

Atom-Economic, Regiodivergent, and Stereoselective Coupling of Imidazole Derivatives with Terminal Allenes**

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Abstract: New Rh- and Pd-catalyzed regiodivergent and stereoselective intermolecular coupling reactions of imidazole derivatives with mono-substituted allenes are herein reported. Using a Rh^I/Josiphos system, perfect regioselectivities and high enantiomeric excess were obtained, while a Pd^{II}/dppf system gave linear products with high regioselectivities and high E/Z selectivities. This method permits the atom economic synthesis of valuable branched and linear allylic imidazole derivatives.

Functionalization of nitrogen-containing heterocycles is an important topic since these structural motifs are prevalent in natural products, agrochemicals, and pharmaceuticals (Figure 1).^[1a–c] Additionally, their application in ligand and catalyst design, supramolecular chemistry, and nanotechnology has attracted much attention.^[1b,c] To this end, N-allylation of heterocyclic compounds is of particular interest because of

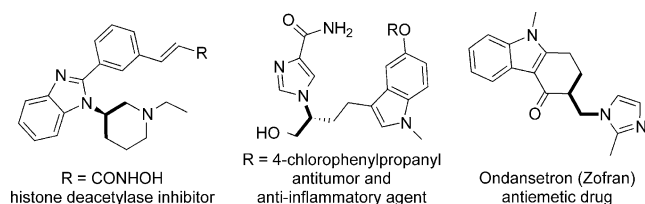
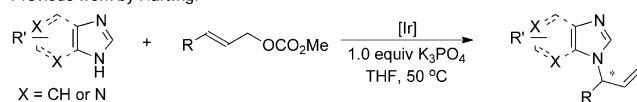


Figure 1. Examples of bioactive imidazole derivatives.

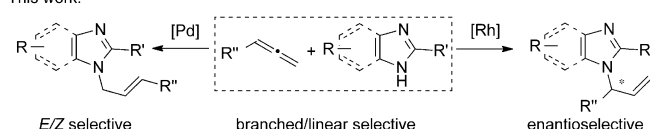
the versatility of the allylic moiety, which allows further elaboration and even straightforward syntheses towards biologically active target molecules.^[2] Despite the importance of the N-allylation of heterocycles, efficient methods are still rare.^[3] Only one example has been reported using imidazole derivatives (Scheme 1).^[3a] Furthermore, the synthesis of the corresponding achiral linear products usually use prefucionalized allylic derivatives with a leaving group under base-promoted or metal-catalyzed conditions.^[4]

Over the past few decades, allylic substitution^[5–9] and allylic oxidation^[10] have been the preferred methods for the

Previous work by Hartwig:



This work:



Scheme 1. Transition metal catalyzed allylation of imidazole derivatives. THF = tetrahydrofuran.

synthesis of allylic derivatives. Limitations of these approaches include the requirement of a stoichiometric amount of a leaving group or an oxidant, thus making them less attractive in terms of atom economy.^[11] Therefore, new methods for atom-economic and selective allylation are highly desirable. Our previous exploration on the rhodium-catalyzed enantioselective coupling of allenes and alkynes with carboxylic acids and anilines has exhibited a powerful atom economical-complement to transition metal catalyzed asymmetric allylic substitutions and allylic oxidations.^[12–15] We report herein a regiodivergent and stereoselective coupling of imidazole derivatives with terminal allenes and it allows access to both α -chiral branched and achiral linear allylic derivatives using rhodium and palladium catalyst systems, respectively (Scheme 1). To our best knowledge, this is the first example of a transition metal catalyzed atom-economic, regiodivergent, and stereoselective coupling of heterocycles with allenes.

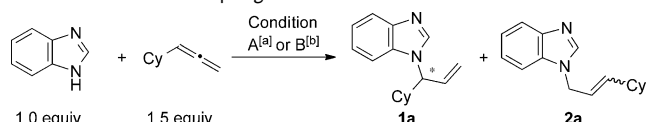
The initial experiments were performed with benzimidazole and cyclohexylallene in the presence of $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ (2.5 mmol %) and DPEphos (10 mmol %) in 1,2-dichloroethane (DCE) at 80 °C. To our delight, the desired branched product was isolated with a promising 49% yield as a single regioisomer. The feasibility of benzimidazole as a pronucleophile encouraged us to screen different types of chiral bidentate phosphine ligands.^[16] Biaryl-type bisphosphine ligands^[16] and the Josiphos ligand **J1** (Table 1, entry 1) led to poor results. We were pleased to observe that changing to the more-electron-rich and bulkier cyclohexyl Josiphos ligand **J2** led to a significant increase in the yield and *ee* value (Table 1, entry 2). A fine tuning of the steric effects by replacing the cyclohexyl group with the *tert*-butyl group resulted in 97% *ee* with a slightly lower yield (72%; Table 1, entry 3). Ligands with a smaller bite angle gave no reaction or only traces of product, and (*R,R*)-diop gave moderate yield

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Table 1: Optimization of rhodium/palladium-catalyzed regiodivergent and stereoselective coupling.



Entry ^[a,b]	Ligand	Yield [%] ^[c]	B/L ^[d]	ee [%] ^[e]	E/Z ^[f]
1	J1	55	100:0	24	—
2	J2	83	100:0	89	—
3	J3	72	100:0	97	—
4	DPEphos	(74) ^[g]	9:91	—	—
5	dppp	(48) ^[g]	9:91	—	—
6	dppb	(71) ^[g]	5:95	—	—
7	(±)-Binap	78	14:86	—	—
8	Xantphos	(77) ^[g]	7:93	—	—
9	dppf	71	< 1:99	—	> 99:1
10 ^[h]	dppf	89	< 1:99	—	> 98:2

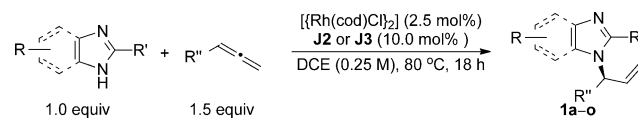
[a] Entries 1–3, Conditions A: $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %), ligand (10 mol %), DCE (0.25 M), 80 °C, 18 h. [b] Entries 4–10, Conditions B: $[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2$ (2.5 mol %), ligand (5.0 mol %), THF (0.4 M), 80 °C, 18 h. [c] Yield of isolated product. [d] Branched and linear ratio was determined by ^1H NMR analysis of the crude reaction mixture. [e] Determined by HPLC using a chiral stationary phase. [f] Determined by ^1H NMR spectroscopy of the isolated products. [g] Yield of linear products in the crude reaction mixture as determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [h] 1.2 equiv benzimidazole. binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DPEphos = bis[(2-diphenylphosphino)phenyl]ether, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane, Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

(69%) but disappointing enantioselectivity (22%).^[16] In all cases, the branched product was observed exclusively.

We speculated that a suitable palladium catalyst in combination with an achiral bidentate diphosphine ligand might give access to the regiosubstituted linear allylation product.^[13] Our preliminary study focused on identification of a suitable ligand. Indeed, by using $[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2$ (2.5 mol %) and DPEphos (5.0 mol %), the desired linear product (74%) was obtained with good linear/branched (L/B) selectivity (91:9). We then tested a range of achiral bidentate diphosphine ligands with different bite angles. The ligand dppf proved to be superb in terms of the regioselectivity (Table 1, entry 4–9), and a slight excess of benzimidazole (1.2 equiv) led to an increased yield of 89% with excellent L/B and E/Z selectivity (Table 1, entry 10). Surprisingly, the reaction proceeded smoothly without any additive.^[13]

With the optimized reaction conditions in hand, we then investigated the scope of different imidazole derivatives with allenes. For the synthesis of chiral branched products,^[17a] a wide range of imidazole derivatives were suitable substrates with good to excellent yield and enantioselectivity (Table 2).^[17b] Both electron-withdrawing (**1f** and **1h**) and electron-donating substituents (**1b** and **1d**) were tolerated with up to 99% yield (**1b**) and up to 98% enantioselectivity

Table 2: Scope of the rhodium-catalyzed enantioselective coupling of imidazole derivatives with allenes.



Entry	Imidazole Derivative	Yield [%]	ee [%]
1a	1a (J3)	72%	97%
1b	1b (J2)	99%	87%
1c	1c (J2)	78%	77%
1d	1d (J3)	77%	98%
1e	1e (J2)	74%	81%
1f	1f (J2)	80%	82%
1g	1g (J2)	77%	86%
1h	1h (J3)	76%	98%
1i	1i (J2)	74%	92%
1j	1j (J3)	77%	91%
1k	1k (J3)	70%	92%
1l	1l (J2)	95%	85%
1m	1m (J2)	77%	89%
1n	1n (J3)	84%	92%
1o	1o (J2)	80%	90%

Yield is that of the isolated product. The branched and linear ratio was determined by ^1H NMR analysis of the crude reaction mixture. The ee values were determined by HPLC using a chiral stationary phase. [a] Reaction was carried out at 100 °C. Chp = cycloheptyl, TBS = *tert*-butyldimethylsilyl, Trt = trityl, Phth = phthaloyl.

(**1d** and **1h**). A halogenated imidazole substrate gave good yield (**1g**) and permits further elaboration on the imidazole ring. To our delight, a free hydroxy group was tolerated, albeit at a slightly elevated temperature was required (**1e**). To expand the scope of allenes, the monosubstituted allenes were readily prepared in one or two steps from commercially available starting materials.^[16] Both α -branched allenes (**1a** and **1o**) and linear alkyl-substituted allenes (**1j** and **1m**) were suitable substrates. Allenes bearing protected alcohols (**1k** and **1n**) and phthalimide (**1l**) were also compatible, and could afford useful hydroxy and amino groups upon deprotection.

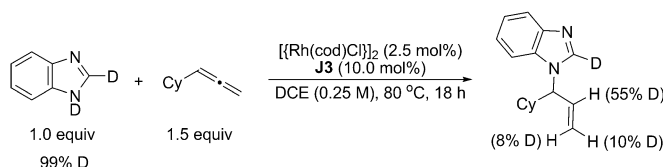
In the case of the palladium-catalyzed coupling reactions, various imidazole derivatives reacted smoothly with the allenes to give the complementary linear allylation products with good to excellent yields, and excellent linear and E selectivities in most cases (**2a–2h**; Table 3).^[17c] Imidazole bearing an unprotected aldehyde group has no detrimental effect on the reaction (**2i**). Different monosubstituted allenes were also compatible under the palladium-catalyzed conditions (**2j–2p**), albeit slightly lower E selectivities were obtained when less bulky α -linear substituted allenes were used.

To study the possible mechanism, isotope-labeling experiments were conducted with $[\text{D}_2]$ benzimidazole and cyclohexylallene under standard rhodium-catalyzed conditions

Table 3: Scope of the palladium-catalyzed linear-selective coupling of imidazole derivatives with allenes.

$\text{R}-\text{Imidazole}-\text{R}' + \text{R}''-\text{allene} \xrightarrow[\text{THF (0.4 M), 80 }^\circ\text{C, 18 h}]{[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2 \text{ (2.5 mol\%)} \text{ dppe (5.0 mol\%)}} \text{R}-\text{Imidazole}-\text{R}'-\text{R}'' \text{ (2a-p)}$			
1.2 equiv	1.0 equiv		
2a , yield: 89% L/B > 99:1 E/Z > 98:2	2b , yield: 82% L/B = 95:5 E/Z = 96:4	2c , yield: 82% L/B = 97:3 E/Z = 97:3	2d , yield: 70% L/B > 99:1 E/Z = 90:10
2e , yield: 88% L/B > 99:1 E/Z = 99:1	2f , yield: 67% L/B = 95:5 E/Z = 97:3	2g , yield: 80% L/B = 97:3 E/Z = 98:2	2h , yield: 85% L/B > 99:1 E/Z = 95:5
2i , yield: 79% L/B = 91:9 E/Z = 97:3	2j , yield: 71% L/B = 93:7 E/Z = 86:14	2k , yield: 80% L/B = 96:4 E/Z = 99:1	2l , yield: 68% L/B = 98:2 E/Z = 88:12
2m , yield: 96% L/B > 99:1 E/Z > 83:17	2n , yield: 79% L/B = 85:15 E/Z = 88:12	2o , yield: 94% L/B = 98:2 E/Z = 87:13	2p , yield: 69% L/B = 94:6 E/Z = 97:3

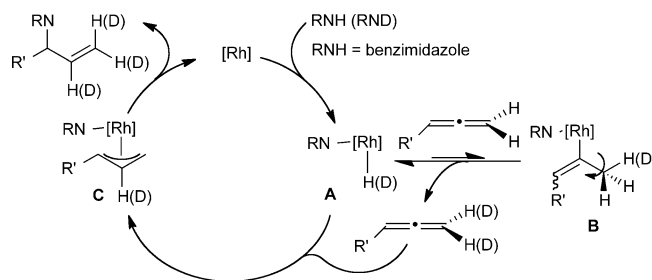
Yield is that of the isolated product. The branched and linear ratio was determined by ^1H NMR analysis of the crude reaction mixture. The E/Z ratio was determined by ^1H NMR spectroscopy of the isolated products.



Scheme 2. Isotope-labeling experiments with $[\text{D}_2]$ benzimidazole.

(Scheme 2). Deuterium incorporation was observed at all positions of the alkene, and is in accordance with our previous reported results.^[15a,b,d]

Based on the labeling experiments, the following mechanism can be proposed (Scheme 3). Oxidative addition of benzimidazole to Rh^{I} generates the Rh^{III} complex **A**.^[18a] Hydrometalation of the terminal allene double bond affords the vinyl/ Rh species **B**, which undergoes β -hydride elimination and explains the deuterium incorporation at the terminal positions. Hydrometalation of the more-substituted double bond could generate the σ - or π -allyl/ Rh complex **C**, which could generate the desired branched N-allylic heterocycles by reductive elimination (or external benzimidazole attack). The regioselectivity of this step is in accordance with that observed previously for other allylrhodium complexes.^[18b-d]



Scheme 3. Proposed mechanism of the rhodium-catalyzed coupling of imidazole derivatives with allenes.

The palladium-catalyzed reactions may follow a similar mechanism, but the reductive elimination (or external attack) step favors the less hindered position and thus affords the linear product.^[19,20]

To conclude, we have developed the first atom-economic, regiodivergent, and stereoselective coupling of imidazole derivatives with allenes by using rhodium and palladium catalyst systems. A broad range of imidazole derivatives smoothly coupled with various allenes to obtain both chiral branched and achiral linear products. Excellent regioselectivities and stereoselectivities were achieved in most cases. Future studies will focus on mechanistic investigations and the extension of this methodology to other nitrogen-containing heterocycles as well as their applications in target-oriented synthesis.

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