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Enantioselective C2-Allylation of Benzimidazoles Using 1,3-Diene Pronucleophiles

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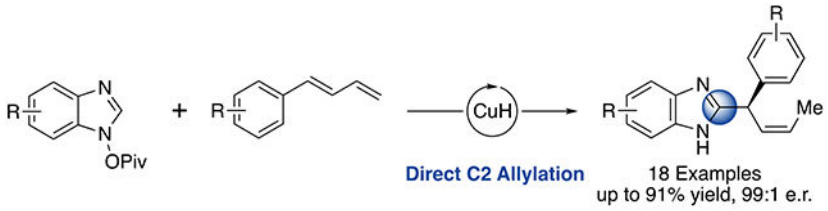
Abstract

Although substituted benzimidazoles are common substructures in bioactive small molecules, synthetic methods for their derivatization are still limited. Previously, several enantioselective allylation reactions of benzimidazoles have been reported that functionalize the nucleophilic nitrogen atom. Herein, we describe a reversal of this inherent selectivity toward *N*-allylation by using electrophilic *N*–OPiv benzimidazoles with readily available 1,3-dienes as nucleophile precursors. This CuH-catalyzed approach utilizes mild reaction conditions, exhibits broad functional-group compatibility and forms exclusively the C2-allylated product with excellent stereoselectivity.

Graphical Abstract



The development of effective small-molecule therapeutics often requires the evaluation of a library of compounds containing diverse chemical structures.[1] Thus, the discovery of new methods for the rapid derivatization of substructures commonly represented in biologically active molecules is an important goal for organic synthesis. Benzimidazoles are one such class of heterocycles found in a variety of pharmaceuticals and interesting natural products.[2] In many of these compounds, the benzimidazole core is functionalized at C2 with a chiral substituent (Figure 1).[3] However, despite the prevelance of these substructures in bioactive molecules, methods for their synthesis are limited, especially in an enantioselective manner. Most protocols for the syntheses of C2-substituted benzimidazoles involve late-stage

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Supporting Information

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

Experimental details, characterization of the products and starting materials (PDF)

Crystallographic data (CIF)

The authors declare no competing financial interests.

construction of the imidazole ring and often require the use of harsh reaction conditions, being limited to the synthesis of achiral products.[4] Approaches for the asymmetric functionalization of benzimidazoles predominantly involve bond-formation at the nucleophilic nitrogen. For example, Hartwig and Breit have independently demonstrated that enantioenriched *N*-allylated benzimidazoles can be prepared from allyl carbonates or allenes, and chiral iridium or rhodium catalysts (Figure 2A).[5] Of the few reported examples of enantioselective C2-functionalization of benzimidazoles,[6] most rely on an intramolecular cyclization of an N1-tethered alkene (Figure 2B).[7]

Our laboratory and others have previously shown that CuH-based catalysts can reliably convert olefins to chiral alkyl copper intermediates, which can be utilized to form new bonds stereoselectively.[8] This chemistry has enabled a variety of C–N and C–C bond-forming reactions, including hydroacylation,[9] hydroamidation,[10] and formal hydrocyanation[11] of olefins as well as the allylations of both imines[12] and ketones.[13] Recently, we have employed this hydrofunctionalization strategy to alkylate indole electrophiles with divergent site-selectivity, enabling C- or N-alkylation depending on the supporting ligand that is selected (Figure 2C).[14a] A similar tack has also enabled the C3-allylation of indazoles.[14b] We reasoned that by using an electrophilic *N*–OPiv benzimidazole as a substrate, we might be able to extend this chemistry to achieve asymmetric addition to the C2 position of benzimidazoles (Figure 2D).

We began by investigating the reaction of potential alkene coupling partners with *N*–OPiv benzimidazole (**6**), using (*S,S*)-Ph-BPE (**L4**) as a ligand and $(MeO)_2MeSiH$ (DMMS) as the silane. Our initial results with *p*-phenylstyrene were unsatisfactory, giving only 18% yield and poor e.r. (see the Supporting Information for details). However, with (*E*)-1-phenyl-1,3-butadiene (**7**), we observed a 65% ^{1}H NMR yield of the allylated product (**8**) with 95:5 e.r. It was found, not unexpectedly, that the use of geometrically pure (*E*)-butadienes was critical, as employing an *E*/*Z* mixture resulted in decreased enantioselectivity. Notably, the product obtained was almost exclusively the *Z*-isomer, regardless of the geometry of the diene starting material (>20:1 *Z:E,* see the Supporting Information for details). Several chiral bisphosphines were examined as supporting ligands, and high enantioselectivity was observed employing (*R,R*)-QuinoxP* (**L2**), (*R*)-DTBM-SEGPHOS (**L3**), and (*S,S,*)-Ph-BPE (**L4**) (Table 1, entries 1–4). Although the utilization of either **L3** or **L4** provided comparable enantioselectivity, the use of **L4** provided **8** in the highest yield. A comparison of solvents (entries 5–8) revealed that the reaction was most efficient in MTBE. The use of silanes other than DMMS led to a decrease in product yield (entries 9–11).[15]

We next explored the scope of this method by examining the use of an assortment of benzimidazole electrophiles (Table 2). The reaction proceeded efficiently with both electron-rich and electron-poor benzimidazoles, giving the C2-allylated products in good yields and enantioselectivities (**9**, **10**). The reaction also worked well with halogenated benzimidazoles (**12**, **13**). The stereochemical assignment of **13** was confirmed by X-ray crystallography. We note that we were also able to utilize the 4-thiophenyl substituted *N*–OPiv benzimidazole to synthesize **11**, a substructure of the histone deacetylase inhibitor **3** (Figure 1),[3c] with excellent yield and enantioselectivity.

Next, we evaluated a number of 1-aryl-1,3-butadienes as pronucleophiles. The use of reagents containing electron-rich arenes generated the allylated benzimidazoles with good yields and high e.r. (**14**, **16**, **17**). Additionally, heterocycle-containing dienes could be utilized, allowing us to obtain products such as indole **18**. Aryl groups substituted with strongly electron withdrawing groups such as *p*-CF_3 were found to give significantly diminished e.r. (**19**). A modest level of enantioselectivity was obtained with more moderately electron poor 1-(3-bromophenyl)-1,3-butadiene, which allowed access to **20**, which contains both an aryl chloride and bromide functional group as potential sites for further diversification. We also found that 1,1-disubstituted butadienes furnished benzimidazoles bearing a C2-adjacent quaternary center with high enantioselectivity (**15**) Of note, **15** was the only allylation product obtained as the predominately *E*-isomer, and both the *E*- and *Z*-isomers of **15** were found to be highly enantioenriched.

Additionally, through the use of 2-aryl-1,3-butadiene pronucleophiles we could access C2-substituted benzimidazole products bearing a methyl substituted stereogenic center and a 1,1-disubstituted alkene (**21**).[16] The reaction proceeded well with 2-substituted butadienes containing electron rich aryl groups, furnishing products such as indole **23**, or compound **25**. Electron poor benzimidazoles could also be utilized to obtain C2-substituted products in high enantioselectivity (**24**), however we found that the use of electron poor 2-substituted butadienes resulted in severely diminished yields (**22**).[17]

Whereas overall this C2-allylation protocol shows generally good functional group tolerance, we did find that substrates containing *N*-tosyl protecting groups performed poorly, oftentimes forming a precipitate during the reaction and giving products in poor yield. Investigating the use of alkyl-substituted dienes, such as 1-cyclohexyl-1,3-butadiene or myrcene suggested these types of pronucleophiles are poorer substrates.

On the basis of our previous studies on the addition of allyl copper species to indazoles, we believe the allylation of benzimidazoles may proceed as depicted in Figure 3.[14b] The *in situ* generated (*S,S*)-Ph-BPE ligated copper hydride **I** undergoes a hydrocupration of diene **7** to generate isomeric allyl copper intermediates, **IIa** and **IIb**, which are presumably in equilibrium.[13, 14b, 18] These engage with **6** in a process that likely proceeds through a six-membered transition state in which the methyl group occupies the endocyclic axial position (**TSA**), leading to the dearomatized intermediate **III**. The corresponding transition state leading to the minor *E*-isomer (**TSB**) would require the methyl group adopt an equatorial orientation, resulting in steric interaction between the methyl group and the large Ph-BPE ligand, perhaps explaining the allylation's observed *Z* selectivity. Next, a net loss of copper pivalate generates **8a**, which may isomerize to **8** following a 1,5-hydride shift. The active CuH species **I** is then regenerated after σ-bond metathesis of **IV** with DMMS. Alternatively, it is conceivable that intermediate **III** may undergo a σ-bond metathesis followed by oxidation to generate the desired product **8**. In depth mechanistic studies to shed light on these proposed elementary steps are ongoing.

In conclusion, we have developed a method for the asymmetric synthesis of C2-allylated benzimidazoles, utilizing 1,3-diene pronucleophiles. The method allows for the preparation of substituted benzimidazoles bearing either aryl or methyl groups at the stereogenic center,

as well as quaternary stereocenters. The reaction tolerates benzimidazoles and dienes with a variety of electron rich, electron poor, and heterocyclic substituents, which we have utilized to generate several substructures found in biologically active compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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(15). Early in our optimization efforts, we discovered that the product epimerized when subjected to chromatographic purification on silica. We found that including triethylamine in the eluting solvent mixture was necessary to prevent this undesired erosion of e.r. See the Supporting Information for details.

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(17). Compound 21 was isolated in analytically pure form by trituration, a process that is at least partially responsible for the low yield. See the Supporting Information for details.

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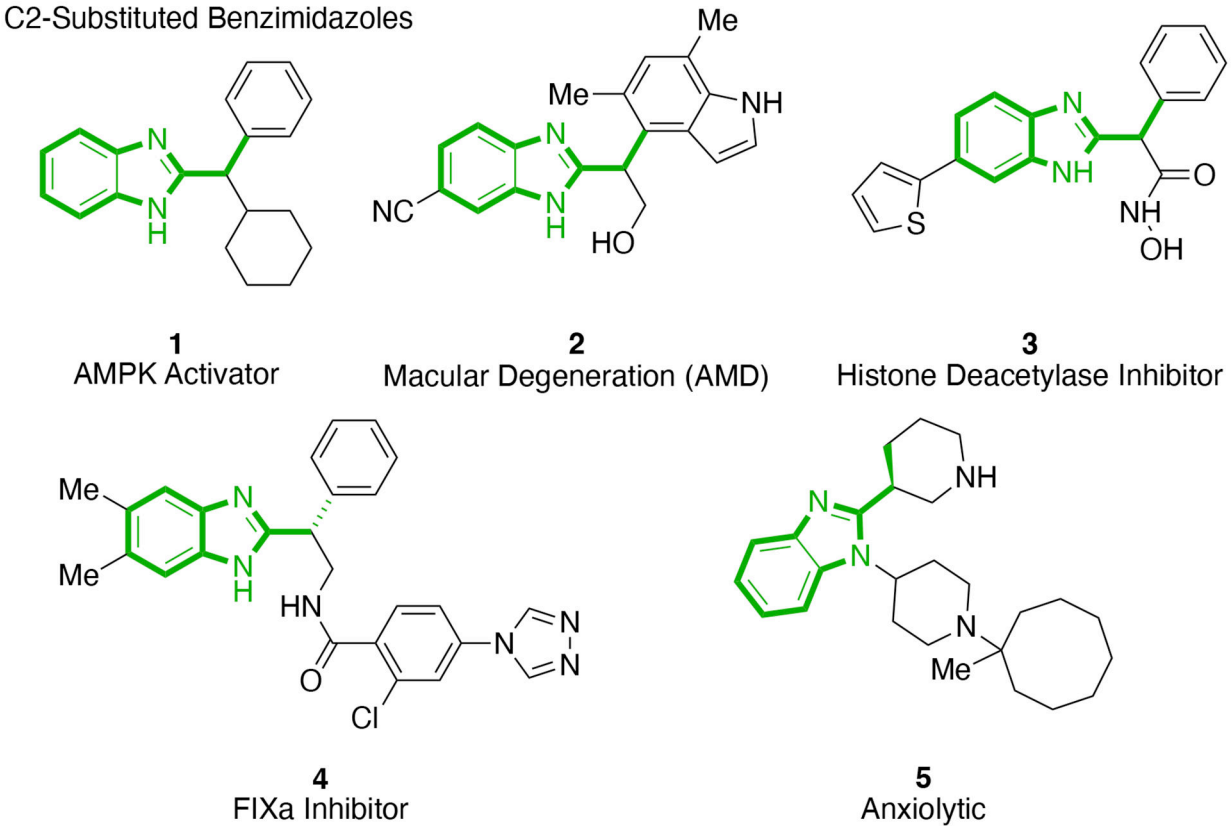


Figure 1.
Representative C2-functionalized benzimidazoles

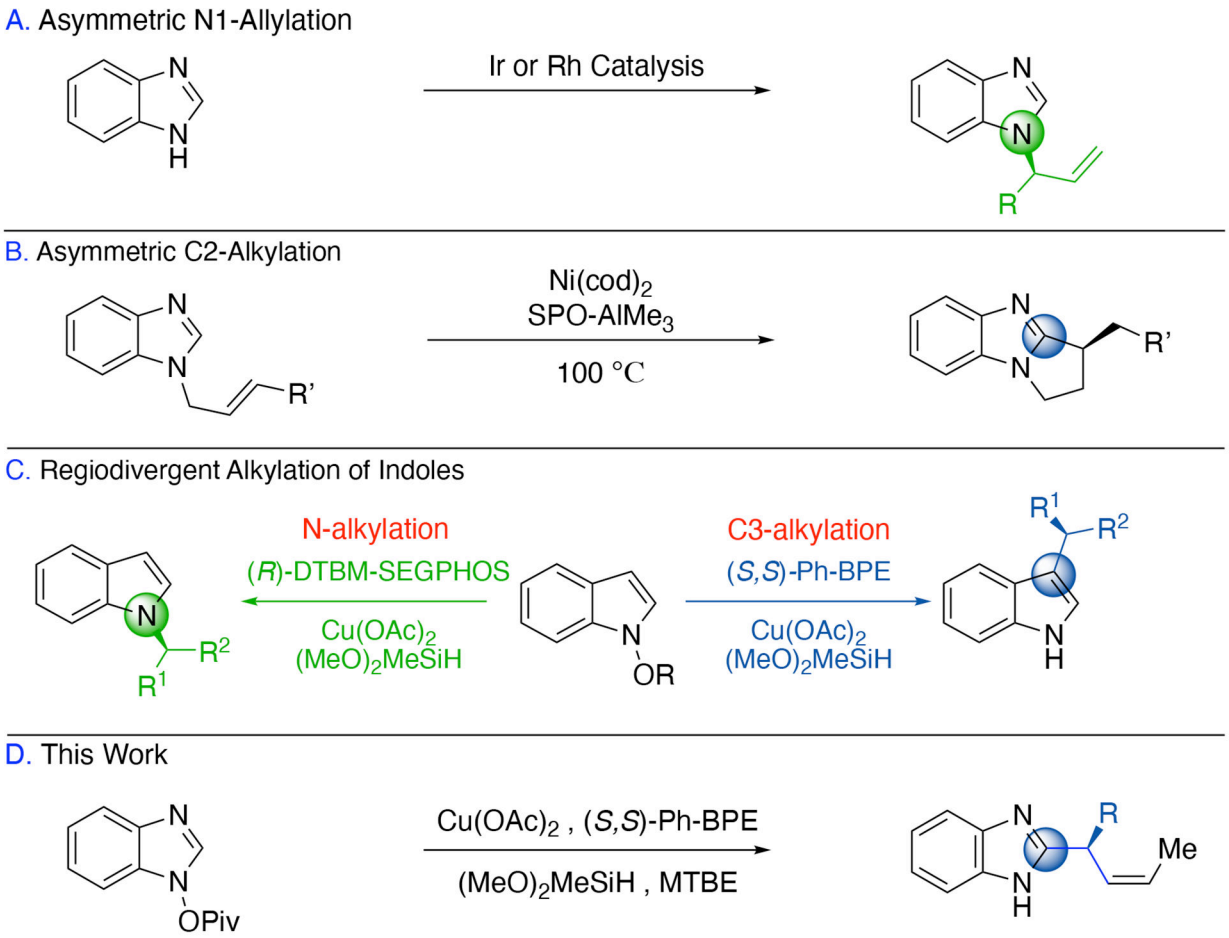


Figure 2.

(A) Hartwig and Breit's asymmetric N1-allylation. (B) Cyclization of N1-tethered alkenes to generate C2-alkylated benzimidazoles. (C) Our group's divergent C- or N-alkylation of indoles. (D) CuH-catalyzed C2-allylation of benzimidazoles.

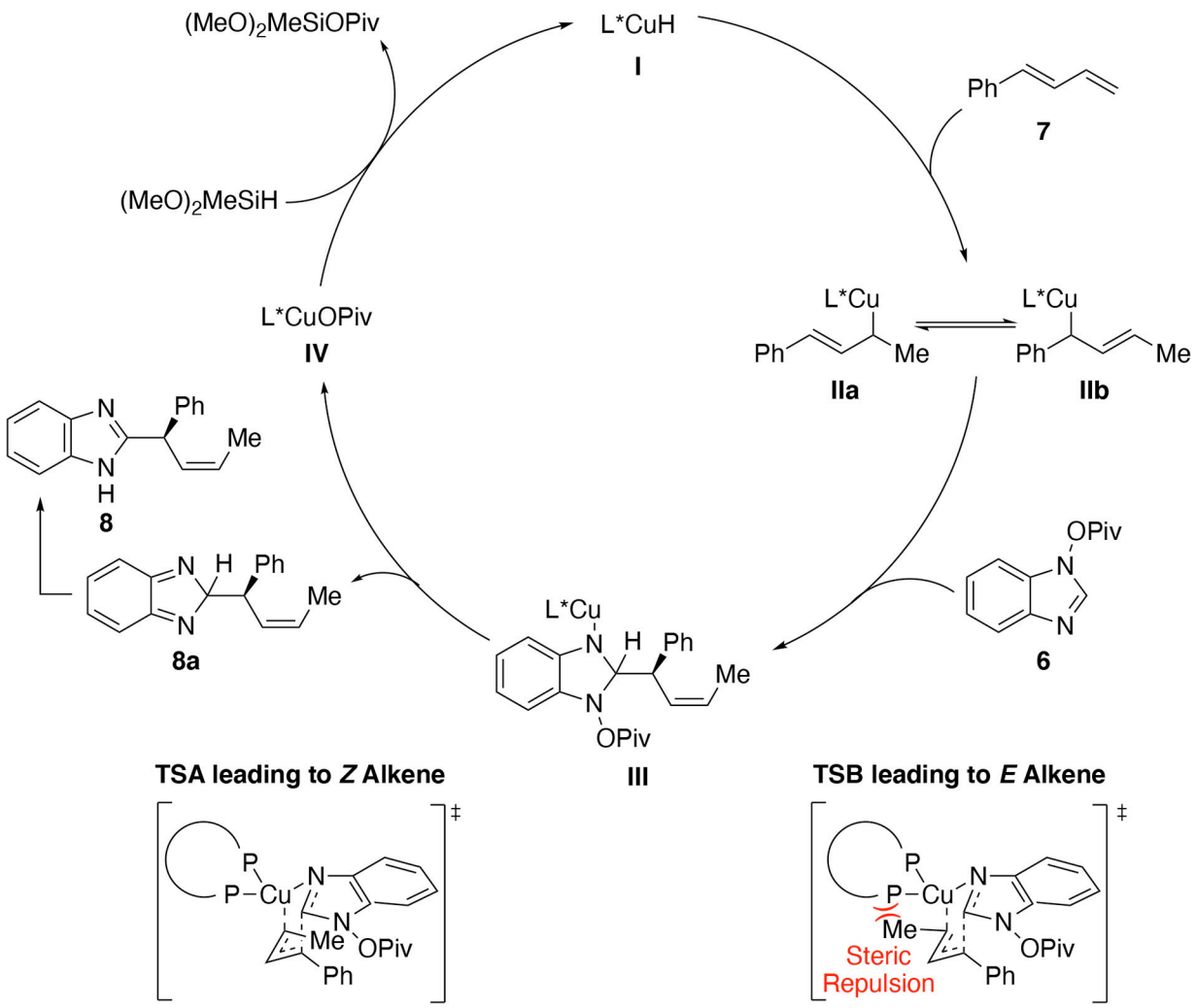
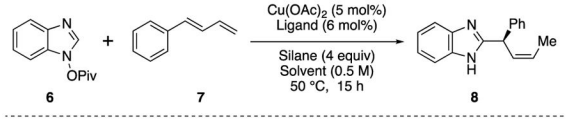


Figure 3.

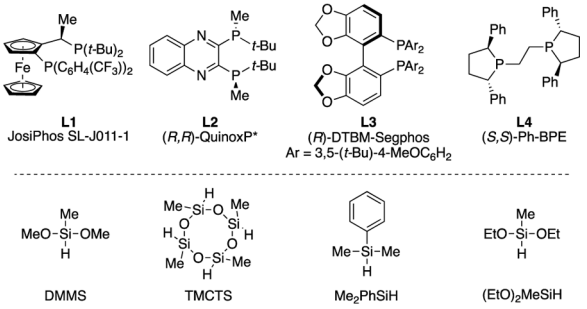
Proposed mechanism for the copper hydride catalyzed C2-allylation of *N*–OPiv benzimidazoles.

Table 1.

Optimization of the Synthesis of 8.[a]



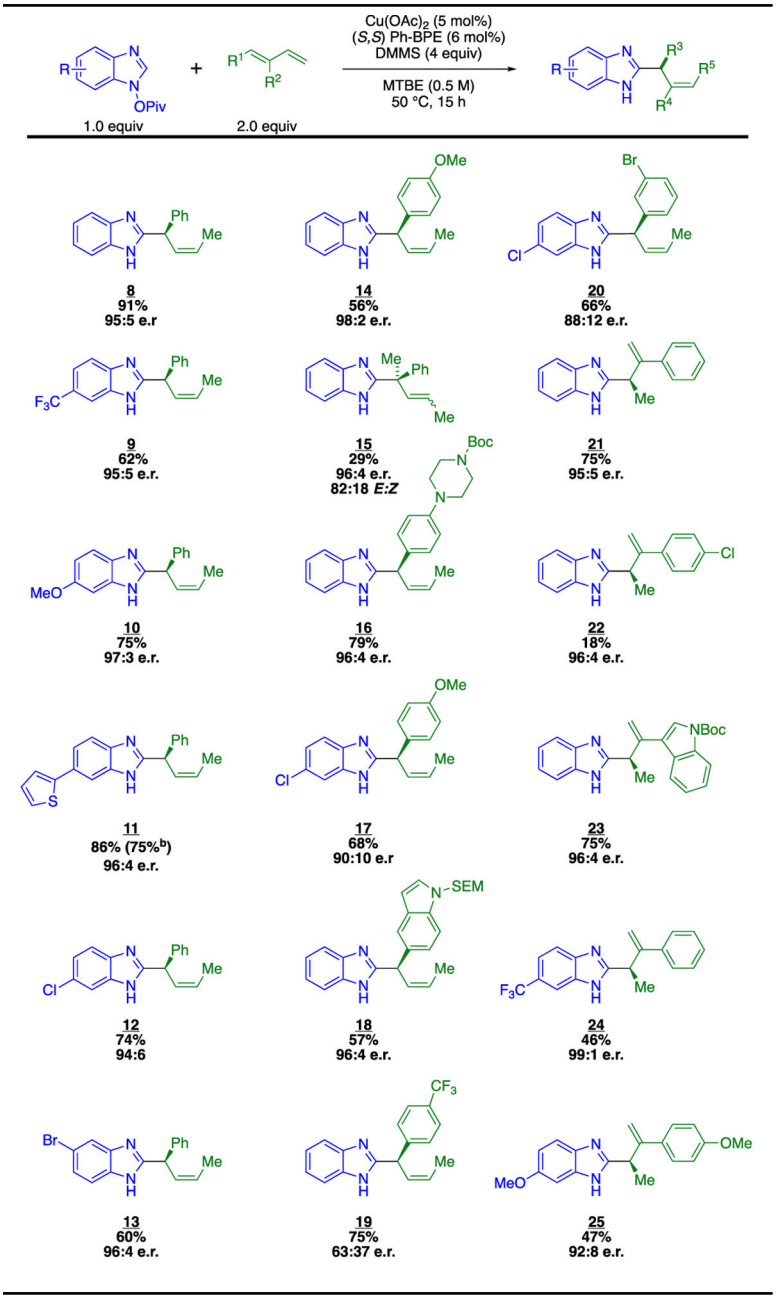
Entry	Ligand	Solvent	Silane	Yield	e.r.
1	JosiPhosJO11	THF	DMMS	93%	69:31
2	QuinoxP*	THF	DMMS	37%	96:4
3	DTBM-Segphos	THF	DMMS	44%	94:6
4	Ph-BPE	THF	DMMS	65%	95:5
5	Ph-BPE	Toluene	DMMS	91%	96:4
6	Ph-BPE	1,4-Dioxane	DMMS	30%	74:26
7	Ph-BPE	Cyclohexane	DMMS	52%	96:4
8	Ph-BPE	MTBE	DMMS	95%	97:3
9	Ph-BPE	MTBE	TMCTS	67%	95:5
10	Ph-BPE	MTBE	Me_2PhSiH	19%	97:3
11	Ph-BPE	MTBE	(EtO),MeSiH	50%	95:5



[a]Reactions were performed using 0.15 mmol of **6**. All yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. Enantiomeric ratios were determined using supercritical fluid chromatography (SFC) employing chiral columns.

Table 2.

Substrate Scope for the CuH-catalyzed C2-allylation of *N*–OPiv Benzimidazoles.[a]



[a]All yields and enantiomeric ratios reported represent the average of at least two runs on a 0.5 mmol scale. Enantiomeric ratios were determined by HPLC and SFC analysis employing chiral columns.

[b]Average of two runs on a 1.00 mmol scale.