



Published in final edited form as:

Nat Chem. 2014 August ; 6(8): 739–744. doi:10.1038/nchem.1989.

Cooperative activation of cyclobutanones and olefins leads to bridged-ring systems by a catalytic [4+2] coupling

Haye Min Ko¹ and Guangbin Dong^{1,*}

¹Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States

Abstract

Bridged-ring systems are widely found in natural products and successful syntheses of them frequently feature intramolecular Diels-Alder (IMDA) reactions. These reactions are subclassified as either type I or type II IMDAs depending on how the diene motif is tethered to the rest of the substrate - type I are tethered at the 1-position of the diene and type II at the 2-position. While the type I IMDA has been used to great success, the molecular scaffolds accessible by type II IMDAs are limited by the strain inherent in the formation of a sp^2 -carbon at a bridgehead position. Here, we describe a complementary approach that provides access to these structures through the C–C activation of cyclobutanones and their coupling with olefins. Various alkenes have been coupled with cyclobutanones to provide a range of bridged skeletons. The ketone group of the products serves as a convenient handle for downstream functionalization.

The intramolecular Diels-Alder (IMDA) reaction, a $[4\pi+2\pi]$ cycloaddition, is one of the most widely utilized reactions for preparing ring systems.^{1–10} According to how the diene motif is tethered to the dienophile, IMDA reactions are classified into two types: type I and type II.⁷ While vast success has been achieved for applying type I-IMDA (tethered at the 1-position of the diene) in fused-ring syntheses, in contrast, much limited scaffolds can be prepared by type II-IMDA (tethered at the 2-position of the diene) due to Bredt's rule¹¹ (unfavorable sp^2 carbon at the bridge-head position). For example, while 6–6 and 5–6 bridged rings are commonly found in various bioactive molecules (Fig. 1a), formation of 6–6 bridged rings ([3.3.1]-bicycle) via type II-IMDA was mainly restricted in gas phase^{12–14} and to our knowledge, no 5–6 bridged rings ([3.2.1]-bicycle) has been observed to date using such an approach (Fig. 1b). Stimulated by the challenge of type II-IMDA, in this communication, we describe an alternative [4+2] coupling method that is capable of providing type II-IMDA-like products via a cooperative C–C bond activation of cyclobutanones. Using this methodology, a complementary scope of bridged skeletons, including a variety of 6–6 and 5–6 bridged rings, can be accessed; furthermore, the ketone group of the products can serve as a convenient handle to access other functional groups or ring systems.

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use:http://www.nature.com/authors/editorial_policies/license.html#terms

*To whom correspondence should be addressed at gbdong@cm.utexas.edu.

Author Contributions

H.M.K. and G.D. conceived and designed the experiments. H.M.K. performed the experiments. H.M.K and G.D. analysed the data. H.M.K. and G.D. co-wrote the manuscript.

Results and discussion

C–C bond activation/functionalization recently merged a useful method for synthesizing complex scaffolds from relatively simpler starting materials.^{15–29} In particular, bridged-ring synthesis can be benefited by this strategy. The intramolecular insertion of alkynes into benzocyclobutendione C–C bonds was first reported by Liebeskind using a stoichiometric Co-complex (Fig. 1c).³⁰ Seminal work by Murakami/Ito described intramolecular insertions of styrene-type olefins into cyclobutanones catalyzed by either cationic Rh^I or Ni⁰, albeit limited to benzo-fused skeletons (Fig. 1c).^{31–32} One key challenge for developing cyclobutanone-olefin couplings via metal-mediated oxidative addition into C–C bonds is the competing decarbonylation reaction (Fig. 1c), which leads to either ring contraction or fragmentation (for cyclobutanone activations via β -carbon elimination, see refs 32–39).³¹ Therefore, in order to develop a general cyclobutanone-olefin coupling that is broadly applicable for synthesizing bridged type II-IMDA-like products, the decarbonylation challenge has to be overcome and the scope of the olefin substrates (e.g. both aryl and alkyl substituted alkenes) as well as the variety of the bridged-scaffolds must be extended.

Our strategy is inspired by a “cofactor”-assisted C–C activation mode initially developed by Jun,^{40–42} which utilizes 2-amino-3-methylpyridine as a co-catalyst to generate an imine intermediate that serves as a directing group for cleaving the imine α C–C bond. This strategy has been effectively utilized to cleave medium to large cyclic ketimines in the presence of alkenes to afford ring-opened products (Fig. 1c). However, to the best of our knowledge, *utilization of this mode in small-ring activation has not been reported previously*. We hypothesized that employment of 2-amino-3-methylpyridine as a co-catalyst would benefit the desired intramolecular cyclobutanone-olefin coupling, depicted in Fig. 2. The amine would first form an imine with the cyclobutanone, which would then direct C–C cleavage through forming a chelation complex with the metal (e.g. Rh). Subsequent olefin migratory insertion followed by reductive elimination is expected to provide the bridged scaffold and regenerate the metal catalyst. Finally, the resulting imine can be hydrolyzed to give the bridged-ketone product and 2-amino-3-methylpyridine, which can be recycled. Hence, this strategy, distinct from the previous cyclobutanone activations,^{31–32, 28} can ease the C–C cleavage but more importantly prevent the aforementioned decarbonylation problem, because the carbonyl group would be *in situ* protected by the imine formation. Moreover, in principle, both the transition metal and the aminopyridine can be catalytic.

To test our hypothesis, cyclobutanone **1a** was used as the model substrate, which was readily prepared in three steps from inexpensive commercially available materials. In the presence of 3-methyl-2-aminopyridine (**3**), a variety of Rh precatalysts, ligands and solvents were examined (for details, see supplementary information). The conditions (cationic Rh with dppp) that gave the best results in the previous example (Fig. 1c, Murakami/Ito)³¹ did not provide any of the desired bicycle (entry 1, Table 1). However, [Rh(COD)Cl]₂ was found to be a promising precatalyst and the desired bridged bicycle (3-azabicyclo[3,3,1]nonanone) **2a**^{43–47} was obtained albeit in low yields (entry 2). The solvent effect was next evaluated and 1,4-dioxane proved to be the best solvent (entries 3–5). While the yield of bicycle **2a** can be improved by adding more COD ligand (entry 6), employment of a monodentate electron-deficient phosphine ligand was found more effective likely due to

that the migratory insertion and reductive elimination steps can be accelerated with more π -acidic ligands (entries 7–9). Use of bidentate ligands, such as dppp and dppb, showed no catalytic activity. $[\text{Rh}(\text{COD})\text{Cl}]_2$ (10 mol %) with $\text{P}(3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2)_3$ (22 mol %) was found to give full conversion with an 82% isolated yield of product **2a** (entry 9). Use of a catalytic amount of cofactor **3** (20 mol %) is also feasible albeit giving a slightly lower yield (76%) with extended reaction time (entry 10). Ultimately, use of 5 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (10 mol% total on Rh) and 24 mol% $\text{P}(3,5\text{-C}_6\text{H}_3(\text{CF}_3)_2)_3$ provided aza[3,3,1]nonanone **2a** in 87% isolated yield (entry 11).

The use of cofactor **3** was critical. In the absence of **3**, no [4+2] product was observed; decarbonylation products and the Rh-carbonyl complex (a dead catalyst, see supplementary information) can be detected by LCMS, HRMS and $^1\text{H-NMR}$ (entry 12). This control experiment strongly supports our hypothesis that decarbonylation can be inhibited by using 2-amino-3-methylpyridine (*vide supra*). The structure of bridged-bicycle **2a** was unambiguously confirmed by ^1H , ^{13}C NMR, IR, HRMS and X-ray crystallography. Given that the nitrogen-containing scaffold was obtained when the nitrogen-tether was employed, we expect this method can potentially be useful for alkaloid synthesis (Fig. 1a).

With the optimized conditions in hand, we next investigated the substrate scope (Table 2). In general, cyclobutanones tethered with 1,1-disubstituted olefins were converted into the corresponding 3-azabicyclo[3,3,1]nonanones smoothly. Not surprisingly, increasing the steric bulk on the olefin substituent from methyl to isopropyl to cyclopentyl slowed the reaction (entries 1–5), but the desired bridged bicycles were all nevertheless obtained in good to modest yields. Monosubstituted olefins can also insert into the C–C bond of cyclobutanones efficiently (entries 6 and 7). Changing the protecting group on the nitrogen from Ts to carbamate (CO_2Me) did not significantly affect the reactivity (entry 7 vs 6). Aryl-substituted olefins were found to be more challenging substrates likely due to their stability issue under the reaction conditions; nevertheless, it is encouraging to note that they can still participate in this transformation, albeit with relatively lower efficiency. The more electron-rich aryl olefins provided much higher yields than the corresponding electron-poor substrates (entries 8–10). Changing the quaternary carbon substitution (from Me to Et) on cyclobutanones did not significantly affect the reactivity (entry 11).

Both *cis* and *trans*-disubstituted olefins are suitable substrates, and higher reactivity was observed with the *cis* substrate (entries 12 and 13). Both substrates **1l** and **1m** provided the products with the same diastereomeric ratio (dr), probably due to an enamine equilibration. Besides forming 6–6 bridged [3.3.1] systems, the 5–6 bridged [3.2.1] scaffolds can also be obtained using this strategy. The vinyl sulfonamide **1n** can participate to give the desired bridged ring (**2n**) (entry 14). In addition, substrates with all-carbon linkages were also found suitable (entries 15 and 16). It is interesting to note that with **1o** as the substrate, a stable enamine derivative of **2o** (with 2-amino-3-methylpyridine **3**) can be isolated as the major product, which was confirmed by X-ray crystallography (see supplementary information). Subsequent hydrolysis with diluted acetic acid provided the ketone **2o** in 54% (81% brsm) yield (entry 15). The substrate with an arene linkage (**1p**)³¹ provided the desired benzo-bicycle (**2p**) in nearly a quantitative yield under the standard conditions, suggesting a potentially broad substrate scope (entry 16).

Substrate **1q** with a spirocyclic center was also investigated for this transformation (Fig. 3a). Two diastereomers of the desired product were obtained due to the diastereotopic difference between the two α -C–C bonds. The products **2q-i** and **2q-ii** contain interesting tricyclic bridged and fused scaffolds, which have been found in a number of aconitum/delphinium alkaloids (Fig. 1a, *vide supra*). Structures of both products were unambiguously confirmed by X-ray crystallography of their 2,4-dinitrophenylhydrazone derivatives (see supplementary information). Furthermore, preliminary studies have revealed that chiral phosphoramidite ligands, such as **4**, effect the desymmetrization of cyclobutanone **1b** with promising levels of enantioselectivity (Fig. 3b, 37% ee).^{48–49} This result suggests that the “cofactor”-assisted C–C activation mode is amenable to asymmetric catalysis, and work on this topic is ongoing.

Finally, we demonstrated the carbonyl group in the formed bridged bicycles can serve as a convenient handle to access other ring systems through either ring contraction or expansion (Fig. 3c). Treatment of **2a** under Baeyer–Villiger oxidation conditions gave the α -chloroketone unexpectedly. Subsequent Favorskii rearrangement afforded the ring-contraction product (**6**) in 78% yield. Oxime formation followed by Beckmann rearrangement provided the ring-expansion product (7–6 bridged amide, **8**) uneventfully.

Conclusion

In summary, we have developed a unique strategy to enable a “saturated analogue” of type II-IMDA reaction between cyclobutanones and simple alkenes via a Rh-catalyzed “cofactor”-assisted C–C activation approach. Substrates with different tethers and olefin substitutions (both aryl and alkyl alkenes) underwent this transformation. The resulting ketone bicycles can be readily further functionalized through carbonyl chemistry. While sharing a common feature to form 6-membered rings, this approach can provide scaffolds that are difficult to prepare using conventional IMDA reactions. Another advantage is that unactivated alkyl or aryl-substituted alkenes, instead of Michael acceptors (typically used in type-II IMDA)⁷, can be used as coupling partners. We expect the strategy developed here may provide inspirations for designing new tactics to synthesize complex natural products and other bioactive molecules.

Methods

In a nitrogen filled glove box, a 1-dram vial was charged with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (1.9 mg, 5 mol%), tris[3,5-bis(trifluoromethyl)phenyl]phosphine (16 mg, 24 mol%) and 2-amino-3-picoline (10 μl , 0.1 mmol). A solution of starting material **1a** (32 mg, 0.1 mmol) in dioxane (1 ml, 0.1 M) was added and the 1-dram vial was capped and the solution was maintained at 152 °C for 48 h. The reaction was removed from the glove box and purified by flash chromatography. The product **2a** was obtained as a bright orange solid (28 mg, 87%). The procedure to prepare compound **2a** is generally representative for all the products shown in Table 2. Any deviations from this protocol are specified in the footnote of the table.

Acknowledgements

We thank CPRIT (R1118) for a startup fund, NIH (1R01GM109054-01) and the Welch Foundation (F 1781) for research grants. G. D. is a Searle Scholar. We thank Profs. Sessler, Siegel and Anslyn for loaning chemicals. Dr. Lynch is acknowledged for X-ray crystallography. We also thank Johnson Matthey for a donation of Rh salts. Chiral Technologies is acknowledged for a donation of chiral HPLC columns. Mr. Thompson is thanked for proof reading of this manuscript.

References

1. Oppolzer W. Intramolecular [4+2] and [3+2] cycloadditions in organic synthesis. *Angew. Chem. Int. Ed.* 1977; 16:10–23.
2. Brieger G, Bennett JN. The intramolecular Diels-Alder reaction. *Chem. Rev.* 1980; 80:63–97.
3. Fallis AG. The intramolecular Diels-Alder reaction: recent advances and synthetic applications. *Can. J. Chem.* 1984; 62:183–234.
4. Craig D. Stereochemical aspects of the intramolecular Diels-Alder reaction. *Chem. Soc. Rev.* 1987; 16:187–238.
5. Roush, WR. *Comprehensive Organic Synthesis*. Trost, BM.; Fleming, I.; Paquette, LA., editors. Vol. 5. Oxford, UK: Pergamon Press; 1991. p. 513–550.
6. Fallis AG. Harvesting Diels and Alder's Garden: synthetic investigations of intramolecular [4+2] cycloadditions. *Acc. Chem. Res.* 1999; 32:464–474.
7. Bear BR, Sparks SM, Shea KJ. The type 2 intramolecular Diels-Alder reaction: synthesis and chemistry of bridgehead alkene. *Angew. Chem. Int. Ed.* 2001; 40:820–849.
8. Marsault E, Toro A, Nowak P, Deslongchamps P. The transannular Diels-Alder strategy: applications to total synthesis. *Tetrahedron.* 2001; 57:4243–4260.
9. Suzuki Y, Murata T, Takao K, Tadano K. The intramolecular Diels-Alder strategy: applications to total synthesis of natural products. *J. Synth. Org. Chem. Jpn.* 2002; 60:679–690.
10. Ciganek E. The Intramolecular Diels–Alder Reaction. *Organic Reactions.* 2004:1–374.
11. Bredt J. Über sterische Hinderung in Brückenringen (Bredtsche Regel) und über die *meso-trans*-Stellung in kondensierten Ringsystemen des Hexamethylens. *Liebigs Ann. Chem.* 1924; 437:1–13.
12. Shea KJ, Wise S. Intramolecular Diels-Alder reaction. A new entry into bridgehead bicyclo[3.n.1]alkenes. *J. Am. Chem. Soc.* 1978; 100:6519–6521.
13. Shea KJ, Wise S. Intramolecular diels-alder cycloadditions. Synthesis of substituted derivatives of bicyclo[3.n.1]bridgehead alkenes. *Tetrahedron Lett.* 1979; 20:1011–1014.
14. Shea KJ, et al. Applications of the intramolecular Diels-Alder reaction to the formation of strained molecules. *Synthesis of bridgehead alkenes. J. Am. Chem. Soc.* 1982; 104:5708–5715.
15. Jones WD. The fall of the C-C bond. *Nature.* 1993; 364:676–677.
16. Murakami M, Ito Y. Cleavage of carbon-carbon single bonds by transition metals. *Top. Organomet. Chem.* 1999; 3:97–129.
17. Rybtchiski B, Milstein D. Metal insertion into c-c bonds in solution. *Angew. Chem. Int. Ed.* 1999; 38:870–883.
18. Perthuisot C, et al. Cleavage of the carbon-carbon bond in biphenylene using transition metals. *J. Catal. Mol. A.* 2002; 189:157–168.
19. van der Boom ME, Milstein D. Cyclometalated phosphine-based pincer complexes: Mechanistic insight in catalysis, coordination, and bond activation. *Chem. Rev.* 2003; 103:1759–1792. [PubMed: 12744693]
20. Jun C-H. Transition metal-catalyzed carbon-carbon bond activation. *Chem. Soc. Rev.* 2004; 33:610–618. [PubMed: 15592626]
21. Miura M, Satoh T. Catalytic processes involving β -carbon elimination. *Top. Organomet. Chem.* 2005; 14:1–20.
22. Jun C-H, Park JW. Directed C-C bond activation by transition metal complexes. *Top. Organomet. Chem.* 2007; 24:117–143.

23. Necas D, Kotora M. Rhodium-Catalyzed C-C Bond Cleavage Reactions. *Curr. Org. Chem.* 2007; 11:1566–1592.
24. Crabtree RH. The organometallic chemistry of alkanes. *Chem. Rev.* 1985; 85:245–269.
25. Kondo T, Mitsudo TA. Ruthenium-catalyzed reconstructive synthesis of functional organic molecules via cleavage of carbon-carbon bonds. *Chem. Lett.* 2005; 34:1462–1467.
26. Ruhland K. Transition-metal-mediated cleavage and activation of C-C single bonds. *Eur. J. Org. Chem.* 2012; 2012:2683–2706.
27. Korotvicka A, Necas D, Kotora M. Rhodium-catalyzed C-C bond cleavage reactions - an update. *Curr. Org. Chem.* 2012; 16:1170–1214.
28. Seiser T, Saget T, Tran DN, Cramer N. Cyclobutanes in catalysis. *Angew. Chem. Int. Ed.* 2011; 50:7740–7752.
29. Dermenci A, Dong G. Decarbonylative C-C bond forming reactions mediated by transition metals. *Sci. China Chem.* 2013; 56:685–701.
30. South MS, Liebeskind LS. Regiospecific total synthesis of (\pm)-nanaomycin A using phthaloylcobalt complexes. *J. Am. Chem. Soc.* 1984; 106:4181–4185.
31. Murakami M, Itahashi T, Ito Y. Catalyzed intramolecular olefin insertion into a carbon-carbon single bond. *J. Am. Chem. Soc.* 2002; 124:13976–13977. [PubMed: 12440879]
32. Murakami M, Ishida N, Miura T. Solvent and ligand partition reaction pathways in nickel-mediated carboxylation of methylenecyclopropanes. *Chem. Commun.* 2006:643–645.
33. Murakami M, Ashida S, Matsuda T. Two-carbon ring expansion of cyclobutanone skeletons by nickel-catalyzed intermolecular alkyne insertion. *Tetrahedron.* 2006; 62:7540–7546.
34. Murakami M, Ashida S, Matsuda T. Nickel-catalyzed intermolecular alkyne insertion into cyclobutanones. *J. Am. Chem. Soc.* 2005; 127:6932–6933. [PubMed: 15884919]
35. Murakami M, Ashida S. Nickel-catalysed intramolecular alkene insertion into cyclobutanones. *Chem. Commun.* 2006:4599–4601.
36. Ashida S, Murakami M. Nickel-catalyzed [4+2+2]-type annulation reaction of cyclobutanones with diynes and enynes. *Bull. Chem. Soc. Jpn.* 2008; 81:885–893.
37. Liu L, Ishida N, Murakami M. Atom- and step-economical pathway to chiral benzobicyclo[2.2.2]octenones through carbon-carbon bond cleavage. *Angew. Chem. Int. Ed.* 2012; 51:2485–2488.
38. Kumar P, Louie J. A single step approach to piperidines via Ni-catalyzed β -carbon elimination. *Org. Lett.* 2012; 14:2026–2029. [PubMed: 22468962]
39. Ishida N, Yuhki T, Murakami M. Synthesis of enantiopure dehydropiperidinones from α -amino acids and alkynes via azetidion-3-ones. *Org. Lett.* 2012; 14:3898–3901. [PubMed: 22799436]
40. Lee H, Jun C-H. Catalytic carbon-carbon bond activation of unstrained ketone by soluble transition-metal complex. *J. Am. Chem. Soc.* 1999; 121:880–881.
41. Park YJ, Park J-W, Jun C-H. Metal-organic cooperative catalysis in C-H and C-C bond activation and its concurrent recovery. *Acc. Chem. Res.* 2008; 41:222–234. [PubMed: 18247521]
42. Jun C-H, Lee H, Lim S-G. The C-C bond activation and skeletal rearrangement of cycloalkane imine by Rh(I) catalysts. *J. Am. Chem. Soc.* 2001; 123:751–752. [PubMed: 11456596]
43. Luo S-P, Guo L-D, Gao L-H, Li S, Huang P-Q. Toward the total synthesis of haliclolin A: construction of a tricyclic substructure. *Chem. Eur. J.* 2013; 19:87–91. [PubMed: 23225701]
44. Mazurov AA, et al. Novel nicotinic acetylcholine receptor agonists containing carbonyl moiety as a hydrogen bond acceptor. *Bioorg. Med. Chem. Lett.* 2013; 23:3927–3934. [PubMed: 23692872]
45. Cheng X, Waters SP. Pyridone annulation via tandem Curtius rearrangement/ 6π -electrocyclization: total synthesis of (-)-lyconadin C. *Org. Lett.* 2013; 15:4226–4229. [PubMed: 23909645]
46. Breining SR, et al. Structure-activity studies of 7-heteroaryl-3-azabicyclo[3.3.1]non-6-enes: a novel class of highly potent nicotinic receptor ligands. *J. Med. Chem.* 2012; 55:9929–9945. [PubMed: 23025891]
47. Jirgensons A, Kauss V, Mishnev AF, Kalvinsh I. The synthesis of 3-amino-methylbicyclo[3.3.1]nonanes: Endo-selectivity in the Ritter reaction of 1,3,5,7 α -tetramethylbicyclo[3.3.1]nonan-3-ol. *J. Chem. Soc. Perkin Trans.* 1999; 1:3527–3530.

48. Parker E, Cramer N. Asymmetric Rhodium(I)-Catalyzed C–C Activations with Zwitterionic Bis-phospholane Ligands. *Organometallics*. 2014; 33:780–787.
49. Souillart L, Parker E, Cramer N. Highly enantioselective rhodium(I)-catalyzed activation of enantiotopic cyclobutanone c-c bonds. *Angew. Chem. Int. Ed.* 2014; 53:3001–3005.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

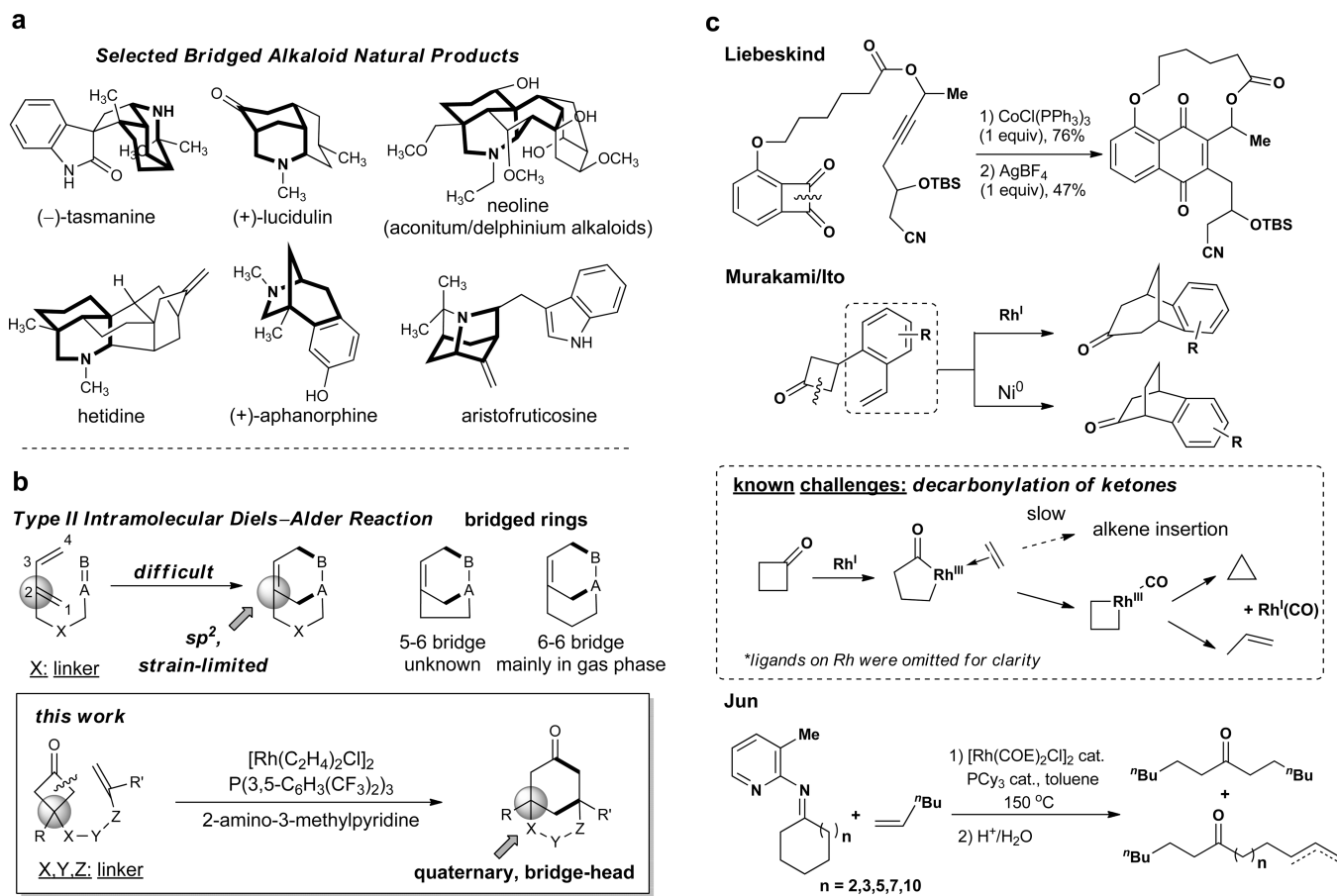


Figure 1. The challenge of bridged-ring synthesis

a, Selected alkaloid natural products with bridged-ring substructures. **b**, Comparison of the type II IMDA reaction - which is synthetically limited by the incipient strain in an unsaturated bridgehead carbon - and the approach described in this work. **c**, Previous work on metal-catalysed C–C activation of cyclobutanones towards coupling and potential challenges due to the decarbonylation of the ketones.

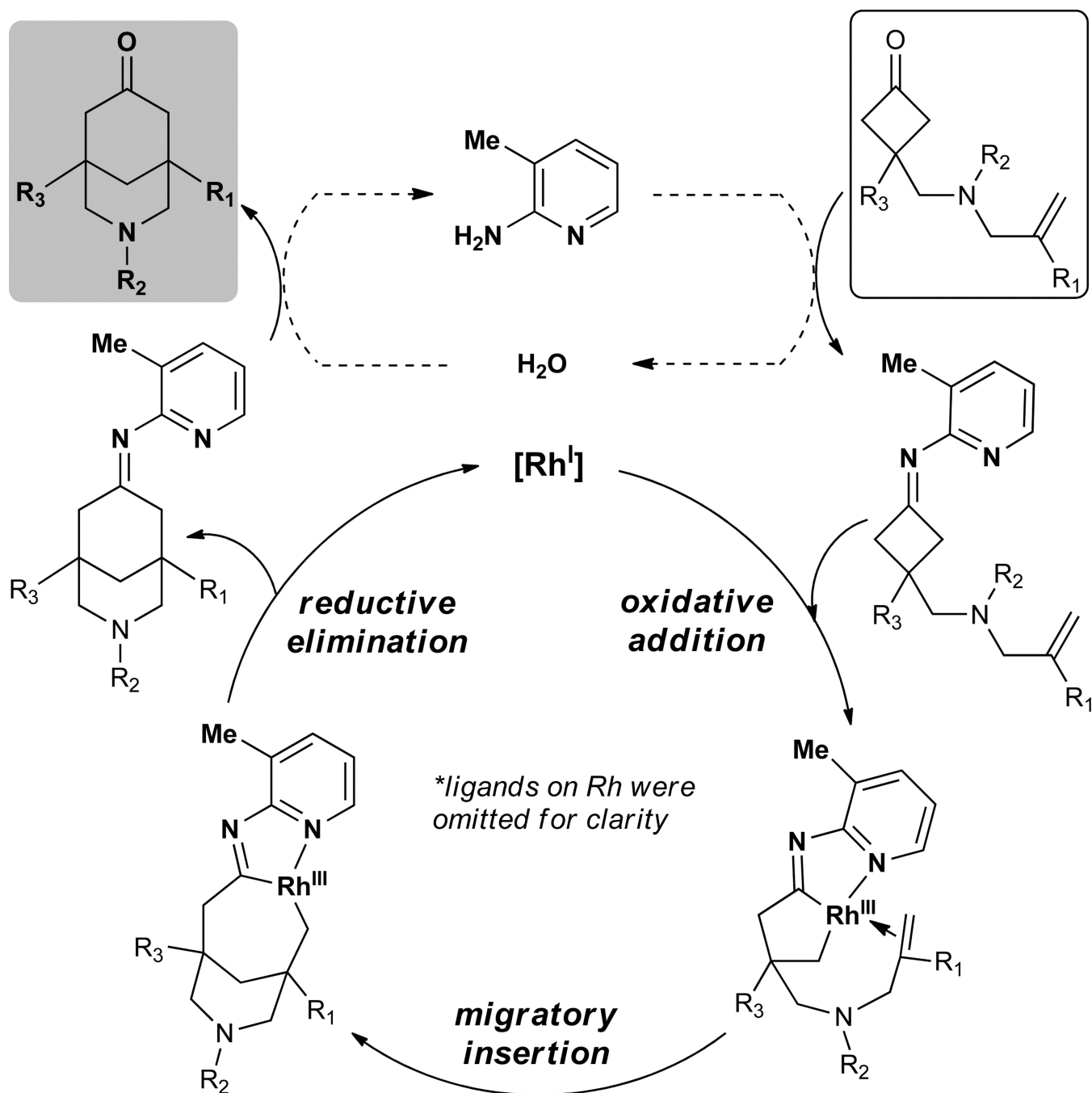


Figure 2. Proposed catalytic cycle

The key features include using metal-ligand cooperative activation of cyclobutanones and *in situ* carbonyl group protection to avoid decarbonylation.

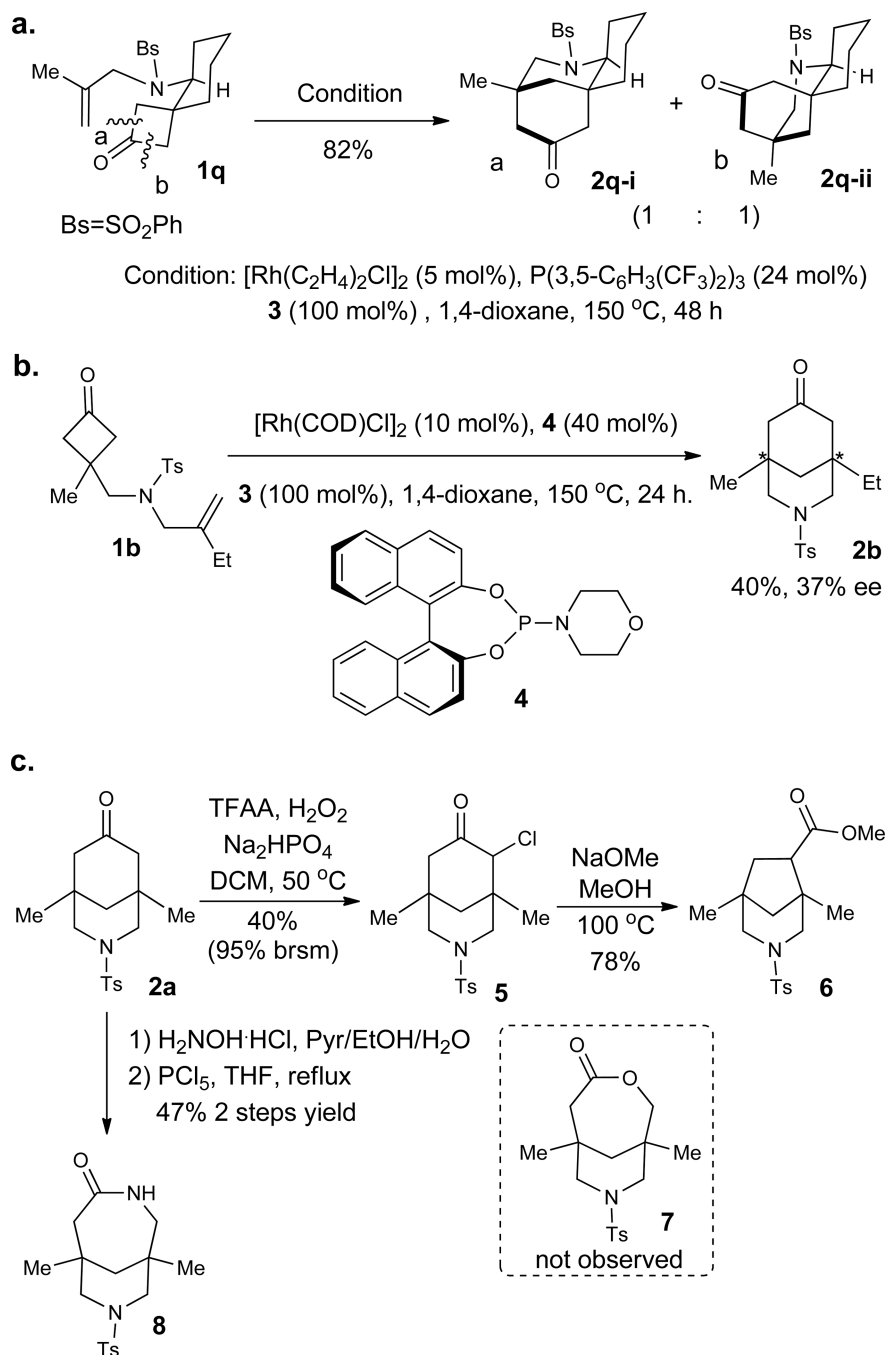
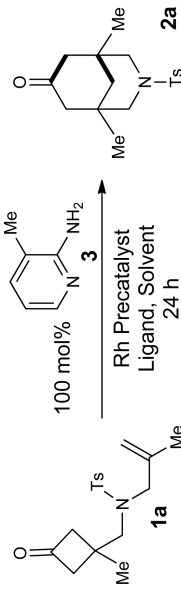


Figure 3. Potentials and applications in bridged-ring synthesis

a. Construction of fused-bridged tricyclic structures. **b.** Potentials for developing an enantioselective transformation. **c.** Use of the carbonyl group in the product as a handle to access ring-contracted and expanded bridged rings.

Table 1

Selected optimization studies



Entry	Catalyst	Ligand/Additive	Solvent	Temp. (°C)	Yield (%) [*]
1	5 mol% [Rh(nbd)dppe]PF ₆	10 mol% BHT	Xylenes	130	0
2	10 mol% [Rh(COD)Cl] ₂		Toluene	130	<5
3	10 mol% [Rh(COD)Cl] ₂		CIPh	150	23(34)
4	10 mol% [Rh(COD)Cl] ₂		Xylenes	150	27(30)
5	10 mol% [Rh(COD)Cl] ₂		1,4-Dioxane	150	43(51)
6	10 mol% [Rh(COD)Cl] ₂	20 mol% COD	1,4-Dioxane	150	47(57)
7	10 mol% [Rh(COD)Cl] ₂	20 mol% P(C ₆ F ₅) ₃	1,4-Dioxane	150	58(65)
8	10 mol% [Rh(COD)Cl] ₂	10 mol% P(3,5-C ₆ H ₃ (CF ₃) ₂) ₃	1,4-Dioxane	150	67(74)
9	10 mol% [Rh(COD)Cl] ₂	22 mol% P(3,5-C ₆ H ₃ (CF ₃) ₂) ₃	1,4-Dioxane	150	82
10	10 mol% [Rh(COD)Cl] ₂ [†]	22 mol% P(3,5-C ₆ H ₃ (CF ₃) ₂) ₃	1,4-Dioxane	150	76(88)
11	5 mol% [Rh(C ₂ H ₄) ₂ Cl] ₂	24 mol% P(3,5-C ₆ H ₃ (CF ₃) ₂) ₃ [§]	1,4-Dioxane	150	87
12	5 mol% [Rh(C ₂ H ₄) ₂ Cl] ₂ [†]	24 mol% P(3,5-C ₆ H ₃ (CF ₃) ₂) ₃ [§]	1,4-Dioxane	150	0//

* Isolated yield; numbers in parentheses are brsm yield.

^r 20 mol% **3** was used with 71 h reaction time.

^r no **3** was added.

^s The reaction time was 48 h.

//Decarbonylation products were observed as an inseperable mixture.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Substrate Scope*		Yield (%) [†]	
Entry	Substrate	Product	Yield (%) [‡]
1			87
2			81
3			63(86)
4			63
5			52(75)
6			79
7			80
8			56(69) ^{†, §}
9			66(78) ^{†, §}
10			39(43) ^{†, §}
11			76
12			74 [§] d.r. = 2.4:1 (major isomer)
13			46 [§] d.r. = 2.4:1 (major isomer)
14			50(75)
15			54(81) [§] E = CO ₂ Et
16			98 [§]

* Reaction condition: [Rh(C₂H₄)₂Cl]₂ (5 mol%), P(3,5-C₆H₃(CF₃)₂)₃ (24 mol%), **3** (100 mol%), 1,4-dioxane, 150 °C, 48 h.

[†] Isolated yield; numbers in parentheses are brsm yield.

[‡] [Rh(C₂H₄)₂Cl]₂ (10 mol%) and P(3,5-C₆H₃(CF₃)₂)₃ (48 mol%) were used.

[§] 24 h.