic studies indicate that the retro-Mannich type ring-opening and subsequent intramolecular Povarov reaction account for the ring reorganization. Our mechanistic studies also revealed that skeleton-reorganizing amination between anilines and cycloalkenones can be achieved with acid. The synthetic utilization of this skeleton-reorganizing coupling reaction was showcased with a gram-scale reaction, synthetic derivatizations, and the late-stage modification of commercial drugs.

Introduction

The chemospecific assembly of molecular complexity from readily available starting materials is a persistent pursuit among synthetic and pharmaceutical chemists.[1] For this purpose, traditional elementary reactions, such as addition, elimination and substitution reactions, are widely utilized by the stepwise transformation in various peripheral modifications[2] (Scheme 1a). On the other hand, atom-insertion, deletion, exchange or rearrangement protocols are also exploited to build a complex molecular framework in a straightforward manner.[3] In this scenario, classic rearrangement reactions have been disclosed during the past decades.[4] A few notable examples by the groups of Levin, Sarpong, Antonchick, and Lu recently demonstrated an elegant single-atom strategy for the ring-contraction or expansion of heterocycles.[5] These intramolecular manipulations exhibit indispensable potential in the late-stage modification of some structurally specialized drugs or well-defined substrates. However, intermolecular skeletal reorganization reactions, which merge common cross-coupling reactions with in situ skeletal reorganization, have still rarely been explored.

Nitrogen-containing heterocycles are prevalent structural motifs that are widely found in natural products and pharmaceuticals.[6] Of particular importance are 1,2-dihydroquinolines (1,2-DHQs), which display a broad range of intriguing pharmacological and biological properties, such as antibacterial,[7] antitrypanosomal,[8] antioxidative,[9] and anti-allergic activity.[10] Therefore, the selective synthesis of 1,2-dihydroquinoline compounds with various substituents around their core structure has gained considerable attention.[11] Although advancements have been achieved in this field, the fused 1,2-dihydroquinolines still remain an intractable task.[12] Due to the synthetic efficiency and atomic economy, catalytic hydroamination of conjugated dienes was established as a robust protocol for construction of nitrogen-containing molecules.[13] In 2006, Hartwig's group pioneered a palladium-catalyzed hydroamination of cycloheptatriene to deliver azabicyclic tropene product **3** via a sequential intermolecular and intramolecular hydroamination (Scheme 1b).[14] Interestingly, a few 1,2-hydroquinoline side-products **4** were also observed in some case with an unexplainable mechanism. Inspired by these precedents and our research interest in chemospecific manipulation,[15] we report herein our endeavors in the metal-diverted skeleton-reorganizing coupling reactions of cycloheptatriene with amines. Careful investigations were performed to reveal the mechanistic details. With the mechanism elucidated, this ring-reorganized version can be further verified by concise acid-promoted reactions between anilines and cycloalkenones (Scheme 1c).

Results and Discussion

In 2019, our group revealed a metal-controlled strategy for regioselective coupling between indoles and isoprene.[15a] The prenylated or reverse prenylated products could be respectively obtained under Pd-hydride or Rh-hydride catalysis. These findings encouraged us to postulate whether such a protocol could also be applied in switching the chemoselectivity of this skeleton-reorganizing coupling. To test this hypothesis, cycloheptatriene **1** and 4-fluoroaniline **2a** were chosen as the model substrates under rhodium

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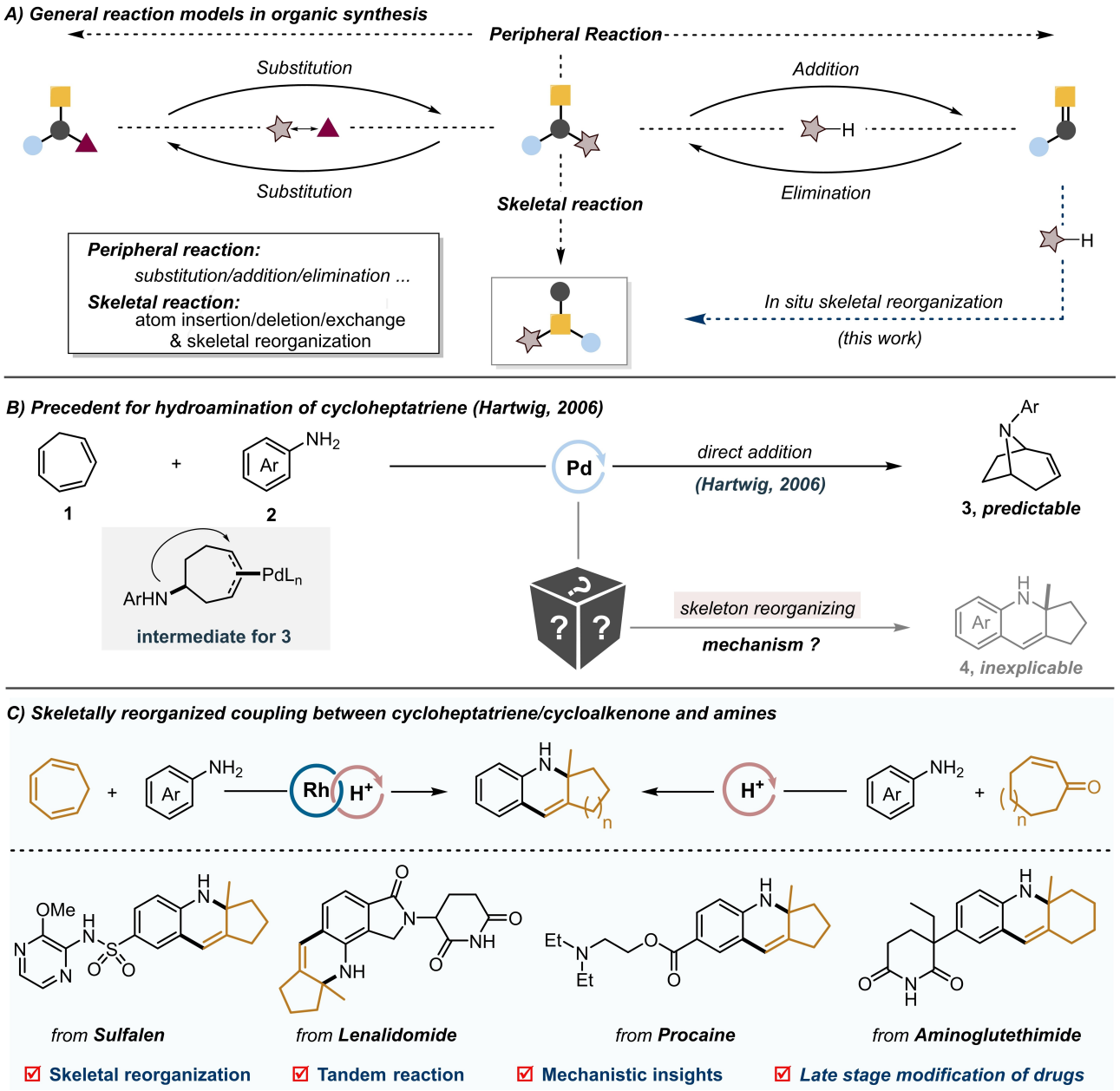
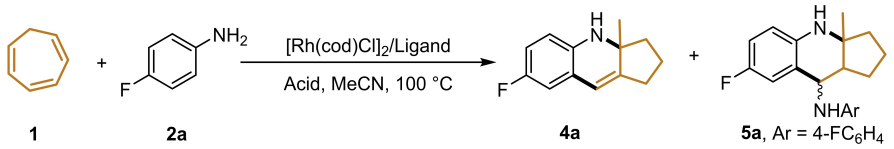


Scheme 1. Skeleton-reorganizing coupling between cycloheptatriene/cycloalkenone and amines.

catalysis (Table 1). When the reaction was performed in MeCN at 100 °C with $[Rh(cod)Cl]_2$ as catalyst precursor and dppp as ligand, quinoline derivative **4a** and aminated quinoline derivative **5a** were unexpectedly obtained in 14 % and 21 % yield, respectively (entry 1). The structure of **5a** was confirmed by single-crystal X-ray crystallography (CCDC: 2165398).[16] Notably, tropene-type product **3a**, which was the major product in previous palladium-catalyzed processes,[14] was not detected under our current conditions. While the yields of **4a** and **5a** changed upon adding 20 mol % carboxylic acid to the reaction system (entries 2 and 3), the yield of **4a** was remarkably increased to 73–77 % with excellent selectivity when a stronger Brønsted acid, $(PhO)_2PO_2H$ or TsOH, was employed (entries 4 and 5). In comparison, only 17 % yield of **4a** was achieved in the presence of inorganic acid HCl (entry 6). Selecting TsOH as the optimal choice, we evaluated various ligands. To our delight, all tested bisphosphine ligands gave **4a** exclusively whereas DPEphos exhibited the best performance in terms of yield (entries 7–13). Further screening of solvents showed that the yield of product **4a** could be further increased to 84 % in dioxane/NMP mixed solvents (entry 14, see Table S1 for details). It should be noted that the reaction completely shuts down in the absence of the rhodium catalyst.

Subsequently, the framework-reorganizing coupling reactions of cycloheptatriene with various arylamines were carried out under the optimized conditions (Scheme 2).

Table 1: Optimization of the reaction conditions.



1 **2a** **4a** **5a**, Ar = 4-FC_6H_4

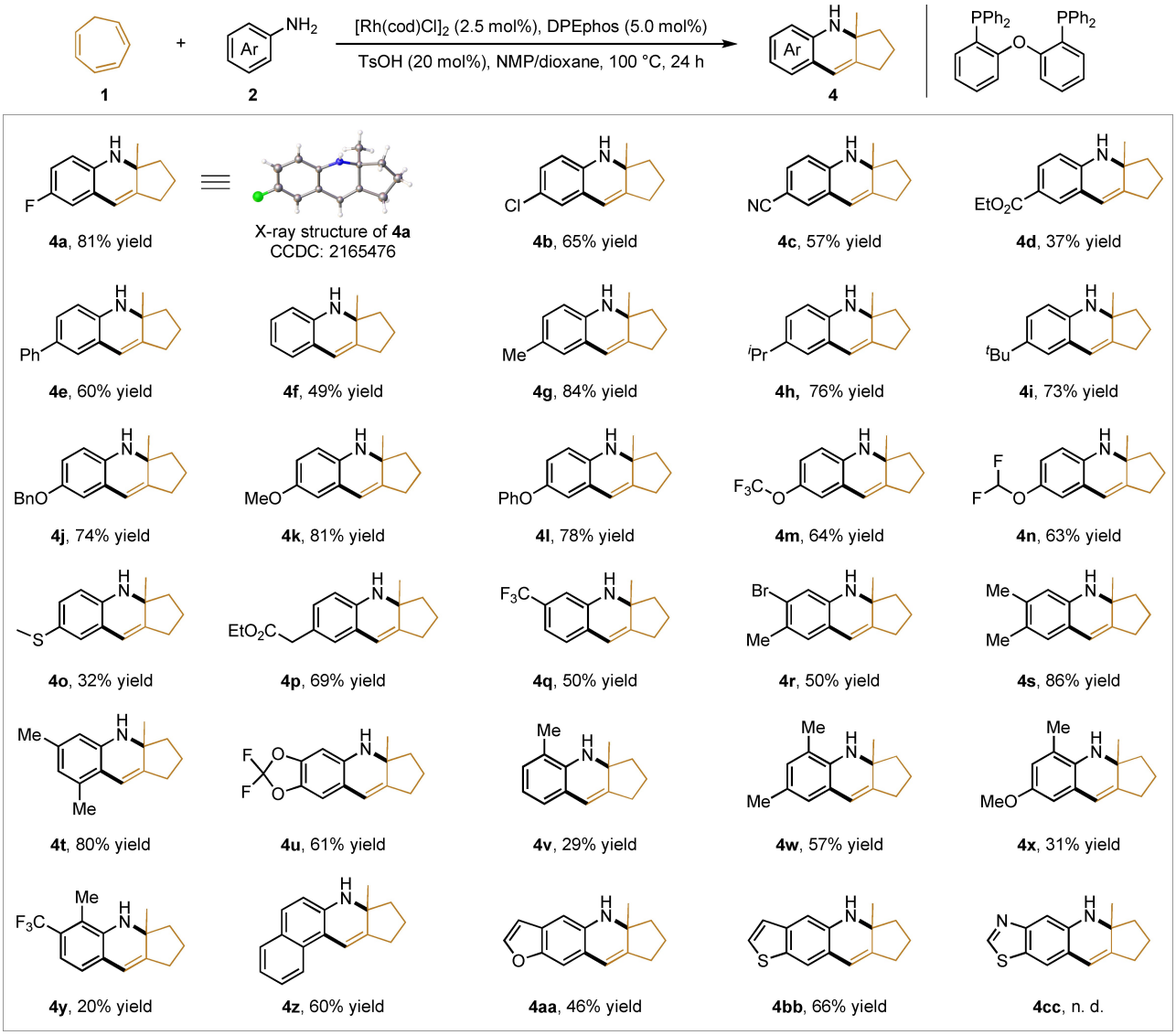
entry	ligand	acid	yield [%]	
			4a	**5a**
1	dppp	–	14	21
2	dppp	AcOH	40	17
3	dppp	$PhCO_2H$	7	19
4	dppp	$(PhO)_2PO_2H$	73	trace
5	dppp	TsOH	77	trace
6	dppp	HCl	17	trace
7	dppm	TsOH	3	trace
8	dppe	TsOH	9	trace
9	dppb	TsOH	80	trace
10	dppf	TsOH	5	trace
11	DPEphos	TsOH	82	trace
12	Xantphos	TsOH	11	trace
13	BINAP	TsOH	trace	trace
14[a]	DPEphos	TsOH	84 (81)[b]	trace
15[a,c]	–	TsOH	n. d.	n. d.

Reaction conditions: **1** (0.40 mmol), **2a** (0.20 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), ligand (5 mol%), MeCN 0.4 mL, 100 °C, 24 h. Unless otherwise noted, yields were determined by ^{19}F NMR analysis of the crude reaction mixture using 4-fluorobiphenyl as the internal standard. [a] In NMP/dioxane (1/1, v/v). [b] Isolated yield. [c] Without $[Rh(cod)Cl]_2$ and ligand. dppp: 1,3-bis(diphenylphosphino)propane. dppm: bis(diphenylphosphino)methane. dppe: 1,2-bis(diphenylphosphino)ethane. dppb: 1,2-bis(diphenylphosphino)butane. dppf: 1,1′-bis(diphenylphosphino)ferrocene. DPEphos: bis(2-diphenylphosphinophenyl)ether. Xantphos: 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene. BINAP: 2,2′-bis (diphenylphosphino)-1,1′-binaphthyl. NMP: *N*-methylpyrrolidone.

Anilines bearing electron-withdrawing groups at the *para*-position of the phenyl ring could all be applied, affording the products in 37–81% yields (**4a**–**4e**). The structure of **4a** was further confirmed by single-crystal X-ray crystallography (CCDC: 2165476).[16] Simple aniline **2f** was also a suitable substrate for this transformation, delivering product **4f** in 49% yield. Besides, electron-donating substituents, such as alkyl (**2g**–**2i**), alkoxy (**2j** and **2k**), phenoxy (**2l**), fluoromethoxy (**2m** and **2n**) and methylthiol groups (**2o**), were all tolerated under the current reaction conditions. Notably, a substrate bearing an activated methylene group was also compatible with this process and gave the product **4p** in 69% yield. Then, several *meta*-substituted phenylamines were further tested and these substrates all furnished the products predominantly at the sites with less steric hindrance (**4q**–**4u**). Due to the steric cumbrance during Rh-catalyzed hydroamination, ortho-substituted anilines showed lower reactivities (**4v**–**4y**). Naphthyl and heteroarylamines were feasible substrates and the products could be obtained in decent yields (**4z**–**4bb**). However, the reaction with benzothiazole-5-amine failed to yield the corresponding product (**4cc**), presumably due to the strong coordinating ability between the heterocyclic N-atom and the metal center.

To shed light on the mechanistic details, interconversion reactions with **4a** and **5a** were conducted. Our study showed that **4a** could not yield side-product **5a** through an alkene hydroamination process. Instead, the deamination of **5a** smoothly delivered **4a** in 85% yield under the standard conditions and in 81% yield in the absence of a rhodium catalyst (Scheme 3a). These observations indicate that **5a** is a possible precursor of **4a** via an acid-promoted deamination. Next, a retrosynthetic analysis of ring-contracted product **4** was proposed (Scheme 3b). First, the formation of quinoline-type product **4** is attributed to the spontaneous deamination process from the side-product **5**, which was also observed during condition optimization. Scission of two C–C bonds in compound **5** reveals a linear precursor **Int A** or its diimine isomer **Int B** and this transformation may occur via an intramolecular Povarov reaction.[15d,17] Then **Int B** may derive from cyclic *β*-aminoimine **Int C** through a retro-Mannich-type fragmentation.[18] Next, intermediate **C** is expected to be produced from Rh–H mediated alkene isomerization of **Int D**, which can be accessed by Rh-catalyzed sequential amination of cycloheptatriene **1**. It should be noted that it is the second hydroamination of intermediate **E** under rhodium catalysis that diverts the chemoselectivity from previous palladium catalysis, in which **Int E** proceeds through an intermolecular hydroamination that preferably releases tropene-type product **3**.

In order to probe this ring-fragmentation pathway and verify the validity of **Int C**, cyclohept-2-en-1-one **6** was prepared to react with aniline **2a**. Delightfully, the reaction successfully generated **5a** in the absence of acid and the ring-fragmented product **4a** was furnished as the major product when an acid catalyst was added (Scheme 3c). Therefore, it can be presumed that this ring-opening process may derive from a retro-Mannich-type fragmentation of

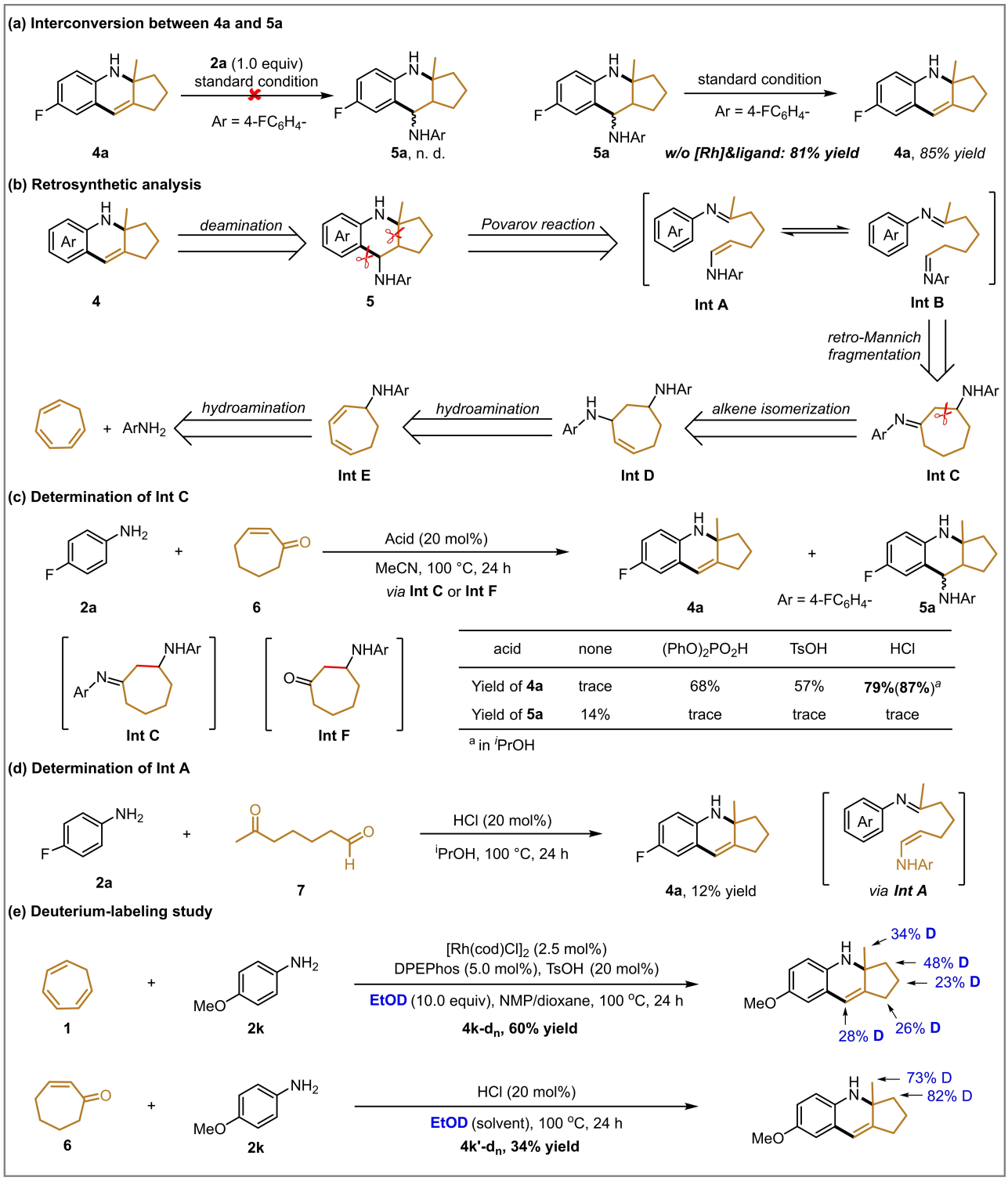


Scheme 2. Rh-catalyzed skeletally reorganized amination of cycloheptatriene. Reaction conditions: **1** (0.40 mmol), **2** (0.20 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), DPEphos (5.0 mol%), TsOH (20 mol%), NMP (0.2 mL), dioxane (0.2 mL), 100 °C, 24 h. Isolated yields are given.

intermediate **C** or **F**. Moreover, this easily operated reaction conditions encouraged us to examine other reaction parameters to enhance the reactivity (see Table S4 and S5 for details). Satisfactorily, the reaction between **6** and **2a** could be promoted to 87% yield in ^{i}PrOH with 20 mol% HCl as catalyst.

When subjecting 6-oxoheptanal **7** to react with aniline **2a** under acidic conditions, the reaction also successfully gave product **4a** in 12% yield (Scheme 3d). This result supports the hypothesis that the in situ generated **Int A** is the possible precursor for the construction of the quinoline-type skeleton. Under Rh/acid tandem catalysis or with the acid-catalyzed processes respectively, deuterium-labeling studies were then carried out with 4-methoxyaniline as the substrate (Scheme 3e). In the reaction with cycloheptatriene, the deuterium was found scrambled into all the positions of the cycloheptatriene skeleton, implying a reversible addition process of Rh–H to cycloheptatriene is probably involved. In contrast, when the experiment was run with cyclohept-2-en-1-one **6**, deuterium incorporation was only observed at the two β-positions of the amino group, which might be attributed to the enol tautomerism.

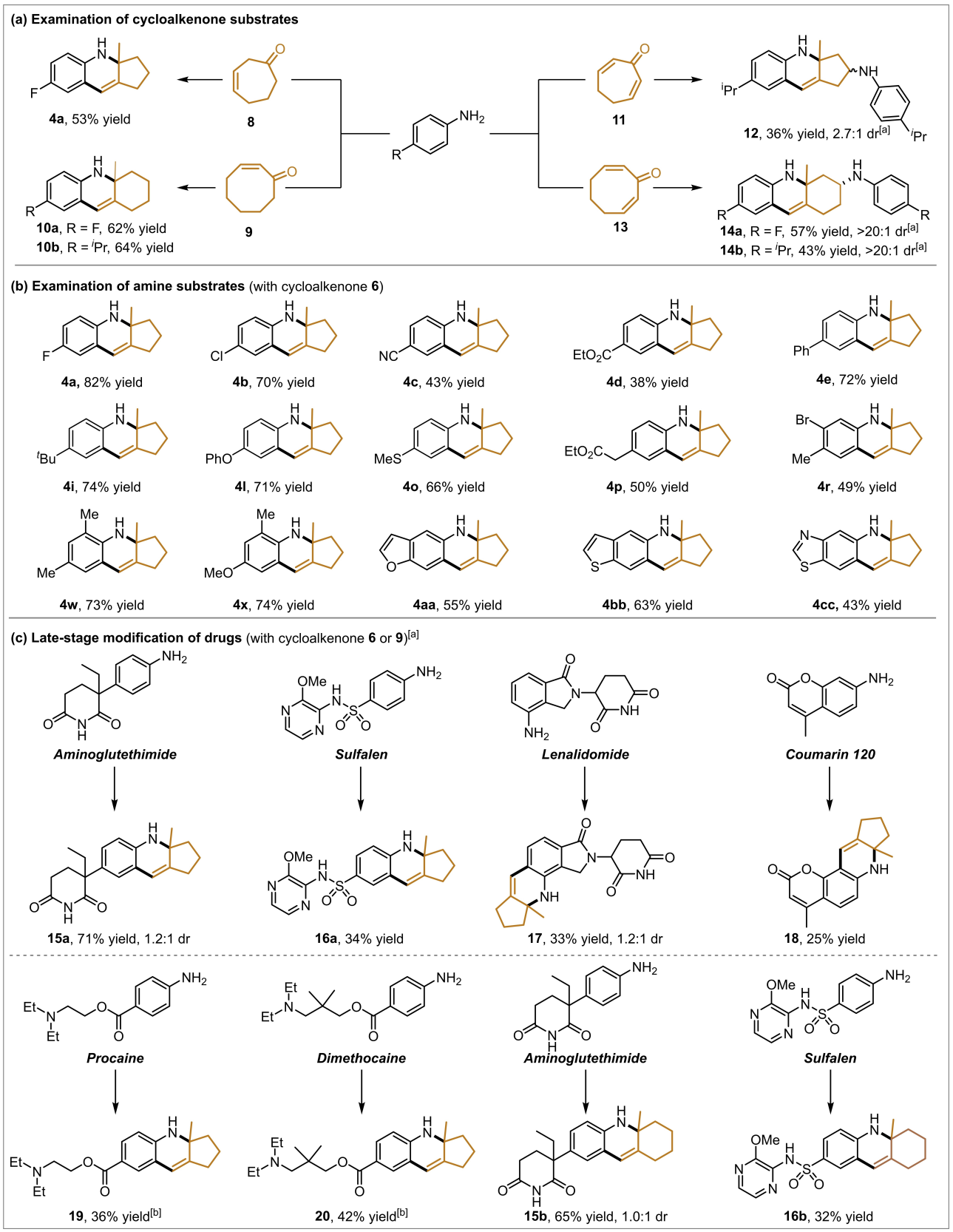
Based on the above mechanistic investigations, a plausible mechanism is proposed (Scheme S1 in Supporting Information). First, oxidative addition of acid and Rh^{I} complex affords the Rh^{III}-hydride **I**, followed by migratory insertion with cycloheptatriene **1** to deliver complex **II**. Then, nucleophilic substitution between **II** and arylamine **2** gives intermediate **III**, which proceeds through the second migratory insertion to produce complex **IV**. The subsequent C–N coupling step may furnish intermediate **V**. With the aid of Rh^{III}-hydride catalyst, alkene isomerization probably occurs via the complex **VI** and generates intermediate **C**/**C′**. Next, a retro-Mannich-type C–C cleavage of intermediate **C**



Scheme 3. Mechanistic insights.

can release linear intermediate **B** and its tautomer **A**. Finally, an intramolecular Povarov reaction of intermediate **A** successfully delivers the ring-reorganized product **5**, which may undergo a deamination reaction to form the desired product **4** in the presence of acid.

Taking advantage of the catalytic simplicity and substrate accessibility, we explored the skeletal fragmentation of cycloalkenones with anilines under metal-free conditions (Scheme 4a). Cyclohept-3-en-1-one **8**, which could also form a β-aminoimine intermediate with aniline via acid-catalyzed enol tautomerism, proceeded through the ring-fragmented

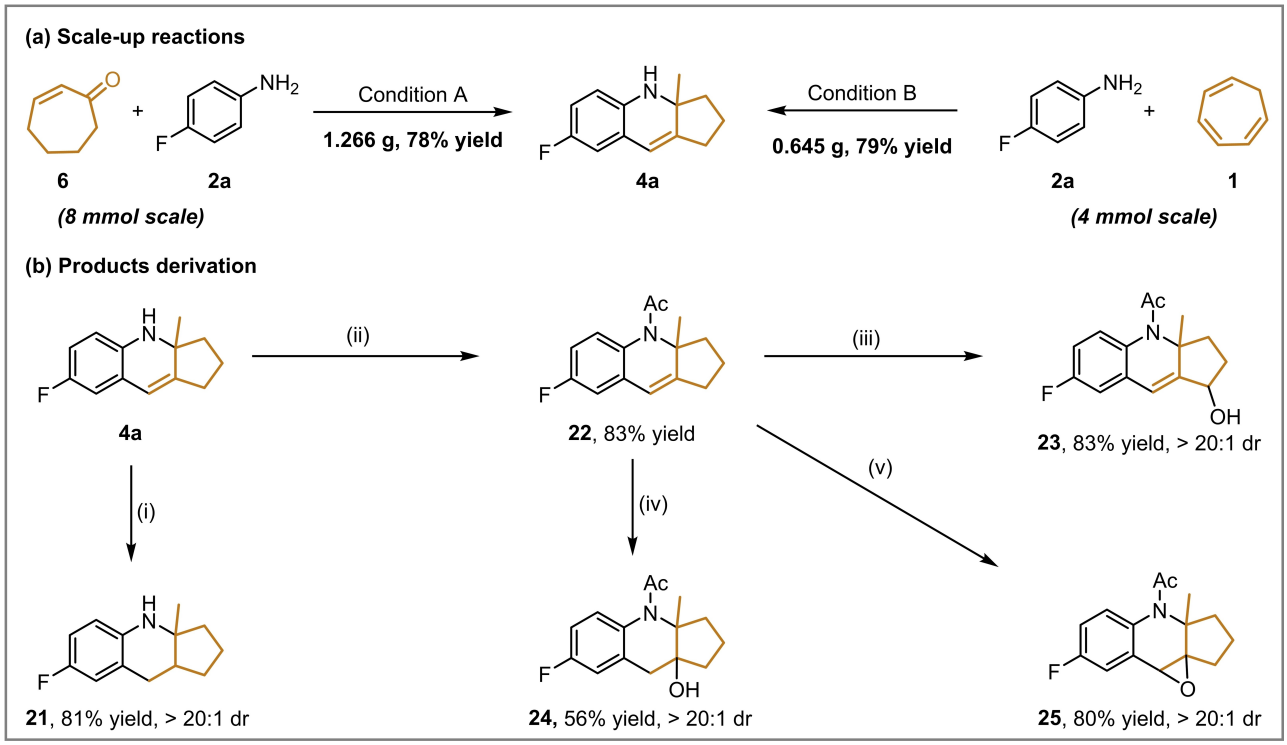


Scheme 4. Acid-promoted skeleton-reorganizing amination of cycloalkenones. Reaction conditions: Cycloalkenone (0.20 mmol), aniline (3.0 equiv), HCl (20 mol%, 4 M in dioxane), ^{i}PrOH (1.0 mL), 100 °C, 24 h. [a] 120 °C. [b] HCl (3.2 equiv)

reaction smoothly to deliver product **4a** in 53 % yield. Eight-membered cycloalkenone was feasible under this condition and gave ring-fragmented products in acceptable yields (**10a** and **10b**). To our surprise, this concise protocol was suitable for cyclodienones **11** and **13** as well. In this case, diaminated products **12** and **14** were successfully obtained in 36–57 % yield. The structure of **14a** was confirmed by single-crystal X-ray crystallography (CCDC: 2165418).[16] In terms of aniline substrates, this metal-free condition also showed excellent functional group tolerance (Scheme 4b). Fragile but synthetically versatile groups, such as –F (**4a**), –Cl (**4b**),–CN (**4c**), –CO_2Et (**4d**) and -Br (**4r**), all remained intact and produced the corresponding products in decent to good yields (Scheme 4b). Electron-donating groups were tolerated by the current process as well (**4e**, **4i**, **4l** and **4o**). Unlike for the Rh-catalyzed strategy, sterically hindered anilines with an ortho-substituent underwent the fragmentation amination with good performance (**4w** and **4x**). Heterocyclic substrates of particular interest, including benzothiazole-5-amine, could be applied (**4aa**–**4cc**), highlighting the complementarity of the Rh-catalyzed conditions.

Encouraged by the generality of this acid-promoted aminated fragmentation, the late-stage modification of aniline-containing bioactive molecules was tested with 7- or 8-membered cycloalkenones (Scheme 4c). Aminoglutethimide, an effective aromatase inhibitor, reacted with cyclohept-2-en-1-one **6** and generated product **15a** in 71 % yield. Similar diversification was also applicable for sulfalen (**16a**) and lenalidomide (**17**), both bearing reactive amidated N–H bonds. Other molecular drugs with an arylamine framework, such as coumarin 120, procaine, and dimethocaine, all successfully delivered the ring-fused products in 25–42 % yield (**18**–**20**). Likewise, with cyclooct-2-en-1-one **9** as the editing unit, aminoglutethimide and sulfalen could also be converted into ring-fused products in 65 % and 32 % yield, respectively (**15b** and **16b**).

To further demonstrate the synthetic utility of this ring-reorganizing process, scale-up reactions and additional transformations were demonstrated. As illustrated in Scheme 5a, fluoride product **4a** was isolated in 78 % yield and 1.266 g from the acid-promoted reaction between aniline **2a** and cycloalkenone **6**. With the Rh/acid catalysis, **4a** could also be produced in 0.645 g with 79 % yield. In the presence of 10 mol % Pd/C, the hydrogenation of **4a** efficiently delivered tetrahydroquinoline **21** in 81 % yield. After acylation, the *N*-acetyl product **22** underwent allylic hydroxylation smoothly to give product **23** in 83 % yield. On the other hand, an iron-catalyzed alkene hydration of compound **22** furnished tertiary alcohol **24** with 56 % yield.[19] In addition, the alkene epoxidation reaction also proceeded efficiently with the aid of *m*-CPBA and the epoxide **25** was obtained in 80 % yield.



Scheme 5. Synthetic utilization. Reaction conditions A: **6** (8.0 mmol), **2a** (24.0 mmol, 3.0 equiv), HCl (20 mol %, 4 M in dioxane), ^{i}PrOH, 100 °C, 24 h; Reaction condition B: **1** (8.0 mmol), **2a** (4.0 mmol), $[Rh(cod)Cl]_2$ (2.5 mol %), DPEphos (5.0 mol %), TsOH (20 mol %), NMP/dioxane, 100 °C, 24 h; (i) **4a** (0.15 mmol), Pd/C (10 mol %), H_2 (100 psi), EtOH, rt, 12 h; (ii) **4a** (2.0 mmol), acetyl chloride (3.0 equiv), DMAP (20 mol %), pyridine (3.0 equiv), DCM, 0 °C to rt, 48 h; (iii) **22** (0.10 mmol), SeO_2 (40 mol %), TBHP (2.0 equiv), DCE, 60 °C, 2 h; (iv) **22** (0.10 mmol), $Fe(acac)_3$ (2.5 mol %), $PhSiH_3$ (3.0 equiv), $NaHCO_3$ (2.0 equiv), MeOH, 0 °C–rt, 12 h; (v) **22** (0.10 mmol), *m*-CPBA (1.5 equiv), DCM, rt, 5 h.

Conclusion

In conclusion, we have developed a unique skeleton-reorganizing coupling reaction of cycloheptatriene and cycloalkenones with anilines. Under Rh/acid catalysis, 1,2-dihydroquinolines were selectively obtained by editing the cycloheptatriene skeleton with various anilines. Mechanistic studies showed that the reaction proceeded through a bimolecular hydroamination initially, followed by a retro-Mannich-type ring-opening and subsequent Povarov reaction, which led to the ring-reorganization process. To simplify the reaction model and extend the substrate scope, we developed an acid-promoted protocol for the skeleton reorganization of cycloalkenones with anilines. Gram-scale reactions, synthetic transformations and late-stage modification of various commercial pharmaceuticals were also presented to highlight the practical utilization. Further applications of this skeleton-reorganizing coupling reaction are underway in our laboratory.

Acknowledgements

We thank Prof. Daniel K. Kim (Temple University) for helpful discussions and paper revisions. Financial support from the Dalian Outstanding Young Scientific Talent (2020RJ05), the National Natural Science Foundation of China (22071239), the China Postdoctoral Science Foundation (2022M713083), and the Doctoral Research Startup Fund Project of Liaoning Province (2022BS013) is acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: 1,2-Dihydroquinolines · Cycloalkenones · Cycloheptatrienes · Hydroamination · Skeleton Reorganization

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[16] Deposition numbers 2165476 (for **4a**), 21653987 (for **5a·Ac**) and 2165418 (for **14a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Manuscript received: September 5, 2022
Accepted manuscript online: November 13, 2022
Version of record online: December 7, 2022