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Iridium-Catalyzed Enantioselective Synthesis of *α*-Chiral Bicyclo[1.1.1]pentanes by 1,3-Difunctionalization of [1.1.1]Propellane

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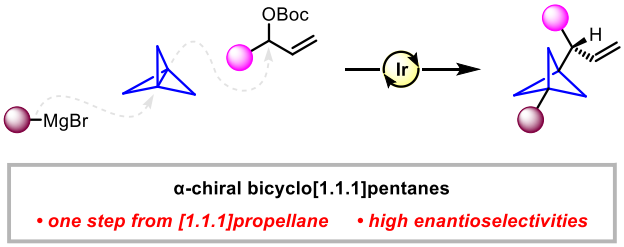
Supporting Information Placeholder



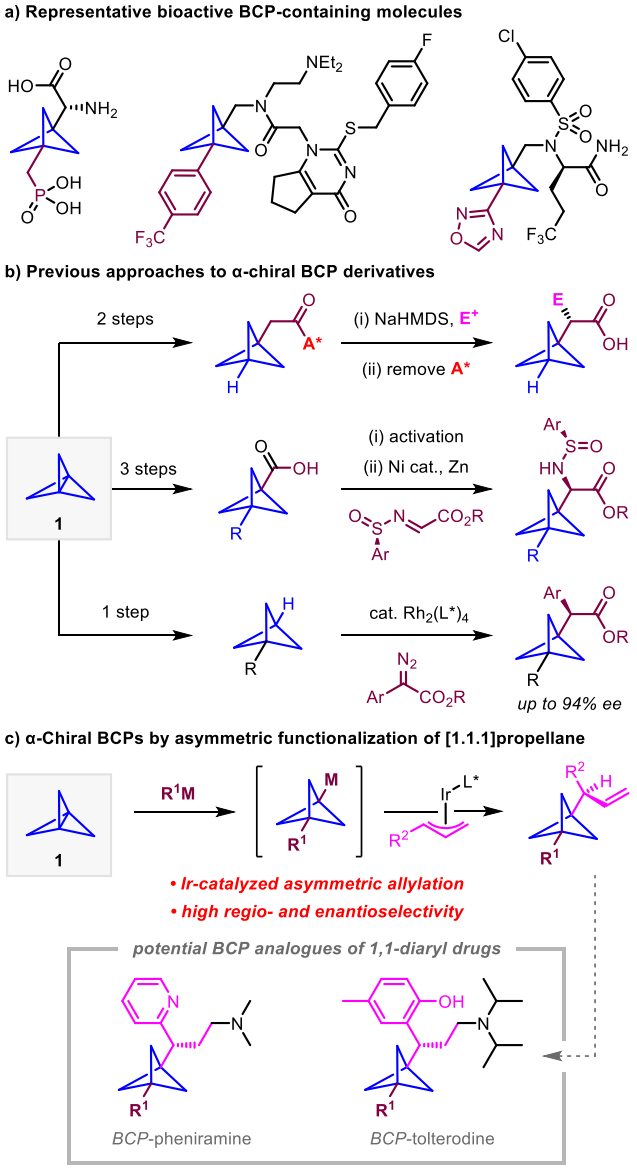
ABSTRACT: Bicyclo[1.1.1]pentanes (BCPs) have found application as bioisosteres of aromatic rings in drug development. However, catalytic construction of this motif with adjacent stereocenters in high enantioselectivity from readily available starting materials still constitutes a significant synthetic challenge. Herein, we report a direct stereoselective synthesis of α-chiral allylic BCPs by 1,3-difunctionalization of [1.1.1]propellane with Grignard reagents and allyl carbonates using iridium catalysis. This mild protocol proceeds via initial organometallic addition to [1.1.1]propellane followed by asymmetric allylic substitution, providing the products in high enantioselectivities over a broad range of substrates. Further derivatization of the products demonstrates the applicability of this method to the preparation of structurally diverse libraries of chiral BCP derivatives.

Structural modification of known biologically active molecules to improve their physicochemical properties is an attractive strategy in late-stage pharmaceutical evolution.[1] Methods to achieve this include installing polar groups, removal of lipophilic functionality, and replacement of suboptimal groups with suitable bioisosteres.[2] Bicyclo[1.1.1]pentanes (BCPs) have been shown to be privileged bioisosteres of aromatic rings due to their unique three-dimensional carbon framework, which can significantly improve aqueous solubility, membrane permeability, and metabolic stability (Scheme 1a).[3] In this regard, many efforts have been dedicated to the preparation of functionalized BCPs.[4] The most commonly employed approach is via addition reactions to readily available [1.1.1]propellane (**1**),[5] which is a versatile strategy due to the facile cleavage of the inverted central σ-bond under both radical[6] and anionic pathways.[7] In spite of the considerable advances in this area, there are limited methods that have been developed for the enantioselective construction of functionalized BCPs featuring *α*-stereogenic centers, and no reports that achieve this in a single step from **1** using asymmetric catalysis. This is largely a result of the high reactivity of **1**, which is susceptible to rearrangement reactions in the presence of transition metal catalysts.[8] To circumvent this issue, methods to access *α*-chiral BCP derivatives have relied on multi-step syntheses, where **1** is first transformed to a functionalized BCP before installation of the stereogenic center. Furthermore, to obtain high stereoselectivities, this typically requires stoichiometric chiral reagents[9] or chiral auxiliaries (Scheme 1b).[10] It is only very recently that the feasibility of asymmetric catalysis has been demonstrated, including copper-catalyzed hydroboration of alkenyl-BCPs or rhodium-catalyzed C–H functionalization of mono-substituted BCPs with diazo compounds (Scheme 1b).[9b,11]

To streamline the preparation of α-chiral BCPs, it would be advantageous to access these motifs using asymmetric catalysis in a direct multicomponent 1,3-difunctionalization of [1.1.1]propellane. This would provide rapid access to diverse chiral BCPs, thus facilitating their application in medicinal chemistry. Previous work by the groups of Szeimies, Knochel and Gleason has shown that BCP-metal species, generated in situ from **1** and organometallic reagents, can react in palladium- and copper-catalyzed cross couplings.[7a–c,12] However, to date, cross couplings of these BCP-metal reagents have only been applied in the synthesis of achiral products. We recognised iridium-catalyzed asymmetric allylic substitution as a potential route to *α*-chiral BCPs (Scheme 1c),[13] as these cata-

lyst systems tolerate hard nucleophiles, including organozinc reagents,[14,15] reminiscent of those formed upon addition of organometallic reagents to **1**.[7b] Whilst chiral iridium catalysts have been successfully used in asymmetric allylations of aryl[14] and primary alkyl zinc reagents with allylic carbonates,[15] we questioned whether the increased steric hindrance of the tertiary BCP-species would

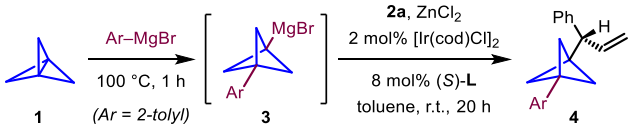
Scheme 1. Bioactive BCPs and Stereoselective Approaches to α-Chiral BCPs



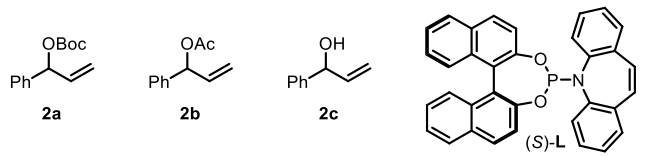
be compatible with the bulky iridium π-allyl complexes and provide branched allylic products in high regio- and enantioselectivity, especially considering the lower selectivities previously observed with secondary alkyl zinc reagents.[15a] If such a process were possible, the use of 1-aryl allylic electrophiles (R^2 = aryl, Scheme 1c) would provide rapid access to products that represent an interesting class of bioisosteres of 1,1-diaryl compounds, where one of the aryl rings is replaced with the three dimensional BCP. The chiral 1,1-diaryl motif is one of the most important pharmacophores in medicinal chemistry, with applications in over 20 different major disease areas.[16] We now report a direct and highly enantioselective iridium-catalyzed transformation of [1.1.1]propellane into α-chiral 1,3-difunctionalized BCPs.

To explore the feasibility of our hypothesis, we investigated the allylation of BCP-metal reagents with racemic Boc-protected allylic alcohol **2a** (Table 1). The addition of 2-tolylmagnesium bromide to [1.1.1]propellane (**1**) led to BCP-Grignard intermediate **3**,[7b,9b] which was subsequently reacted with **2a** at room temperature in toluene in the presence of 2 mol% $[Ir(cod)Cl]_2$ and 8 mol% (*S*)-phosphoramidite ligand **L**.[15a] The desired coupling reaction occurred to give allylic BCP product **4** in 61% yield and 12% ee with a 5:1 branched/linear ratio (entry 1). The moderate regioselectivity led us to suspect that a non-catalyzed pathway was also operative.[17] This was confirmed by the formation of **4** in 49% yield (B/L = 1:2) when the reaction was performing in the absence of the iridium catalyst (entry 2). On the other hand, only trace product was observed when $ZnCl_2$ was added prior to **2a**, presumably due to the formation of the less nucleophilic BCP-zinc species (entry 3). Pleasingly, when the BCP-zinc species was generated prior to the addition of the iridium catalyst and **2a**, **4** was formed in high yield and with excellent enantioselectivity (entry 4). We subsequently investigated different allyl electrophiles and found that acetate **2b** reacted with similar efficiency to **2a**, while allylic alcohol **2c** failed to generate the desired product (entries 5 and 6). Evaluation of different solvents showed toluene to be optimal (entries 7-9), and an iridium-to-ligand ratio of 1:2 was found to be essential for obtaining high yield (entry 10). Finally, lowering the catalyst loading resulted in a marginal decrease in yield while still maintaining the excellent enantioselectivity (entry 11).

Table 1. Optimization Studies[a]

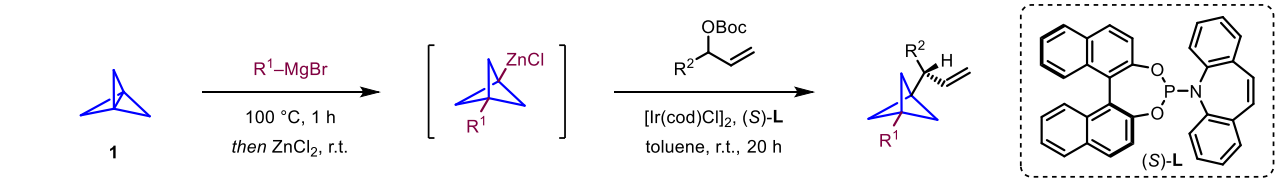


Entry	variation from above conditions	yield (%)[b]	B/L[c]	% ee[d]
1	No $ZnCl_2$	61[b]	5:1	12
2	No $ZnCl_2$, no Ir/**L**	49[c]	1:2	-
3	No Ir/**L**	<5	>20:1	-
4	None	78	>20:1	99
5	**2b** instead of **2a**	74	>20:1	98
6	**2c** instead of **2a**	<5	>20:1	-
7	CH_2Cl_2 as solvent	55	>20:1	96
8	THF as solvent	72	>20:1	92
9	MeOAc as solvent	81	>20:1	94
10	4 mol% **L**	34	>20:1	98
11	1 mol% $[Ir(cod)Cl]_2$/4 mol% **L**	74	>20:1	98

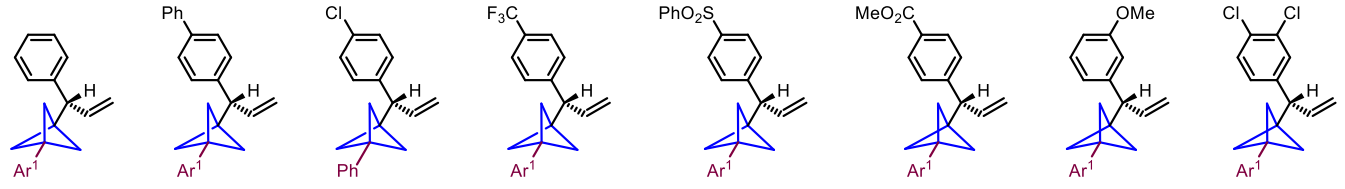


[a] Reaction conditions: Allyl electrophile (0.40 mmol), **1** (3.2 equiv), 2-tolylmagnesium bromide (1.6 equiv), $ZnCl_2$ (2.0 equiv), $[Ir(cod)Cl]_2$ (2.0 mol%), **L** (8.0 mol%), solvent (2 mL), r.t., 20 h. [b] Isolated yields. [c] B/L (branched/linear ratio) determined by GC/MS analysis. [d] Determined by HPLC analysis.

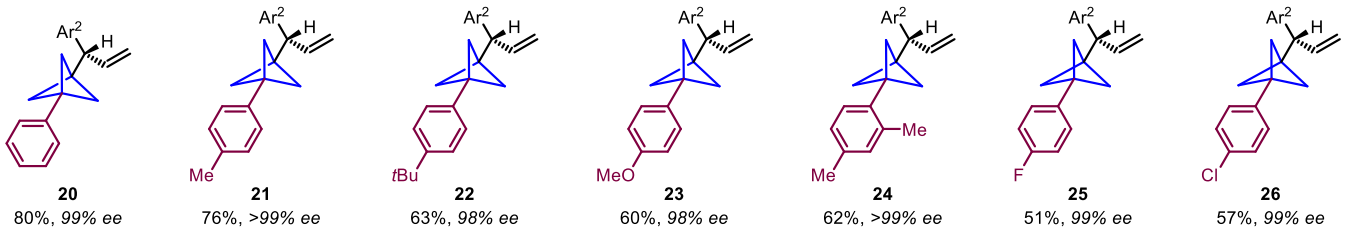
Scheme 2. Substrate Scope[a]



A) Allyl carbonates[b]



B) Grignard reagents[e]



[a] Reaction conditions: **1** (3.2 equiv), 2-tolylmagnesium bromide (1.6 equiv), $ZnCl_2$ (2.0 equiv), allyl electrophile (0.40 mmol), $[Ir(cod)Cl]_2$ (2.0 mol%), (*S*)-**L** (8.0 mol%), toluene (2 mL), r.t., 20 h. Yields are of isolated products. The ee values were determined by HPLC analysis. [b] Ar^1 = 2-tolyl. [c] 1 mmol scale. [d] Using (*R*)-**L** (8 mol%). [e] Ar^2 = 2-naphthyl. [f] Yield determined after hydroboration/oxidation.

Having identified optimal conditions, we assessed the scope of the reaction (Scheme 2). A series of 1-aryl allylic carbonates with various substituents on the aromatic ring provided the allylic BCP products **4**–**16** in high yields and excellent enantioselectivities. Various functionality was tolerated, including halides (**6**, **11**, **13**–**14**), trifluoromethyl (**7**), phenylsulfonyl (**8**), ester (**9**), and alkoxy groups (**10**). Substrates derived from nitrogen heterocycles, including quinolines (**14**–**15**) and pyridines (**16**) were also suitable, although a 3-pyridyl substrate, which possesses a sterically

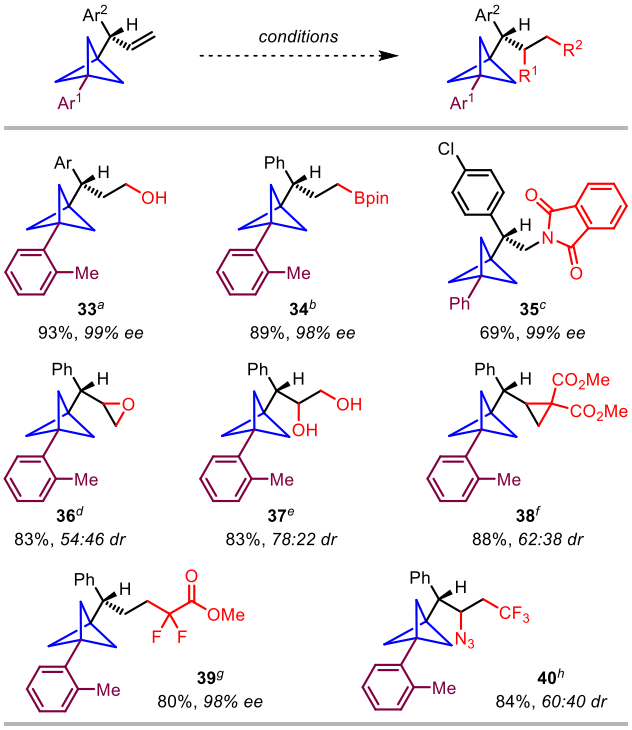
unhindered basic nitrogen atom, provided only a moderate yield of product **16** but still with excellent enantioselectivity. Although enantiocontrol was consistently high for the majority of substrates (98–99% ee), those with strong electron-withdrawing groups in the *para*-position of the aromatic ring (**9**), or those with *ortho*-substituents (**13**–**14**) gave slightly reduced enantioselectivities (87–89% ee). In addition to 1-aryl allylic carbonates, a 1,4-enyne (**17**) and a polysubstituted 1,4-diene derived from the natural product (−)-perillaldehyde (**18**) also furnished the products in high yields and stereoselectivities. Interestingly, during the synthesis of perillaldehyde-derived product **18**, we observed low diastereocontrol when using the (*S*)-configured ligand (*S*)-**L** but high selectivity for the same diastereomer with (*R*)-**L**, which demonstrates a surprisingly high level of substrate-control considering the remoteness of the stereocenters. Unfortunately, when a more sterically hindered diene substrate derived from (1*R*)-(−)-myrtenal was used, the linear regioisomer **19** was formed as the major product in low yield. As commonly observed with related systems,[15] the presence of an adjacent π-system and terminal olefin on the allyl substrate was found to be crucial for the substitution reaction, as the reactions failed for tert-butyl (1-cyclohexylallyl) carbonate and (*E*)-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl acetate.

We next examined the generality of the reaction with respect to the Grignard reagent. Various functionalized aryl Grignards provided the corresponding chiral aryl-BCP derivatives (**20**-**27**) good yields and with excellent enantioselectivities. Alkenyl Grignards were also found to be compatible for the ring-opening of **1**, providing the bis-alkene-functionalized BCP product **28** in 97% ee. In addition to C(sp^2)-Grignard reagents, C(sp^3)-Grignard reagents were also applicable in this [1.1.1]propellane derivatization, providing alkyl-BCPs functionalized with allyl (**29**), primary alkyl (**30**), and cycloalkyl (**31**–**32**) groups.

To demonstrate the potential application of our strategy for the preparation of diverse libraries of chiral BCP derivatives, various transformations of the terminal alkene of the allyl-BCP products were performed (Scheme 3). Alcohol **33** was accessed in excellent yield by a hydroboration/oxidation sequence with 9-BBN, or iridium-catalyzed hydroboration with pinacolborane provided boronic ester **34**.[18] Amine-substituted BCP derivative **35** was prepared by reductive ozonolysis and subsequent Mitsunobu-type nucleophilic substitution with phthalimide. Oxidation of the alkene with *m*-CPBA or OsO_4 provided high yields of epoxide **36** and vicinal diol **37**, respectively. Cyclopropanation was readily accomplished with dimethyl diazomalonate in the presence of a rhodium catalyst, affording cyclopropane **38** in 88% yield.[19] Finally, alkenyl-BCP **4** was shown to undergo various radical-mediated transformations without erosion of enantioselectivity, including a photocatalyzed hydrofluoroalkylation and a copper-catalyzed trifluoromethylazidation, which provided fluorinated BCP-derivatives **39** and **40** in high yields, respectively.[20,21]

To determine the absolute configuration of the α-chiral BCP products formed using this iridium-catalyzed allylation, we compared the optical rotation to the reported value for the previously synthesized phthalimide-derivative **35**.[11] This allowed us to confirm that the products formed using (*S*)-**L** had an (*R*)-configuration, which is consistent with those previously described for Ir/**L**-catalyzed reactions of allyl electrophiles with various nucleophiles,[13a] including primary alkyl zinc reagents,[15a] and is indicative of a similar mechanistic pathway.[22] It is noteworthy that our new approach to α-chiral BCP derivatives allowed access to phthalimide **35** in 3 steps from **1** with 51% overall yield and 99% ee, whereas the previously reported synthesis required 6 steps and proceeded in 23% yield and 90% ee.

Scheme 3. Product Derivatizations



Conditions: [a] **5** (Ar = 4-biphenyl), 9-BBN, THF, then H_2O_2, NaOH; [b] **4**, HBpin, $[Ir(cod)Cl]_2$, dppb, THF; [c] **6**, O_3, CH_2Cl_2/MeOH, $NaBH_4$, then phthalimide, PPh_3, DIAD, THF; [d] **4**, *m*-CPBA, CH_2Cl_2; [e] **4**, K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, DABCO, *t*BuOH/H_2O; [f] **4**, dimethyl diazomalonate, $Rh_2(esp)_2$, CH_2Cl_2; [g] **4**, $FSO_2CF_2CO_2Me$, $Ir(ppy)_3$, NMP, blue LEDs; [h] **4**, Togni reagent II, $TMSN_3$, $Cu(MeCN)_4PF_6$, MeCN.

In summary, we have developed a new strategy for the highly enantioselective construction of α-chiral BCPs in a single step from readily available [1.1.1]propellane. This was accomplished by a highly efficient iridium-catalyzed asymmetric allylic substitution of BCP-zinc intermediates, which are readily formed through the reaction of Grignard reagents, [1.1.1]propellane, and $ZnCl_2$. Using this approach, we have synthesized an array of enantioenriched 1,3-difunctionalized BCPs tethered with a terminal alkene, which provided a versatile synthetic handle for the preparation of a diverse range of highly functionalized α-chiral BCPs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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