Enantioselective C–H Functionalization of Bicyclo[1.1.1]pentanes

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ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs) are highly strained carbocycles which have fascinated the chemical community for decades because of their unique structure. Despite the immense interest in this scaffold and extensive synthetic efforts, the construction of BCP derivatives still relies significantly on the manipulation of dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate. Additionally, BCPs which contain a proximal stereocenter are underrepresented in the literature, and their generation requires stoichiometric chiral auxiliaries. Here, we explore enantioselective C–H functionalization of BCPs as a conceptually innovative strategy which provides access to chiral substituted BCPs. For this purpose, enantioselective intermolecular sp^3 C–H insertion reactions of donor/acceptor diazo compounds catalyzed by the chiral dirhodium complex, $Rh_2(TCPTAD)_4$, were employed to forge new C–C bonds at the tertiary position of a variety of BCPs. This work also establishes that highly strained molecules can undergo direct C–H insertion without losing the integrity of their carbocyclic framework.

Introduction

The highly strained bicyclo[1.1.1]pentane (BCP) motif has generated considerable recent interest. [1,2,3,4] The pharmaceutical industry has recognized the three-dimensional carbon framework as a suitable bioisostere which can replace phenyl,[5] *tert*-butyl,[6] and alkyne functional groups[7] thus altering pharmacokinetic properties[8,9,10] (See Figure 1A). Additionally, BCPs are incorporated in material sciences as molecular building blocks towards the synthesis of molecular rods.[11] Wiberg and coworkers achieved the first synthesis of bicyclo[1.1.1]pentane[12] motivated because this carbocycle constituted an avenue for studying the effects of placing two non-bonding atoms in close proximity to each other, and later reported several transformations used to make BCPs from [1.1.1.]propellane.[13] Unfortunately, many of these reactions are low-yielding, produce mixtures of compounds, or result in polymerization or ring-fragmentation products. Some BCP scaffolds like bicyclo[1.1.1]pentylamine have garnered more

significant attention with several synthetic routes reported.[14,15,16] Most recently Baran and coworkers reported conditions for the synthesis of bicyclo[1.1.1]pentylamine which are scalable, thus permitting its commercialization.[17,18] However, most other substituted BCP frameworks rely on dimethyl bicyclo[1.1.1]pentane-1,3-dicarboxylate as the precursor, which limits synthetic versatilty[19] despite some recent efforts which demonstrate new strategies for generating substitute BCPs via reactions with propellane.[20,21,22,23,24] All of these efforts acknowledge the considerable difficulty in constructing complex molecules which possess BCPs embedded within the molecule's framework. More importantly, efforts towards devising methods for producing BCPs with proximal stereocenters are limited and rely on stoichiometric chiral auxiliaries like Ellman's auxiliary[25] for radical addition reactions (Figure 1B), chiral aminoalcohols[26,27,28,29,30] for asymmetric Strecker reactions (Figure 1B) or Evans' auxiliaries[31] for alkylation reactions.

Despite this body of work, no studies have been conducted in which achiral starting materials are transformed by asymmetric catalysis into enantio-enriched BCPs. Because of the overall interest in this carbocycle and because chiral BCP-containing syntheses are lacking, we hypothesized that an enantioselective dirhodium-catalyzed C–H functionalization could provide a conceptually different solution for producing chiral substituted BCPs. For this reaction to be successful, the C–H functionalization must occur without disrupting the strained carbocyclic framework while simultaneously pinpointing one C–H bond on the BCP. The potential challenges associated with substituting BCPs selectively can be readily seen in a radical chlorination reaction where 6 different substitution products are formed in low overall yield (Figure 1C).[31] Other efforts to nucleophilically intercept carbocations situated at the tertiary site of a BCP also failed due to rapid ring fragmentation (Figure 1C).[32] This study shows that the chiral dirhodium catalyst Rh_2(*S*-TCPTAD)$_4$ could be utilized for the enantioselective functionalization of the tertiary C–H bond as the sole product without loss of the integrity of the BCP scaffold. The selectivity for the tertiary C–H bond is very high even though the tertiary C–H bond is the least prevalent sp^3 C-H bond in the substrate (1 tertiary: 6 secondary: 9 primary) (Figure 1D).

Figure 1. Application and Synthesis of Strained Bicyclo[1.1.1]pentanes

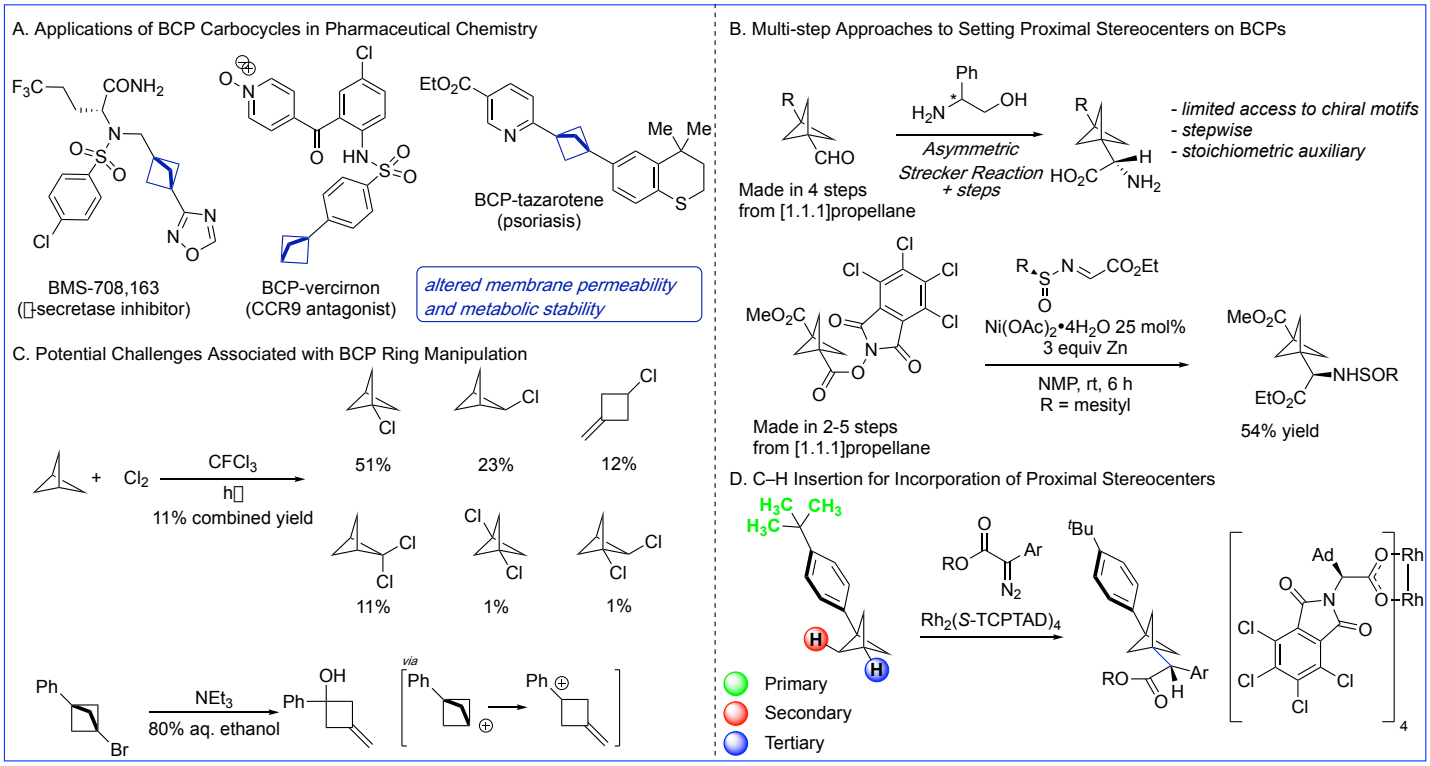


Fig. 1 Applications and synthesis of bicyclo[1.1.1]pentanes related to the current work. a, BCPs are incorporated into pharmaceutical compounds as phenyl, *tert*-butyl, and alkyne bioisosteres changing overall membrane permeability and metabolic stability. **b,** Setting proximal stereocenters on a BCP-containing scaffold can require multiple steps, and these strategies require the use of stoichiometric chiral auxiliaries. **c**, Inherent challenges associated with selectivity and ring fragmentation arise in attempts to generate substituted BCPs. Chlorination reactions of BCP result in low yields, low selectivity, and ring fragmentation products. Ring fragmentation occurs in solvolysis reactions mediated by the putative formation of a tertiary carbocation. **d**, The current work describes selective C–H functionalization of BCPs using donor/acceptor diazo compounds and dirhodium tetracarboxylate catalysts. It offers a useful strategy towards chiral substituted BCPs.

The intermolecular insertion of donor/acceptor carbenes stabilized by dirhodium tetracarboxylate catalysts into C–H bonds is one tactic within the broad field of C–H functionalization logic[33] that would be well suited for the desired transformation. While the spectrum of C–H bonds which can be selectively functionalized using this tactic is historically limited to substrates with C–H bonds which possess labilities enhanced by the stabilization of positive charge development in the transition state,[34] our group has recently introduced 2,2,2-trihaloethyl aryldiazoacetates[35] and several new dirhodium tetracarboxylate catalysts for highly selective functionalization of unactivated C–H bonds (Figure 2). These catalysts include Rh_2(*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP)$_4$, Rh_2(*S*-TCPTAD)$_4$, and Rh_2(*R*-tris(*p*-^{t}BuC_6H_4)TPCP)$_4$ which can selectively functionalize either secondary,[36] tertiary,[37] or primary[38] unactivated C–H bonds, respectively. Our group has also shown that Rh_2(*S*-2-Cl-5BrTPCP)$_4$ can accomplish C–H functionalization of distal C–H bonds in the presence of activated benzylic sites.[39]

Most recently, Rh_2(*S*-TPPTTL)$_4$ was shown to be able to desymmetrize cyclohexane rings.[40] This newfound ability to selectively functionalize unactivated C–H bonds has inspired increased effort towards developing transformations which revise the standard guidelines for C–H functionalization reactivity. As such, we decided to explore whether this strategy would be a viable means for constructing new chiral, substituted BCPs.

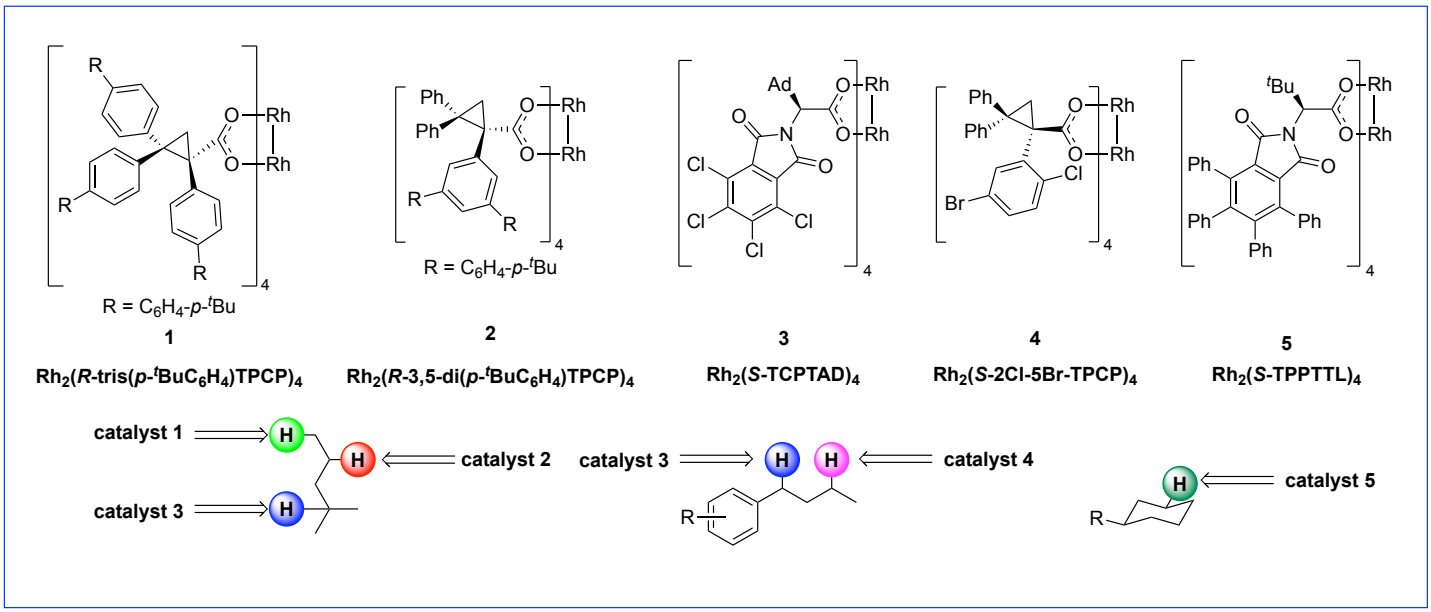


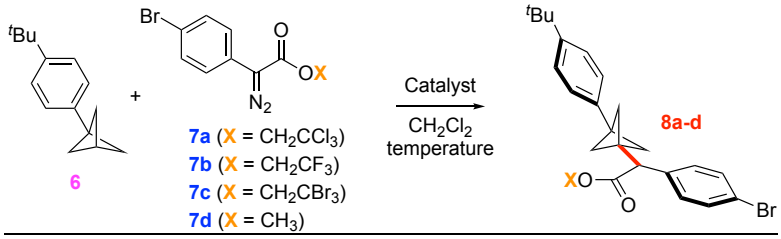
Fig. 2 Structures and applications of other dirhodium catalysts for site selective functionalization of unactivated C–H bonds. A toolbox of catalysts have been developed with different steric features, which enables selective reactions for specific C–H bonds. Catalysts **1-3** react preferentially at either primary (green), secondary (red) or tertiary (blue) C–H bonds. Catalyst **4** will react at the most accessible unactivated secondary C–H bond (pink) even in the presence of an electronically activated secondary C–H bond (blue). Catalyst **5** will cause the reaction to occur preferentially at the C3 equatorial C–H bond (green), resulting in desymmetrization of the cyclohexane.

This present work describes our efforts towards applying the catalyst toolbox for the successful transformation of the tertiary C–H bond of 1-substituted BCPs into 1,3-disubstituted BCPs bearing a proximal stereocenter. This was attained by evaluating the catalyst toolbox available in our laboratory which determined Rh_2(TCPTAD)$_4$ to be the best chiral catalyst. Then, several different BCPs were evaluated with this catalytic system producing new disubstituted BCPs with up to 99% yield and 94% ee. This method was further amenable to the synthesis of matched molecular pairs which further validates the hypothesis that BCPs can serve as viable replacements for phenyl rings in biologically relevant scaffolds. Finally, computational investigations rationalize the preference for C–H insertion at the tertiary site by describing the energetic difference between secondary and tertiary insertion events and unveiling the unique role of the BCP framework for sustaining positive charge buildup during the tertiary C–H insertion event.

Results

Experimental Studies on C–H Functionalization of Bicyclo[1.1.1]pentanes

The study began by determining the optimum catalyst for the C–H functionalization reaction of 1-(4-(*tert*-butyl)phenyl)bicyclo[1.1.1]pentane with aryldiazoacetates. (see Figure 3) These investigations revealed that $Rh_2(TCPTAD)_4$ is the optimum catalyst in terms of stereoselectivity, producing the desired compound in 88% ee (entry 4). To overcome the low product yield, the identity of the limiting agent was reversed, allowing the formation of the desired product in quantitative yields (entry 5). Attempts to further improve enantioselectivity by lowering the temperature were unsuccessful and led to poorer product formation (entry 6-7). Two equivalents of diazo compound were adequate for maintaining high yields (entry 8-10). Lastly, different esters were examined on the diazo compound, and the trichloroethyl ester remained the best in terms of both yield and enantioselectivity, although it should be noted that the methyl ester was able to produce the C–H insertion product with 95% ee (entry 13) but in lower yield that the trichoroethyl ester. It should also be recognized that the only side products of this reaction result from dimerization of the diazo compound; no C–H insertion event is observed at the secondary sites. Furthermore, reactions where the yield is lower, results from low efficiency of the reaction of the carbene with the BCP and not due to decomposition of the BCP starting material.



Entry	Catalyst	X	Equiv of 6 : 7	Temp.	Yield	8° ee[b]
1	**Rh_2(*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP)$_4$ (2)**	CH_2CCl_3	3 : 1	37 °C	**<5%**	**n/d**
2	**Rh_2(*S*-2Cl-5Br-TPCP)$_4$ (3)**	CH_2CCl_3	3 : 1	37 °C	**62%**	**-74%**
3	**Rh_2(*S*-TPPTTL)$_4$ (4)**	CH_2CCl_3	3 : 1	37 °C	**68%**	**84%**
4	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	3 : 1	37 °C	**61%**	**88%**
5	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	1 : 3	37 °C	**99%**	**90%**
6	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	3 : 1	-40 °C	**<5%**	**n/d**
7	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	1 : 3	-40 °C	**32%**	**90%**
8	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	1 : 2	37 °C	**99%**	**90%**
9	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	1 : 1.5	37 °C	**82%**	**90%**
10	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CCl_3	1 : 1	37 °C	**44%**	**90%**
11	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CF_3	1 : 2	37 °C	**84%**	**87%**
12	**Rh_2(*S*-TCPTAD)$_4$ (5)**	CH_2CBr_3	1 : 2	37 °C	**44%**	**90%**
13	**Rh_2(*S*-TCPTAD)$_4$ (5)**	OMe	1 : 2	37 °C	**55%**	**95%**

[a]Reaction conditions: Diazo compound 7 in 3.0 mL solvent was added over 3 h to a solution of the bicyclo[1.1.1]pentane 6 and catalyst (1.0 mol%) in 1.5 mL solvent at indicated temperature. The reaction was allowed to stir an additional 2-4 h after complete addition. All yields of 8 are isolated yields. [b]The enantioselectivity was determined by chiral HPLC analysis of the isolated product. n/d = not determined.

Fig. 3 Evaluation of the optimization catalysts for C-H functionalization of [1.1.1]-bicyclopentanes. The catalyst designed for tertiary functionalization of tertiary C-H bonds, Rh_2(*S*-TCPTAD)$_4$ was determined to be the optimum catalyst for the C–H functionalizatiuon of [1.1.1]-bicyclopentanes.

Next, the substrate scope was evaluated with Rh_2(*R*-TCPTAD)$_4$ and the results are summarized in Figure 4A. A variety of different functional groups were tolerated including halogens, silyl-protected oxygen, silicon and esters, leading to the formation of the BCP derivatives **9**-**27**. Insertion occurred selectively at the BCP in the presence of benzylic C–H bonds (**20**, **21**) and aliphatic ester groups (**26**,**27**). Interestingly, **15** and **16** were generated as the exclusive regioisomers even though the cyclopropane contains a benzylic C–H bond. The selectivity of the catalyst was further challenged by evaluating 1-(p-tolyl)bicyclo[1.1.1]pentane which possesses primary benzylic C–H bonds and the C–H bonds of the BCP (Figure 4B). In this case, the use of Rh_2(*S*-TCPTAD)$_4$ led to a mixture of regioisomers, **28** and **29**, where C–H functionalization occurred at the benzylic position and/or at the BCP tertiary site. The preference for the benzylic site can be rationalized from an electronics (the benzylic site is more activated) and statistical argument (more C–H bonds are available at the benzylic

site for functionalization). In contrast, the use of the more sterically demanding catalyst, Rh_2(*S*-p-Ph-TPCP)$_4$[41], permitted selective insertion into the benzylic methyl group for formation of **29** with a 99% yield, >20:1 regioselectivity, and 96% ee. This selective insertion sparked our curiousity about the concept of sequential C–H functionalization reactions where the same substrate is functionalized by two different diazo compounds using two different catalysts at two different sites. This was demonstrated by first scaling up the formation of **32**, and then reacting **32** with 2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate in the presence of Rh_2(*R*-TCPTAD)$_4$ as catalyst to produce **32** bearing two stereocenters in high diastereoselectivity. To demonstrate the opportunity this strategy offers, the isomer **31**, where the aryl substitution of the diazo compound is reversed, was produced by changing the order of the C–H functionalization reactions.

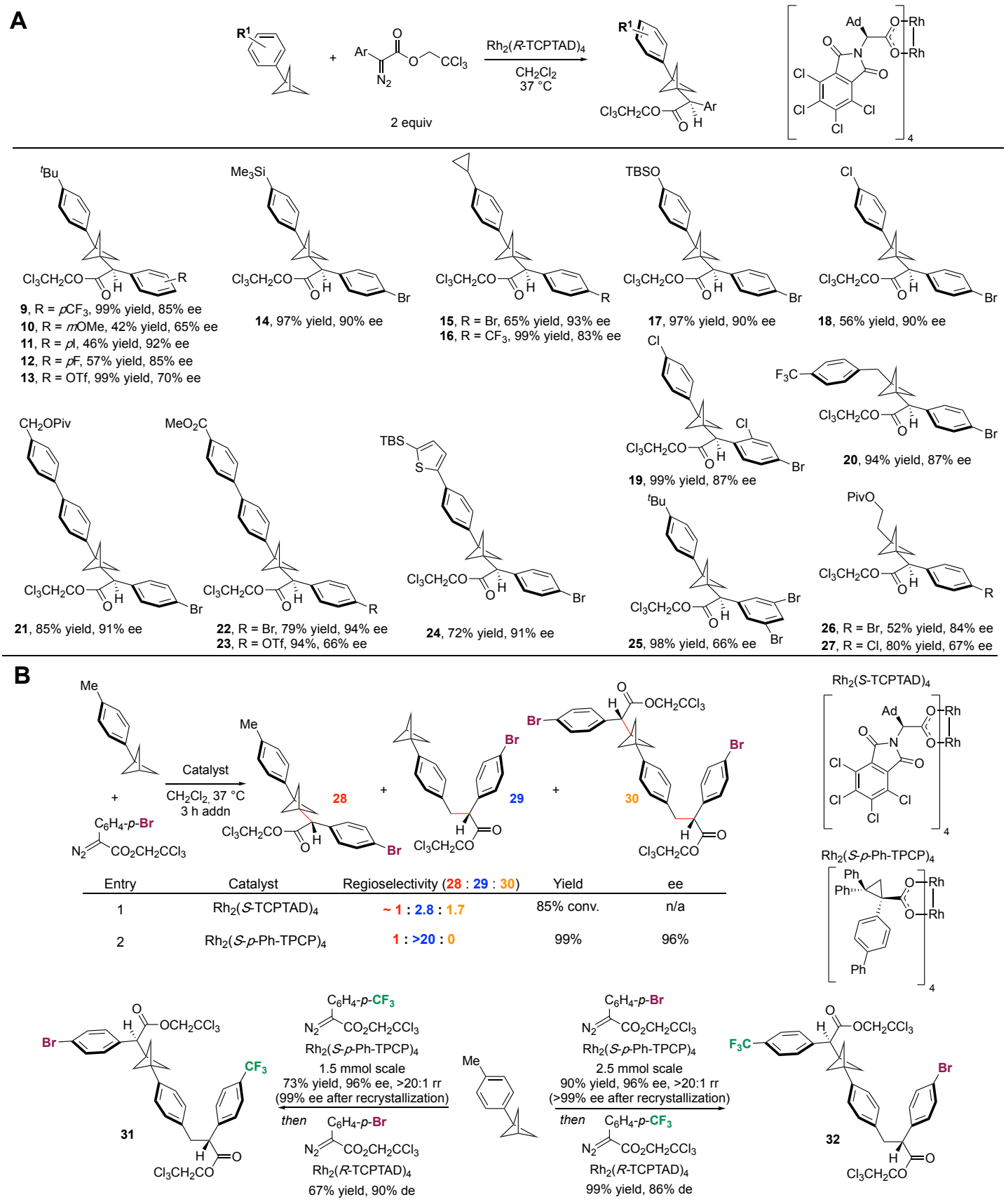
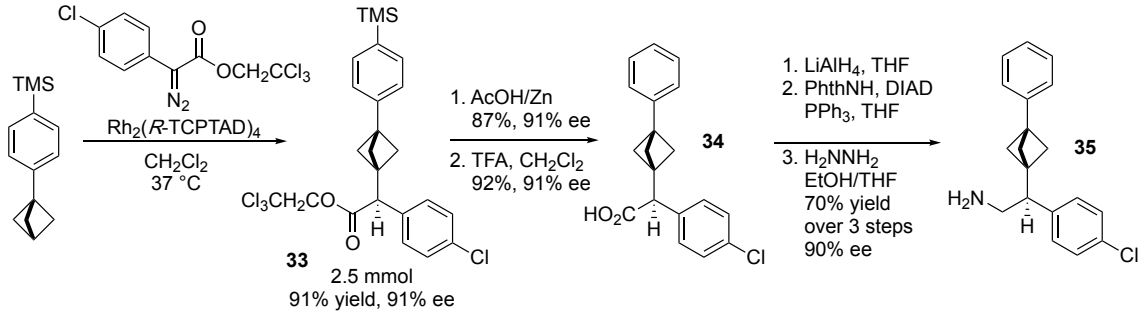


Fig. 3 Scope of the reaction with respect to substrates and aryldiazoacetates. a, functionalization of substituted bicyclo[1.1.1]pentanes (BCPs) with donor/acceptor carbenes. A variety of aryl- and alkyl-substituted BCPs undergo C–H insertion at the tertiary site of the BCP in high yields and high selectivities. **b,** The C–H functionalization of 1-(*p*-tolyl)bicyclo[1.1.1]pentane generates a mixture of products **28**-**30** when Rh_2(*S*-TCPTAD)$_4$ is used as catalyst, but the use

of Rh_2(*S*-*p*-Ph-TPCP)$_4$ permits selective functionalization at the benzylic site. This allows sequential C–H functionalization strategies to be tested which allows generation of isomers **31** and **32** simply by reversing the order of C–H functionalization. See Supplementary Information Section 4 for experimental details.

Bicyclo[1.1.1]pentanes as Bioisosteres of Phenyl Groups

The literature suggests that a departure from phenyl-containing molecules to a more three-dimensional design of compounds will result in better ADME properties.[42] To illustrate the utility of the BCP group in this endeavor, we synthesized the BCP matched molecular pairs (**34** and **35**) of **36**[43] and **37**.[44] Notably, access to enantiomerically pure **34** and **35** from (4-(bicyclo[1.1.1]pentan-1-yl)phenyl)trimethylsilane (the easily removed *p*-TMS substituent was necessary to obviate undesired cyclopropanation of the aryl ring; see ref. 39) was enabled by the chemical method presented herein and would have been exceedingly difficult using conventional methods. We found that solubility of the BCP derivatives dramatically increased as compared to the biphenyl compounds. We assessed the logD values of the BCP derivative **35** and found that increase in solubility correlates well with a decrease in logD (See Figure 5), indicating that increase in solubility is mainly driven by reduction of lipophilicity (and not crystal packing). We also found that stability of **37** and its BCP derivative **35** in human liver microsomes are comparable and conclude that the BCP did not introduce a liability for metabolic stability. These results confirm the hypothesis that increased three-dimensionality can improve ADME properties.



Compound	Predicted cLogP	Measured LogD
34 (chiral)	5.1	2.6
35 (racemate)	5.2	2.8
35 (chiral)	5.2	2.8
37 (racemate)	5.5	3.5
36 (racemate)	5.4	nd

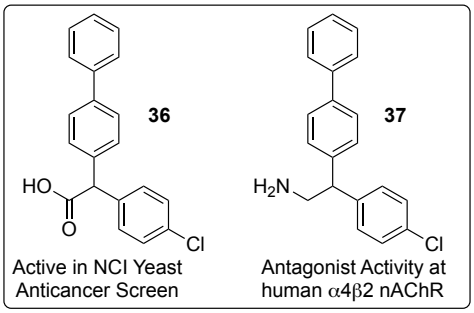


Fig. 5 Synthesis of analogs of known biologically active compounds and comparison of solubility and microsomal stability. a, synthesis of BCP containing analogs **34** and **35**. **b**, introduction of the BCP improves solubility by reducing logD and does not change microsomal clearance (HLM: human liver microsomes).

Mechanistic Studies on C-H Functionalization of Bicyclo[1.1.1]pentanes

The exclusive formation of products derived from C–H insertion at the tertiary site without BCP fragmentation was curious, and we wanted to understand this transformation further. Kinetic isotope effect studies were therefore conducted (see SI104 for details) which showed a kinetic isotope value of 1.9, aligning with previous investigations, which suggests that the mechanism of C–H insertion likely proceeds by a concerted asynchronous three-centered hydride transfer event.[45] We then turned to computational studies using a model catalyst to compare the energetics of insertion at the tertiary site versus insertion at the secondary sites around the periphery of the BCP. Density functional theory computations revealed free energy barriers of 19.7 kcal/mol for tertiary C–H insertion compared to 22.8 kcal/mol^{-1} for secondary C–H insertion (Figure 6). While the tertiary C–H bond (computed bond dissociation energy of 110.8 kcal/mol) is indeed weaker than the secondary C–H bond (computed bond dissociation energy of 111.3 kcal/mol), this small difference in bond dissociation energies of 0.5 kcal/mol cannot account for the substantial 3.1 kcal/mol preference for tertiary C–H insertion and the exclusive observation of tertiary C–H insertion products.

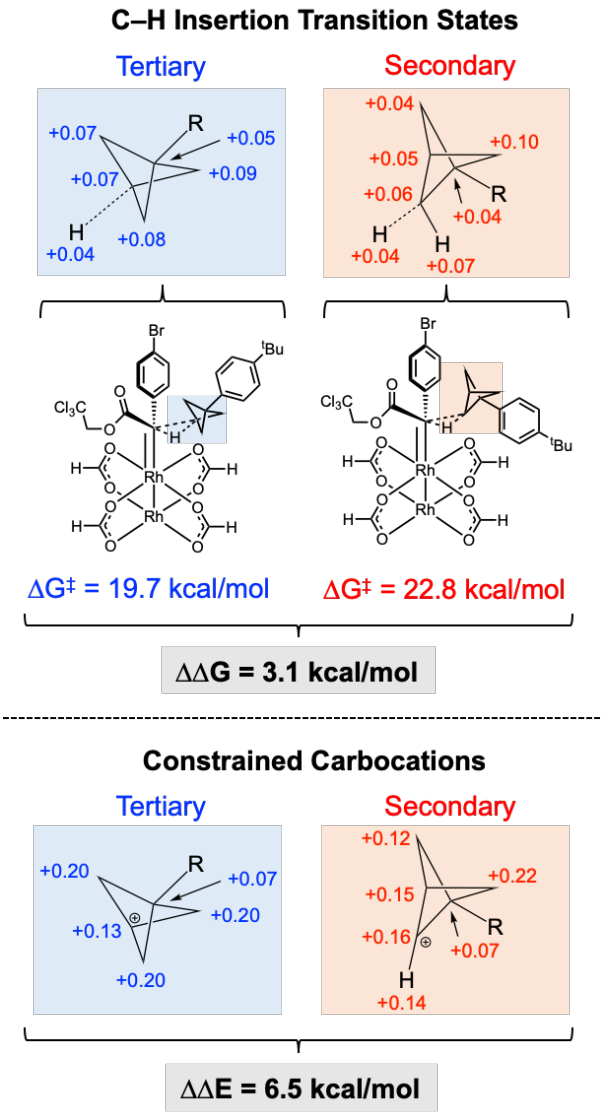


Fig. 6 Computational analysis of C–H insertion into bicyclo[1.1.1]pentanes. (Top) Computation of the free energy barriers for C–H insertion at the tertiary and secondary sites of the BCP substrate, as well as the Hirshfeld charges throughout the BCP scaffold in the transition states, using a model catalyst system. **(Bottom)** Computation of the stability difference between the corresponding tertiary and secondary BCP carbocations, as well as the Hirshfeld charges throughout the BCP scaffold in the carbocations. Charges on hidden hydrogen atoms are summed into the corresponding carbon atom.

Instead, as shown in Figure 4, the computed Hirshfeld charges reveal the development of substantial positive charge throughout the BCP scaffold in both the tertiary and secondary C–H insertion transition states. Moreover, computational models of the corresponding tertiary and secondary carbocations (constrained to prevent rearrangements; see S113) reveal that the tertiary carbocation is more stable than the secondary carbocation by 6.5 kcal/mol, consistent with previous reports that, although the tertiary BCP carbocation is constrained by the bicyclic ring system to be non-planar, it is stablized by favorable orbital interactions that delocalize the positive charge over the entire ring system.[32,46] (Without

constraints, the fully-formed parent biyclo[1.1.1]pentyl-1 cation spontaneously rearranges to bicyclo[1.1.0]butyl-1-carbinyl cation.[47,48]) The charges in the tertiary and secondary C–H insertion transition states are approximately *half* the magnitude of the charges in the corresponding carbocations, and correspondingly the transition states exhibit a free energy difference that is approximately *half* as large as the difference in carbocation stability. Taken together, the computational results reveal that the preference for C–H insertion at the tertiary site of BCP is driven by the development of substantial carbocation character in the transition states and the stabilizing interactions present in the BCP tertiary carbocation.

Conclusion

In conclusion, this study illustrates how C–H functionalization can generate access to new chemical space, which could be useful as enabling technology for drug discovery. It describes the regio- and stereoselective catalytic C–H functionalization reaction of BCPs producing a variety of new chiral substituted BCPs. The optimum dirhodium catalyst for these studies was the tetrachlorphthalimido derivative, Rh_2(*R*-TCPTAD)$_4$. In the one case this catalyst gave a mixture of products, effective site selectivity could be restored by using the more sterically demanding catalyst, Rh_2(*S*-p-Ph-TPCP)$_4$. This reaction enabled the synthesis of BCP matched molecular pairs which would be challenging to make by conventional synthesis, and this synthetic endeavor provides further evidence that BCPs can serve as bioisosteres.

Methods

An oven-dried 4 dram vial equipped with stir bar, septa and cap was cooled under vacuum. This vial was backfilled with argon, and then flame dried once under vacuum. After backfilling with argon, dirhodium tetracarboxylate catalyst was added to the vial. Then, the bicyclo[1.1.1]pentane was added to the vial. (If the bicyclo[1.1.1]pentane was an oil, it was added first, prior to the addition of catalyst). The catalyst and bicyclo[1.1.1]pentane were then dissolved in dichloromethane (heat was then applied if the reaction was conducted under heating). An oven-dried round bottom flask was cooled under vacuum. The flask was flame-dried and purged with argon once. The diazo compound was added to the flask, and the flask was evacuated and backfilled with argon 3x. Then, anhydrous dichloromethane was added, and this solution was added via syringe pump over 3 h to the vial containing substrate and catalyst. Upon completion of the addition, the reaction was allowed to stir for at least 2 h. Residual solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography using ether/hexanes (gradient 0%->5%) or ethyl acetate/hexanes (gradient 0%->5%) unless otherwise noted.

Data Availability: Crystallographic data for the structures reported in this Letter have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 1855619, 1855620 and 1855295. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Complete experimental procedures and compound characterization data are available in the Supplementary Information; any other data is available from the authors upon request.

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Competing Interests: H.M.L.D. is a named inventor on a patent entitled ‘Dirhodium catalyst compositions and synthetic processes related thereto’ (US 8,974,428, issued March 10, 2015). The other authors declare no competing interests.