nature chemistry

ARTICLES

PUBLISHED ONLINE: 6 JULY 2014 | DOI: 10.1038/NCHEM.1989

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

Haye Min Ko and Guangbin Dong*

Bridged ring systems are widely found in natural products, and successful syntheses of them frequently feature intramolecular Diels–Alder reactions. These reactions are subclassified as either type I or type II 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). Although the type I reaction has been used with great success, the molecular scaffolds accessible by the type II reactions are limited by the strain inherent in the formation of an 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 one of two types: type I or type II[7]. Although there has been great success in the application of type I IMDA reactions (tethered at the 1-position of the diene) in fused-ring syntheses, only very limited scaffolds can be prepared using type II IMDA reactions (tethered at the 2-position of the diene) because of Bredt's rule[11] (unfavourable sp^2 carbon at the bridge-head position). For example, 6–6 and 5–6 bridged rings are commonly found in various bioactive molecules (Fig. 1a), but the formation of 6–6 bridged rings ([3.3.1]-bicycle) via type II IMDA has mainly been restricted to the gas phase[12–14], and to our knowledge, no 5–6 bridged rings ([3.2.1]-bicycle) have as yet been observed using such an approach (Fig. 1b). Stimulated by the challenge of type II IMDA, we describe here 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.

Results and discussion

C–C bond activation/functionalization has recently emerged as a useful method for synthesizing complex scaffolds from relatively simpler starting materials[15–29]. In particular, bridged ring synthesis can benefit from 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 and Ito described intramolecular insertions of styrene-type olefins into cyclobutanones catalysed by either cationic Rh^I or Ni^0, 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 ring contraction or fragmentation[31] (for cyclobutanone activations via β-carbon elimination, see refs 32–39). Accordingly, to develop a general cyclobutanone–olefin coupling that is broadly applicable for the synthesis of bridged type II IMDA-like products, the decarbonylation challenge must be overcome and the scope of the olefin substrates (for example, both aryl and alkyl-substituted alkenes) and the variety of bridged scaffolds must be extended.

Our strategy was 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 used effectively 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. We hypothesized that the use of 2-amino-3-methylpyridine as a co-catalyst would benefit the desired intramolecular cyclobutanone–olefin coupling (Fig. 2). The amine would first form an imine with the cyclobutanone, which would then direct C–C cleavage by forming a chelation complex with the metal (for example, 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 hydrolysed to give the bridged ketone product and 2-amino-3-methylpyridine, which can be recycled. Hence, this strategy, unlike previous cyclobutanone activations[28,31,32], can ease the C–C cleavage and, more importantly, prevent the aforementioned decarbonylation problem, because the carbonyl group would be protected *in situ* 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. This 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 Table 1).

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, USA. *e-mail: gbdong@cm.utexas.edu

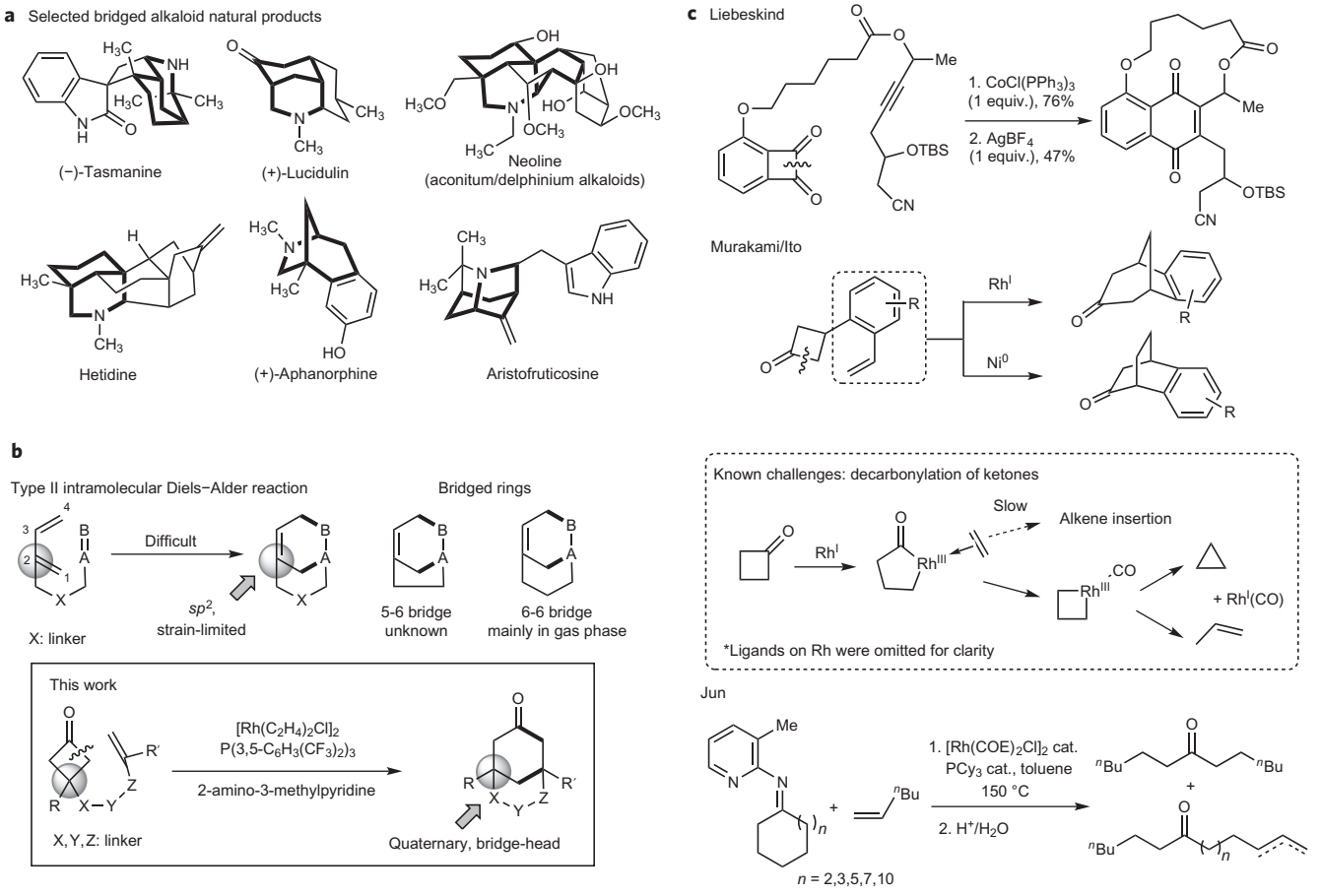


Figure 1 | The challenge of bridged ring synthesis. a, Selected alkaloid natural products with bridged-ring substructures. **b**, Comparison of the type II IMDA reaction, which is synthetically limited by the incipient strain in an unsaturated bridgehead carbon, and the approach described in this work. **c**, Previous work on metal-catalysed C–C activation of cyclobutanones towards coupling, and potential challenges due to the decarbonylation of the ketones.

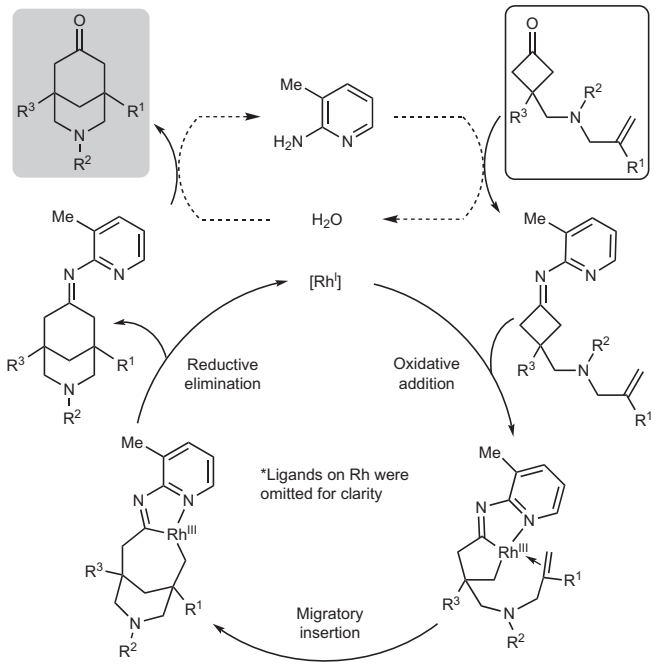
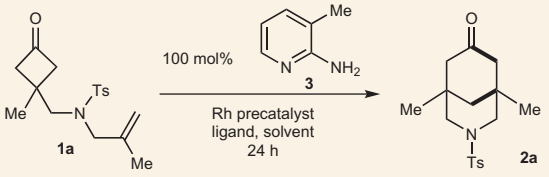


Figure 2 | Proposed catalytic cycle. The key features include using metal–ligand cooperative activation of cyclobutanones and *in situ* carbonyl group protection to avoid decarbonylation.

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, with the desired bridged bicycle (3-azabicyclo[3,3,1]nonanone) **2a**[43–47] obtained, albeit in low yield (entry 2). The solvent effect was next evaluated and 1,4-dioxane proved to be the best solvent (entries 3–5). Although the yield of bicycle **2a** can be improved by adding more COD ligand (entry 6), use of a monodentate electron-deficient phosphine ligand was found more effective, probably due to the fact 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, demonstrated no catalytic activity. $[Rh(COD)Cl]_2$ (10 mol%) with $P(3,5\text{-}C_6H_3(CF_3)_2)_3$ (22 mol%) was found to provide 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, but gave a slightly lower yield (76%) with an extended reaction time (entry 10). Ultimately, the use of 5 mol% $[Rh(C_2H_4)_2Cl]_2$ (10 mol% total on Rh) and 24 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$ 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 Section 'X-ray data') could be detected by liquid chromatography-mass spectrometry, high-resolution mass spectrometry (HRMS) and ^{1}H NMR (entry 12). This control experiment strongly supports our hypothesis that decarbonylation can be inhibited by using

Table 1 | Selected optimization studies.



Entry	Catalyst	Ligand/additive	Solvent	Temperature (°C)	Yield (%)*
1	5 mol% [Rh(nbd)dppp]PF_6‡	10 mol% BHT	Xylenes	130	0
2	10 mol% $[Rh(COD)Cl]_2$		Toluene	130	<5
3	10 mol% $[Rh(COD)Cl]_2$		ClPh	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% $P(C_6F_5)_3$	1,4-Dioxane	150	58(65)
8	10 mol% $[Rh(COD)Cl]_2$	10 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$	1,4-Dioxane	150	67(74)
9	10 mol% $[Rh(COD)Cl]_2$	22 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$	1,4-Dioxane	150	82
10	10 mol% $[Rh(COD)Cl]_2$†	22 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$	1,4-Dioxane	150	76(88)
11	5 mol% $[Rh(C_2H_4)_2Cl]_2$	24 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$§	1,4-Dioxane	150	87
12	5 mol% $[Rh(C_2H_4)_2Cl]_2$‡	24 mol% $P(3,5\text{-}C_6H_3(CF_3)_2)_3$§	1,4-Dioxane	150	0‖

*Isolated yield; numbers in parentheses are yield based on recovered starting material. †20 mol% **3** was used with 71 h reaction time. ‡ No **3** was added. §The reaction time was 48 h. ‖Decarbonylation products were observed as an inseparable mixture. brsm: based on recovered starting material; BHT: butylated hydroxytoluene; COD: 1,5-cyclooctadiene.

2-amino-3methylpyridine (*vide supra*). The structure of bridged bicycle **2a** was unambiguously confirmed by ^{1}H NMR, ^{13}C NMR, infrared, HRMS and X-ray crystallography. Given that the nitrogen-containing scaffold was obtained when the nitrogen tether was employed, we expect this method to have potential use in alkaloid synthesis (Fig. 1a).

With the optimized conditions determined, we next investigated the substrate scope (Table 2). In general, cyclobutanones tethered with 1,1-disubstituted olefins were smoothly converted into the corresponding 3-azabicyclo[3,3,1]nonanones. 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 efficiently into the C–C bond of cyclobutanones (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 versus 6). Aryl-substituted olefins were found to be more challenging substrates, probably due to a 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 the cyclobutanones did not significantly affect the reactivity (entry 11).

Both *cis*- and *trans*-disubstituted olefins are suitable substrates, but 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 (d.r.), probably due to enamine equilibration. As well as forming 6–6 bridged [3.3.1] systems, 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, as confirmed by X-ray crystallography (see Supplementary Section 'X-ray data'). Subsequent hydrolysis with diluted acetic acid provided the ketone **2o** in 54% (81% based on recovered starting material) yield (entry 15). The substrate with an arene linkage (**1p**)[31] provided the desired benzo-bicycle (**2p**) in

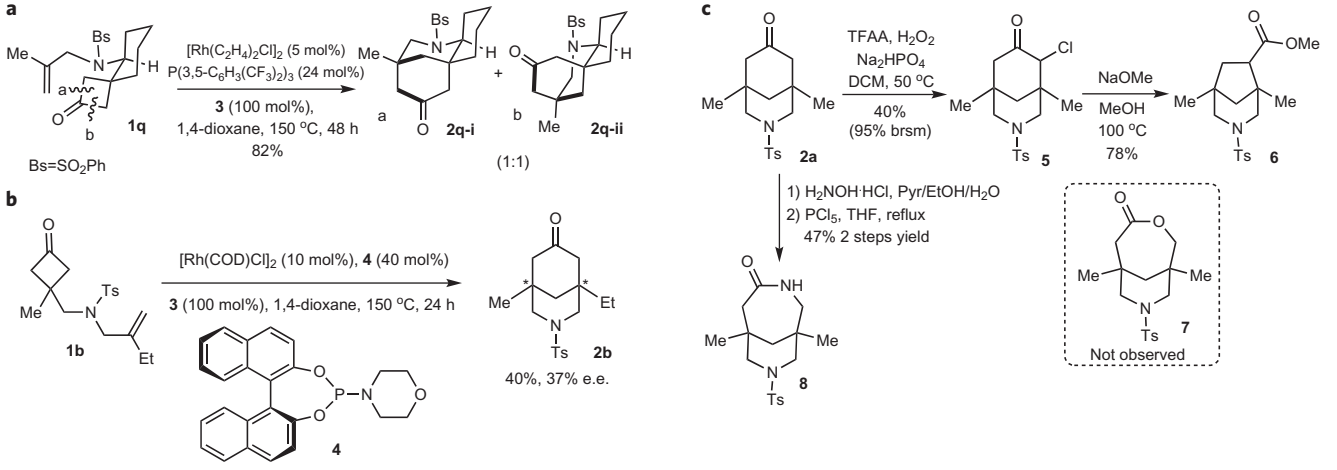
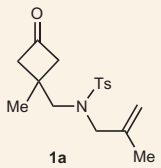
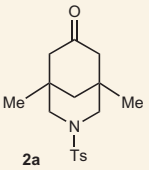
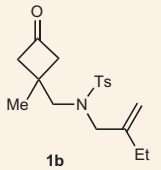
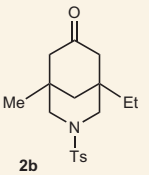
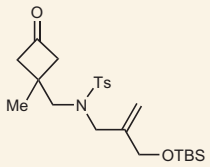
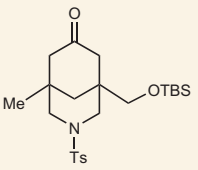
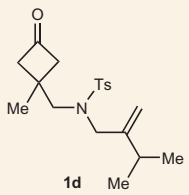
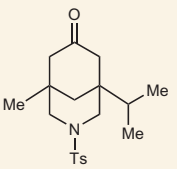
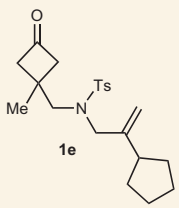
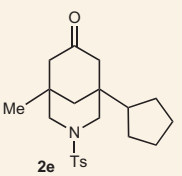
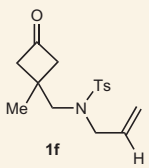
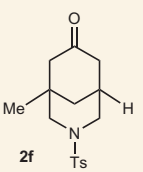
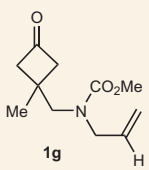
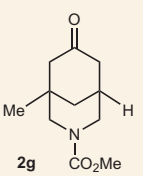
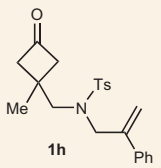
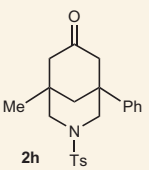
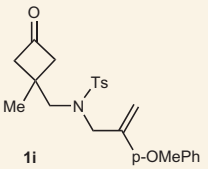
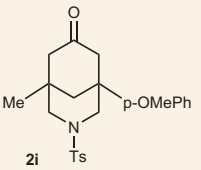
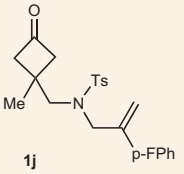
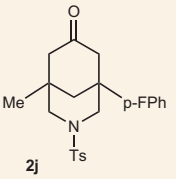
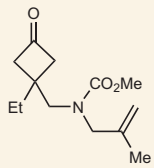
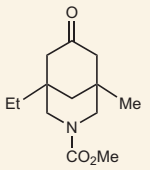
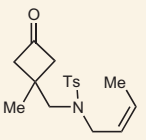
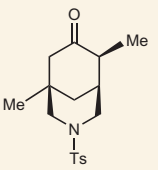
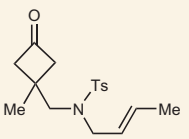
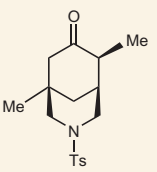
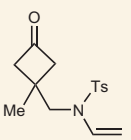
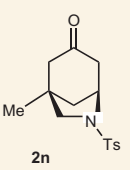
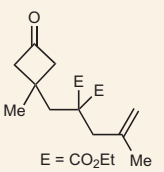
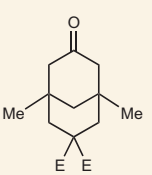
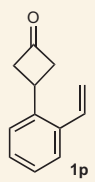
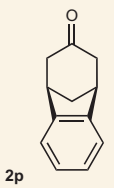


Figure 3 | Potentials and applications in bridged ring synthesis. a, Construction of fused-bridged tricyclic structures. **b**, Potentials for developing an enantioselective transformation. **c**, Use of the carbonyl group in the product as a handle to access ring-contracted and expanded bridged rings.

Table 2 | Substrate scope.

Entry	Substrate	Product	Yield (%)†
1	 **1a**	 **2a**	87
2	 **1b**	 **2b**	81
3	 **1c**	 **2c**	63(86)
4	 **1d**	 **2d**	63
5	 **1e**	 **2e**	52(75)
6	 **1f**	 **2f**	79
7	 **1g**	 **2g**	80
8	 **1h**	 **2h**	56(69)‡, §

Entry	Substrate	Product	Yield (%)†
9	 **1i**	 **2i**	66(78)‡, §
10	 **1j**	 **2j**	39(43)‡, §
11	 **1k**	 **2k**	76
12	 **1l**	 **2l** (major isomer)	74§ d.r. = 2.4:1
13	 **1m**	 **2m** (major isomer)	46§ d.r. = 2.4:1
14	 **1n**	 **2n**	50(75)
15	 **1o**	 **2o** E = CO_2Et	54(81)§
16	 **1p**	 **2p**	98§

Reaction condition: $[Rh(C_2H_4)_2Cl]_2$ (5 mol%), $P(3,5\text{-}C_6H_3(CF_3)_2)_3$ (24 mol%), **3** (100 mol%), 1,4-dioxane, 150 °C, 48 h. †Isolated yield; numbers in parentheses are brsm yield. ‡$[Rh(C_2H_4)_2Cl]_2$ (10 mol%) and $P(3,5\text{-}C_6H_3(CF_3)_2)_3$ (48 mol%) were used. §24 h.

a nearly quantitative yield under the standard conditions, suggesting a potentially broad substrate scope (entry 16).

Substrate **1q**, which has a spirocyclic centre, 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. 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). Structures of both products were unambiguously confirmed by X-ray crystallography of their 2,4-dinitrophenylhydrazone derivatives (see Supplementary Section 'X-ray data'). 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% enantiomeric excess, e.e.)[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 that 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 unexpectedly gave the α-chloroketone. 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 a type II IMDA reaction between cyclobutanones and simple alkenes via a Rh-catalysed 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 further functionalized readily via carbonyl chemistry. While sharing the common feature of forming six-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, rather than Michael acceptors (typically used in type-II IMDA)[7], can be used as coupling partners. We anticipate that the strategy developed here may provide inspiration for the design of new tactics to synthesize complex natural products and other bioactive molecules.

Methods

In a nitrogen-filled glovebox, a 1 dram vial was charged with $[Rh(C_2H_4)_2Cl]_2$ (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 maintained at 152 °C for 48 h. The reaction was removed from the glovebox and purified by flash chromatography. 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 table footnotes.

Received 21 February 2014; accepted 28 May 2014; published online 6 July 2014

References

1. Oppolzer, W. Intramolecular [4+2] and [3+2] cycloadditions in organic synthesis. *Angew. Chem. Int. Ed.* **16,** 10–23 (1977).
2. Brieger, G. & Bennett, J. N. The intramoecular Diels–Alder reaction. *Chem. Rev.* **80,** 63–97 (1980).
3. Fallis, A. G. The intramolecular Diels–Alder reaction: recent advances and synthetic applications. *Can. J. Chem.* **62,** 183–234 (1984).
4. Craig, D. Sterochemical aspects of the intrmolecular Diels–Alder reaction. *Chem. Soc. Rev.* **16,** 187–238 (1987).
5. Roush, W. R. in *Comprehensive Organic Synthesis* Vol. 5 (eds Trost, B. M., Fleming, I. & Paquette, L. A.) 513–550 (Pergamon, 1991).
6. Fallis, A. G. Harvesting Diels and Alder's garden: synthetic investigations of intramolecular [4+2] cycloadditions. *Acc. Chem. Res.* **32,** 464–474 (1999).
7. Bear, B. R., Sparks, S. M. & Shea, K. J. The type 2 intramolcular Diels–Alder reaction: synthesis and chemistry of bridgehead alkene. *Angew. Chem. Int. Ed.* **40,** 820–849 (2001).
8. Marsault, E., Toro, A., Nowak, P. & Deslongchamps, P. The transannular Diels–Alder strategy: applications to total synthesis. *Tetrahedron* **57,** 4243–4260 (2001).
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* **60,** 679–690 (2002).
10. Ciganek, E. 2004. The intramolecular Diels–Alder reaction. *Organic Reactions* http://dx.doi.org/10.1002/0471264180.or032.01 (Wiley, 2004).
11. Bredt, J. Über sterische Hinderung in Brückenringen (Bredtsche Regel) und über die *meso-trans*-Stellung in kondensierten Ringsystemen des Hexamethylens. *Liebigs Ann. Chem.* **437,** 1–13 (1924).
12. Shea, K. J. & Wise, S. Intramolecular Diels–Alder reacition. A new entry into brigehead bicyclo[3.n.1]alkenes. *J. Am. Chem. Soc.* **100,** 6519–6521 (1978).
13. Shea, K. J. & Wise, S. Intramolecular Diels–Alder cycloadditions. Synthesis of substituted derivatives of bicyclo[3.n.1]bridgehead alkenes. *Tetrahedron Lett.* **20,** 1011–1014 (1979).
14. Shea, K. J. *et al.* Applications of the intramolecular Diels–Alder reaction to the formation of strained molecules. Synthesis of bridgehead alkenes. *J. Am. Chem. Soc.* **104,** 5708–5715 (1982).
15. Jones, W. D. The fall of the C–C bond. *Nature* **364,** 676–677 (1993).
16. Murakami, M. & Ito, Y. Cleavage of carbon–carbon single bonds by transition metals. *Top. Organomet. Chem.* **3,** 97–129 (1999).
17. Rybtchiski, B. & Milstein, D. Metal insertion into C–C bonds in solution. *Angew. Chem. Int. Ed.* **38,** 870–883 (1999).
18. Perthuisot, C. *et al.* Cleavage of the carbon–carbon bond in biphenylene using transition metals. *J. Catal. Mol. A* **189,** 157–168 (2002).
19. Van der Boom, M. E. & Milstein, D. Cyclometalated phosphine-based pincer complexes: mechanistic insight in catalysis, coordination, and bond activation. *Chem. Rev.* **103,** 1759–1792 (2003).
20. Jun, C-H. Transition metal-catalyzed carbon–carbon bond activation. *Chem. Soc. Rev.* **33,** 610–618 (2004).
21. Miura, M. & Satoh, T. Catalytic processes involving β-carbon elimination. *Top. Organomet. Chem.* **14,** 1–20 (2005).
22. Jun, C-H. & Park, J. W. Directed C–C bond activation by transition metal complexes. *Top. Organomet. Chem.* **24,** 117–143 (2007).
23. Necas, D. & Kotora, M. Rhodium-catalysed C–C bond cleavage reactions. *Curr. Org. Chem.* **11,** 1566–1592 (2007).
24. Crabtree, R. H. The organometallic chemistry of alkanes. *Chem. Rev.* **85,** 245–269 (1985).
25. Kondo, T. & Mitsudo, T. A. Ruthenium-catalyzed reconstructive synthesis of functional organic molecules via cleavage of carbon–carbon bonds. *Chem. Lett.* **34,** 1462–1467 (2005).
26. Ruhland, K. Transition-metal-mediated cleavage and activation of C–C single bonds. *Eur. J. Org. Chem.* **2012,** 2683–2706 (2012).
27. Korotvicka, A., Necas, D. & Kotora, M. Rhodium-catalyzed C–C bond cleavage reactions—an update. *Curr. Org. Chem.* **16,** 1170–1214 (2012).
28. Seiser, T., Saget, T., Tran, D. N. & Cramer, N. Cyclobutanes in catalysis. *Angew. Chem. Int. Ed.* **50,** 7740–7752 (2011).
29. Dermenci, A. & Dong, G. Decarbonylative C–C bond forming reactions mediated by transition metals. *Sci. China Chem.* **56,** 685–701 (2013).
30. South, M. S. & Liebeskind, L. S. Regiospecific total synthesis of (±)-nanaomycin A using phthaloylcobalt complexes. *J. Am. Chem. Soc.* **106,** 4181–4185 (1984).
31. Murakami, M., Itahashi, T. & Ito, Y. Catalyzed intramolecular olefin insertion into a carbon–carbon single bond. *J. Am. Chem. Soc.* **124,** 13976–13977 (2002).
32. Murakami, M., Ishida, N. & Miura, T. Solvent and ligand partition reaction pathways in nickel-mediated carboxylation of methylenecyclopropanes. *Chem. Commun.* 643–645 (2006).
33. Murakami, M., Ashida, S. & Matsuda, T. Two-carbon ring expansion of cyclobutanone skeletons by nickel-catalyzed intermolecular alkyne insertion. *Tetrahedron* **62,** 7540–7546 (2006).
34. Murakami, M., Ashida, S. & Matsuda, T. Nickel-catalyzed intermolecular alkyne insertion into cyclobutanones. *J. Am. Chem. Soc.* **127,** 6932–6933 (2005).
35. Murakami, M. & Ashida, S. Nickel-catalysed intramolecular alkene insertion into cyclobutanones. *Chem. Commun.* 4599–4601 (2006).
36. Ashida, S. & Murakami, M. Nickel-catalyzed [4+2+2]-type annulation reaction of cyclobutanones with diynes and enynes. *Bull. Chem. Soc. Jpn* **81,** 885–893 (2008).
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.* **51,** 2485–2488 (2012).
38. Kumar, P. & Louie, J. A single step approach to piperidines via Ni-catalyzed β-carbon elimination. *Org. Lett.* **14,** 2026–2029 (2012).
39. Ishida, N., Yuhki, T. & Murakami, M. Synthesis of enantiopure dehydropiperidinones from α-amino acids and alkynes via azetidin-3-ones. *Org. Lett.* **14,** 3898–3901 (2012).

40. Lee, H. & Jun, C-H. Catalytic carbon–carbon bond activation of unstrained ketone by soluble transition-metal complex. *J. Am. Chem. Soc.* **121,** 880–881 (1999).
41. Park, Y. J., 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.* **41,** 222–234 (2008).
42. Jun, C-H., Lee, H. & Lim, S-G. The C–C bond activation and skeletal rearrangement of cycloalkanone imine by Rh(I) catalysts. *J. Am. Chem. Soc.* **123,** 751–752 (2001).
43. Luo, S-P., Guo, L-D., Gao, L-H., Li, S. & Huang, P-Q. Toward the total synthesis of haliclonin A: construction of a tricyclic substructure. *Chem. Eur. J.* **19,** 87–91 (2013).
44. Mazurov, A. A. *et al*. Novel nicotinic acetylcholine receptor agonists containing carbonyl moiety as a hydrogen bond acceptor. *Bioorg. Med. Chem. Lett.* **23,** 3927–3934 (2013).
45. Cheng, X. & Waters, S. P. Pyridone annulation via tandem curtius rearrangement/6π-electrocyclization: total synthesis of (–)-lyconadin C. *Org. Lett.* **15,** 4226–4229 (2013).
46. Breining, S. R. *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.* **55,** 9929–9945 (2012).
47. Jirgensons, A., Kauss, V., Mishnev, A. F. & Kalvinsh, I. The synthesis of 3-amino-methylbicyclo[3.3.1]nonanes: *endo*-selectivity in the Ritter reaction of 1,3,5,7α-tetramethylbicyclo[3.3.1]nonan-3-ol. *J. Chem. Soc. Perkin Trans.* **1,** 3527–3530 (1999).
48. Parker, E. & Cramer, N. Asymmetric rhodium(I)-catalyzed C–C activations with zwitterionic bis-phospholane ligands. *Organometallics* **33,** 780–787 (2014).
49. Souillart, L., Parker, E. & Cramer, N. Highly enantioselective rhodium(I)-catalyzed activation of enantiotopic cyclobutanone C–C bonds. *Angew. Chem. Int. Ed.* **53,** 3001–3005 (2014).

Acknowledgements

The authors thank Cancer Prevention Research Institute of Texas (R1118) for a start-up fund and the National Institutes of Health (1R01GM109054-01) and the Welch Foundation (F 1781) for research grants. G.D. is a Searle Scholar. The authors thank J. L. Sessler, D. R. Siegel and E. V. Anslyn for loaning chemicals. V. Lynch is acknowledged for assistance with X-ray crystallography. The authors also thank Johnson Matthey for a donation of Rh salts. Chiral Technologies is thanked for a donation of chiral high-performance liquid chromatography columns. S. J. Thompson is thanked for proofreading the manuscript.

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.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to G.D.

Competing financial interests

The authors declare no competing financial interests.