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RESEARCH ARTICLE

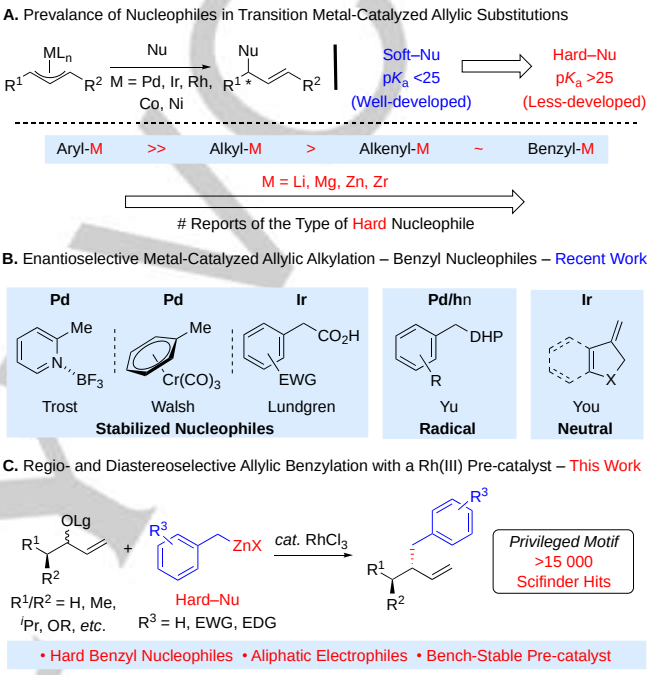
Regio- and Diastereoselective Rhodium-Catalyzed Allylic Substitution with Unstabilized Benzyl Nucleophiles

Debasis Pal, Timothy B. Wright, Ryan O'Connor, and P. Andrew Evans*

Abstract: *We have developed a highly regio- and diastereoselective rhodium-catalyzed allylic substitution of challenging alkyl-substituted branched allylic carbonates with benzylzinc reagents, which are prepared from widely available benzyl halides. This process utilizes rhodium(III) chloride as a commercially available, high-oxidation state and bench-stable pre-catalyst to provide a rare example of regio- and diastereoselective allylic substitution in the absence of an exogenous ligand. This reaction tolerates both electronically diverse benzylzinc nucleophiles and an array of functionalized and/or challenging aliphatic secondary allylic electrophiles. Finally, the configurational fluxionality of the rhodium-allyl intermediate is exploited to develop a novel diastereoselective process for the construction of vicinal acyclic ternary/ternary stereogenic centers, in addition to a cyclic ternary/quaternary derivative.*

Introduction

The transition metal-catalyzed allylic substitution reaction is a particularly versatile C-C and C-X cross-coupling reaction for target-directed synthesis.[1] Nevertheless, despite the recent advances in the repertoire of soft nucleophiles that can be deployed in this process, the development of the analogous process with hard "unstabilized" nucleophiles is significantly more challenging (Scheme 1A).[2-6] This striking dichotomy can presumably be attributed to the high reactivity of hard nucleophiles; namely, main-group organometallic reagents (e.g., M = Li, Mg, *etc*.) towards the metal-allyl intermediate and/or electrophilic functional groups within the substrate. Although recent efforts have expanded the scope of hard nucleophiles, we are only aware of a single allylic benzylation with a benzylic organometallic reagent, which affords the *linear* achiral derivative.[6] Hence, given that this motif is omnipresent in an array of bioactive natural products and medicinally important agents, the preparation of the branched ternary allylic benzyl motif remains highly desirable.[7] Notwithstanding the aforementioned limitations, several elegant and creative approaches that circumvent using a reactive organometallic intermediate have been devised (Scheme 1B). For instance, Trost and Walsh



Scheme 1. Background for the development of the regio- and diastereoselective benzylation of acyclic secondary allylic carbonates with hard benzyl nucleophiles.

independently described the utility of the Lewis acid complexes of 2-methylpyridine and chromium-bound toluene pronucleophiles.[8,9] More recently, Lundgren and coworkers have developed a process that employs electron-deficient aryl acetic acids for allylic benzylation with concomitant decarboxylation.[10] Alternatively, free radical and neutral cross-coupling partners have been employed in allylic benzylation reactions by Yu and You, respectively.[11,12] *Nevertheless, the direct and branched selective allylic alkylation with an unstabilized benzyl nucleophile for the installation of simple and electronically unbiased toluene derivatives has not been reported.* Herein, we now describe the regio- and diastereoselective rhodium-catalyzed allylic alkylation with hard benzylzinc species for the direct construction of vicinal acyclic ternary/ternary stereogenic centers. Notably, this process represents a rare example of an allylic substitution that employs a high-valent transition metal pre-catalyst without the necessity for an exogenous ligand.[13]

In a program directed towards the development of regio- and stereoselective rhodium-catalyzed allylic alkylation reactions,[14,15] we have previously described the arylation of fluorinated allylic carbonates using arylzinc bromides and a *low-valent* rhodium catalyst.[16] We hypothesized that the rhodium-catalyzed allylic substitution with unstabilized benzyl nucleophiles would significantly expand the scope of this process to include sp^3 organometallic reagents, albeit

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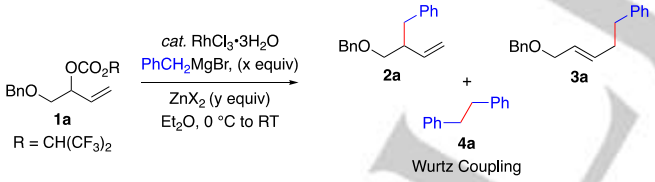
there are several inherent challenges associated with this type of cross-coupling. For instance, the rhodium-catalyzed allylic substitution with benzyl nucleophiles undergoes slower reductive elimination (sp^3 *vs* sp^2),[17] which is further complicated by the tendency of benzylic organometallic species to undergo Wurtz homocoupling.[18] Indeed, the challenges presented by the Wurtz homocoupling process has been a significant obstacle in the deployment of benzyl nucleophiles in metal-catalyzed cross-coupling reactions.[19] Consequently, we envisioned that the development a regioselective rhodium-catalyzed allylic alkylation of unstabilized benzyl nucleophiles would represent a significant advance in this area.

Results and Discussion

Preliminary studies demonstrated that benzylzinc nucleophiles deliver the benzylation product **2a** in moderate to good yields with several rhodium(I) catalysts.[20] However, we envisioned that using a high-oxidation state rhodium(III) pre-catalyst, which could undergo *in situ* reduction[21] to provide an active rhodium(I) catalyst (*vide infra*), may provide a more robust pre-catalyst. The use of a high-valent transition metal complexes (e.g., Rh(III), Ir(III), *etc.*) as pre-catalysts is *rare* in allylic substitution reactions, albeit they are generally deployed in processes that generate a metal-allyl intermediate *via* allylic C-H activation.[22] Remarkably, we found that the commercially available and bench-stable pre-catalyst rhodium(III) chloride trihydrate is capable of delivering the allylic benzylation product with similar efficiency and selectivity.

Table 1. Optimization of the regioselective rhodium-catalyzed allylic substitution with benzyl nucleophiles[a]



Entry	BnMgBr (***x*** equiv)	ZnX_2 (***y*** equiv)		Yield (%)[b]	**2a**:**3a**[c]	**2a**+**3a**: **4a**[c]
1	2.0	-	-	60	81:19	83:17
2	2.0	$ZnCl_2$	1.0	47	98:2	77:23
3	''	$ZnBr_2$	''	39	98:2	75:25
4	''	ZnI_2	''	78	98:2	88:12
5[d]	''	''	''	74	98:2	87:13
6	3.0	''	1.0	41	88:12	72:28
7	1.0	''	1.0	45	99:1	92:8
8	***1.5***	***ZnI_2***	***1.5***	***82(80)***[e]	***99:1***	***93:7***

[a] All reactions were performed on a 0.2 mmol scale using 10 mol% $RhCl_3•3H_2O$, in Et_2O (0.025 M) for *ca.* 16 h. [b] GC yield of **2a**. [c] Determined by GC analysis of the crude reaction mixture. [d] BnMgCl was used. [e] Isolated yield in parenthesis.

Table 1 outlines the development of a highly regioselective allylic benzylation using rhodium(III) chloride as the pre-catalyst. Treatment of the acyclic fluorinated allylic carbonate **1a** (see SI for leaving group study) with 2 equivalents of benzylmagnesium bromide in the presence of catalytic rhodium(III) chloride trihydrate affords the allylic benzylation product **2a** with moderate yield and regioselectivity (Table 1, entry 1). Importantly, the transmetallation of the benzyl Grignard reagent with zinc chloride resulted in a significant improvement in regioselectivity, albeit with reduced efficiency (entry 2). Further studies probed the impact of the zinc(II) halide salt used in the transmetallation, which demonstrated they are identical in the context of regiocontrol. Nevertheless, zinc(II) iodide provides optimal efficiency for the formation of **2a** and minimizes the formation of the Wurtz homocoupling product **4a** (entries 2-3 *vs* 4). In contrast, the identity of the halide within the Grignard reagent is less significant, as benzylmagnesium chloride furnishes **2a** with similar efficiency and selectivity (entry 4 *vs* 5). At this point, while the allylic benzylation of **1a** afforded good efficiency and excellent regioselectivity, the isolation of the target product was complicated by the formation of the Wurtz homocoupling derivative **4a**, which often coelutes with the non-polar allylic alkylation adduct **2a**. Further studies indicate that either increasing or decreasing the amount of Grignard reagent leads to lower efficiency and selectivity (entry 6 and 7), albeit a benzyl Grignard to zinc(II) salt ratio of 1:1 significantly reduces the formation of the Wurtz coupling by-product. Hence, we rationalized that increasing the amount of nucleophile while maintaining the same stoichiometry would provide the optimal efficiency for this process. Gratifyingly, increasing the amount of benzylmagnesium bromide and zinc(II) iodide (1.5 equiv.) furnished the branched allylic benzylation product **2a** with optimal efficiency and selectivity (entry 8).

Table 2 delineates the scope of the benzyl nucleophile,[23] which is tolerant of several 4-substituted benzyl derivatives with both electron-withdrawing and electron-donating substituents (entries 1-6). The ability to employ highly electron-rich benzyl nucleophiles (e.g., 4-OMe) is particularly significant given their propensity to undergo Wurtz homocoupling reactions. For instance, in these cases, the nucleophile was prepared using the method reported by Knochel,[24] which involves the direct insertion of zinc into the benzyl chloride to afford the more challenging allylic benzylation adducts **2ae** and **2af** in moderate yield. The current process is also amenable to a variety of 3-substituents as well as a 2-fluoro derivative, albeit with reduced regioselectivity for the latter case (entries 7-12). Disubstituted aryl substituents also furnish the allylic benzylation adducts with good efficiency and regioselectivity (entries 13-15), which includes a dihalogenated derivative **2am** that can be further functionalized *via* conventional cross-coupling. Table 2 also demonstrates the application of the optimized reaction conditions (Table 1, entry 8) to several acyclic secondary allylic carbonates **1a-o**, which illustrates the process is tolerant of a number of functionalized allylic scaffolds. For example, whereas the copper- and iridium-catalyzed allylic alkylation of hard nucleophiles is generally optimal with cinnamyl derivatives, which presumably circumvent β-hydride elimination to form dienes, the rhodium-catalyzed process is remarkably efficient and regioselective with *aliphatic* electrophiles. For instance, protected hydroxymethyl carbonates (entries 16-17), benzyl and *n*-

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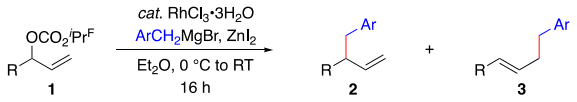
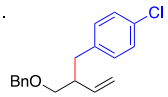
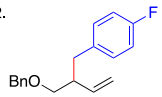
Table 2. Benzyl Nucleophile and allylic carbonate scope of the regioselective rhodium-catalyzed allylic substitution with benzyl nucleophiles [a-e]



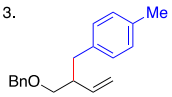
Benzyl Nucleophile Scope

1. 

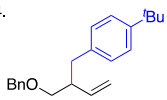
2aa 85%, *b:l* ≥19:1
86%, *b:l* ≥19:1[e]

2. 

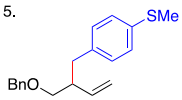
2ab 75%, *b:l* ≥19:1

3. 

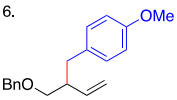
2ac 79%, *b:l* ≥19:1

4. 

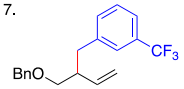
2ad 86%, *b:l* ≥19:1

5. 

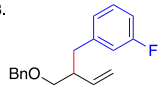
2ae 45%, *b:l* ≥19:1[d]

6. 

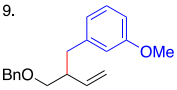
2af 51%, *b:l* ≥19:1[d]

7. 

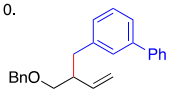
2ag 74%%, *b:l* ≥19:1
73%, *b:l* ≥19:1[e]

8. 

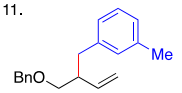
2ah 87%, *b:l* ≥19:1

9. 

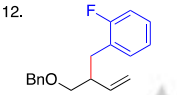
2ai 82%, *b:l* ≥19:1

10. 

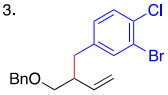
2aj 72%, *b:l* ≥19:1

11. 

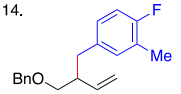
2ak 81%, *b:l* ≥19:1

12. 

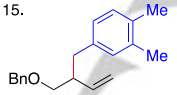
2al 70%, *b:l* ≥19:1

13. 

2am 79%, *b:l* ≥19:1
74%, *b:l* ≥19:1[e]

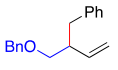
14. 

2an 73%, *b:l* ≥19:1

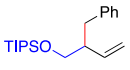
15. 

2ao 74%, *b:l* ≥19:1

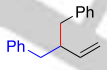
Allylic Carbonate Scope

16. 

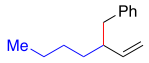
2a 80%, *b:l* ≥19:1
82%, *b:l* ≥19:1[e]

17. 

2b 70%, *b:l* ≥19:1

18. 

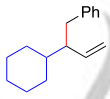
2c 74%, *b:l* = 11:1

19. 

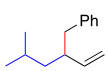
2d 64%, *b:l* ≥19:1

20. 

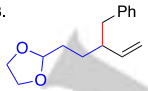
2e 72%, *b:l* ≥19:1

21. 

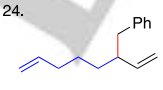
2f 76%, *b:l* ≥19:1

22. 

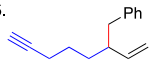
2g 68%, *b:l* = 14:1
65%, *b:l* = 14:1[e]

23. 

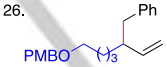
2h 81%, *b:l* ≥19:1

24. 

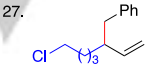
2i 82%, *b:l* = 17:1

25. 

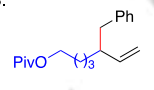
2j 58%, *b:l* = 11:1

26. 

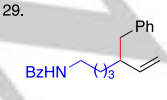
2k 81%, *b:l* = 16:1

27. 

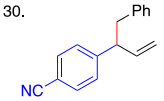
2l 74%, *b:l* = 17:1

28. 

2m 78%, *b:l* = 11:1
77%, *b:l* = 9:1[e]

29. 

2n 75%, *b:l* = 10:1

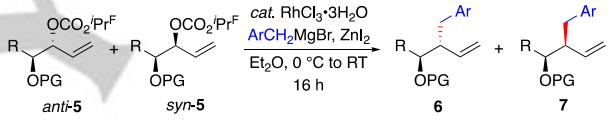
30. 

2o 70%, *b:l* = 6:1

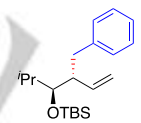
[a] All reactions were performed on a 0.25 mmol scale using 10 mol % $RhCl_3•3H_2O$, 1.5 equiv of $ArCH_2MgBr$ and 1.5 equiv of ZnI_2 in Et_2O (0.025 M) for *ca.* 16 h. [b] Isolated yields. [c] Regioselectivity was determined by 500 MHz ^1H NMR analysis of the isolated products. [d] Benzylzinc nucleophiles generated by direct zinc insertion of benzylchlorides, see SI for details. [e] Reactions were performed 2 mol % $RhCl_3•3H_2O$.

butyl derivatives (entries 18-19) undergo the allylic benzylation in good yield and with excellent branched selectivity. Furthermore, the reaction tolerates a variety of α-, β- and γ-branched substrates (entries 20-23), including a cyclic acetal (entry 23), which all afford excellent efficiency and selectivity. A key feature with this transformation is the regioselective allylic substitution of this substrate class, which is particularly challenging. Additionally, the rhodium-catalyzed benzylation is also tolerant of various functionalized aliphatic allylic carbonates, including terminal alkene, alkyne and *para*-methoxybenzyl ether containing motifs (entries 24-26). Finally, the utility of employing benzylzinc nucleophiles is highlighted by the chemoselective allylic benzylation of substrates bearing potentially reactive functional groups, such as a primary chloride, pivalate ester, secondary amide and aryl nitrile (entries 27-30). *Overall, the ability to facilitate the regioselective benzylation of acyclic allylic carbonates using a bench-stable and commercially available rhodium(III) pre-catalyst in the absence of exogenous ligand with a variety of electronically diverse benzylzinc nucleophiles makes this a versatile protocol for the synthesis of this privileged motif.*

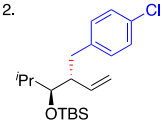
Table 3. Substrate scope of the regio- and diastereoselective rhodium-catalyzed allylic substitution with benzyl nucleophiles [a-d]



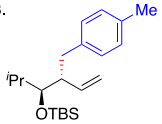
Proof of Hypothesis

1. 

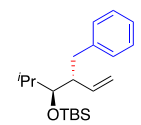
6a 75%, *b:l* ≥19:1
6a:7a ≥19:1
from *anti*-**5a**:*syn*-**5a** = 1:4

2. 

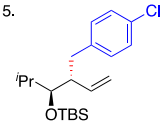
6b 58%, *b:l* ≥19:1
6b:7b ≥19:1
from *anti*-**5a**:*syn*-**5a** = 1:4

3. 

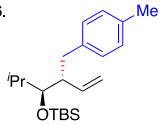
6c 76%, b:l ≥19:1
6c:7c ≥19:1
from *anti*-**5a**:*syn*-**5a** = 1:4

4. 

6a 70%, *b:l* ≥19:1
6a:7a ≥19:1
from *anti*-**5a**:*syn*-**5a** = 3:1

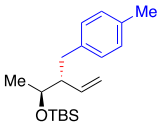
5. 

6b 66%, *b:l* ≥19:1
6b:7b ≥19:1
from *anti*-**5a**:*syn*-**5a** = 3:1

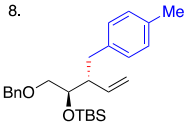
6. 

6c 78%, *b:l* ≥19:1
6c:7c ≥19:1
from *anti*-**5a**:*syn*-**5a** = 3:1

Allylic Carbonate Scope

7. 

6d 74%, *b:l* ≥19:1[d]
6d:7d ≥19:1
from **5b**, *dr* = 4:1

8. 

6e 77%, *b:l* ≥19:1
6e:7e = 9:1
from **5c**, *dr* = 3:1

9.

6f 81%, *b:l* ≥19:1
6f:7f ≥19:1
from **5d**, *dr* = 3:1

Protecting Group Scope

10.

6g 69%, *b:l* ≥19:1
6g:7g = 15:1
from **5e**, *dr* = 4:1

11.

6h 72%, *b:l* ≥19:1[d]
6h:7h ≥19:1
from **5f**, *dr* = 3:1

12.

6i 79%, *b:l* ≥19:1
6i:7i ≥19:1
from **5g**, *dr* = 3:1

[a] All reactions were performed on a 0.25 mmol scale using 10 mol % $RhCl_3•3H_2O$, 2 equiv of $ArCH_2MgBr$ and 2 equiv of ZnI_2 in Et_2O (0.025 M) for *ca.* 16 h. [b] Isolated yields. [c] Regio- and diastereoselectivity was determined by

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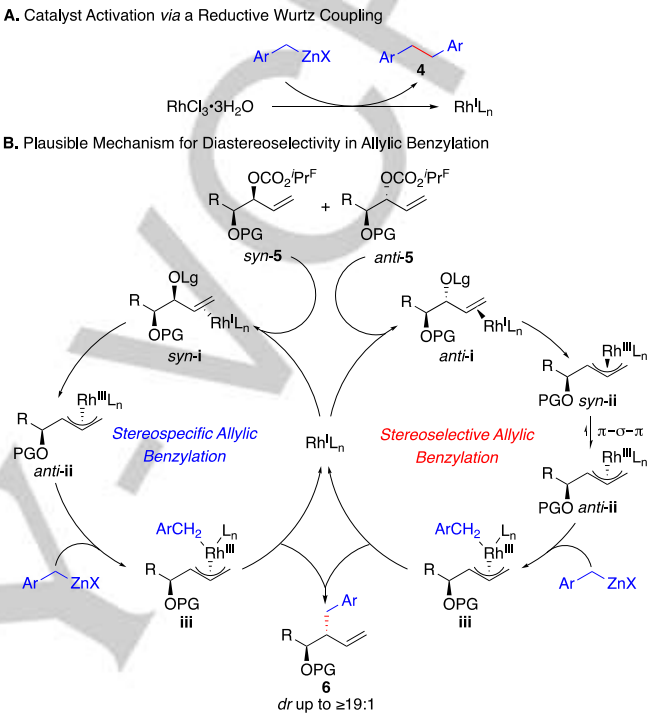
500 MHz ^{1}H NMR analysis of the isolated products. [d] Reactions were performed using 2 mol % $RhCl_3$•$3H_2O$.

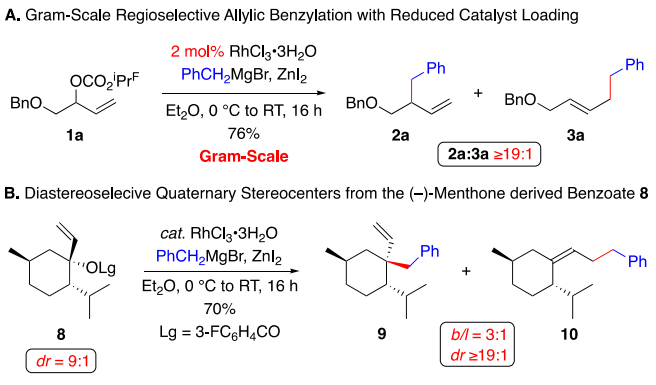
To probe the feasibility of stereoselective carbon-carbon bond formation using this protocol, we investigated the stereospecific benzylation of enantiomerically enriched carbonate (*R*)-**1a**. In sharp contrast to our previous report with arylzinc nucleophiles,[16] the rhodium-catalyzed benzylation affords **2a** with poor conservation of enantiomeric excess (*cee*). Hence, this result is consistent with a fluxional rhodium-allyl intermediate, which undergoes stereochemical leakage *via* a conventional π-σ-π isomerization at a comparable rate to product formation. Consequently, given the excellent regiocontrol with α-branched substrates and considering the fluxional nature of the rhodium-allyl, we hypothesized that this may permit the development of a diastereoselective allylic substitution with allylic carbonates bearing α-stereogenic centers (Table 3). Gratifyingly, the rhodium-catalyzed allylic alkylation of *anti*-**5a**/*syn*-**5a** (1:4), affords **6a** in good yield and with excellent regio- and diastereoselectivity. The process is also applicable to electron-deficient and electron-rich 4-substituted benzyl groups to afford **6b** and **6c** with similar efficiency and selectivity (entries 1-3). Notably, the stereochemistry of the substrate does not significantly impact the level of stereocontrol (entries 4-6), which provide the benzylation adducts **6a-c** with analogous efficiency and diastereoselectivity, indicating that the reaction is feasible from diastereomeric mixtures of **5**. Additional studies examined the allylic carbonate substitution and the nature of the α-alkoxy group. To this end, the methyl, benzyloxymethyl and cyclopentyl substituted allylic carbonates undergo the benzylation in good yield and with moderate to excellent diastereoselectivity (entries 7-9). Furthermore, variations in the α-alkoxy group, such as methyl, benzyl and MOM ethers, also furnish the benzylation products in high yields with good to excellent diastereoselectivity (entries 10-12). The diastereoselective construction of contiguous acyclic stereocenters with a hard benzyl nucleophile represents a novel development, given that 1,2-stereoinduction *via* a fluxional metal-allyl species in an allylic alkylation process has not been reported.

Scheme 2 outlines the proposed mechanism for the origin of diastereoselectivity in this process. The formation of the active rhodium(I) catalyst presumably occurs *via* reductive elimination from the rhodium(III) pre-catalyst as part of a homocoupling process in which the benzylzinc reagent functions as a sacrificial reductant and is converted to the Wurtz-type side product **4** (Scheme 2A). The diastereoselective cross-coupling is thought to involve a stereoconvergent process, which proceeds through both a stereospecific and/or a stereoselective catalytic cycle (Scheme 2B). For instance, in the stereospecific process, the rhodium-catalyst complexes with allylic carbonate *syn*-**5** to afford *syn*-**I**, which permits oxidative addition with inversion of configuration[14,15] to afford *anti*-**ii** that coordinate the benzyl nucleophile to facilitate reductive elimination to furnish **6** with excellent stereospecificity. In contrast, the stereoselective process generates the diastereomeric rhodium-allyl *syn*-**ii**, which undergoes a rapid facial exchange of the metal *via* a conventional π–σ–π rearrangement to afford *anti*-**ii** and presumably alleviate unfavorable steric interactions with the neighboring substituent. The coordination of the nucleophile then promotes reductive elimination in an analogous manner to afford the same diastereoisomer, namely **6**. Consequently, the rate of the facial exchange from *syn*-**ii** to *anti*-**ii** is faster than reductive elimination, which is supported by the fact that the reaction is not stereospecific (*vide supra*). The fact that the diastereochemical outcome is similar regardless of the starting material makes this an attractive process for synthetic applications, given that the reaction can be conducted with diastereomeric mixtures of the starting material.



Scheme 2. Proposed catalytic cycle for the diastereoselective rhodium-catalyzed allylic benzylation.

Additional studies explored the scalability and diastereocontrol with a more challenging ternary allylic electrophile. Gratifyingly, the allylic benzylation can be performed on gram-scale with significantly reduced catalyst loading (2 mol%), which affords similar efficiency and selectivity (Scheme 3A), in addition to a reduction in the amount of Wurtz coupling adduct **4a** (see SI). *Notably, we were able to demonstrate this reduction in catalyst loading with several other substrates (cf. Table 2; Footnote [e] and Table 3; Footnote [d]) on the standard reaction scale.* We also envisioned using this type of diastereoselective process to install a challenging vicinal ternary/quaternary stereogenic centers. For



Scheme 3. Gram-scale reaction and cyclic diastereocontrol in the rhodium-catalyzed allylic benzylation.

instance, the rhodium-catalyzed benzylation of the allylic benzoate **8**, which is prepared from (–)-menthone, affords the alkylation adducts **9/10** in 70% yield and with excellent diastereocontrol for **9**, albeit with modest regioselectivity (Scheme 3B). The direct and stereoselective construction of challenging vicinal quaternary/ternary stereogenic centers in this manner highlights the potential synthetic utility of this process.

Conclusion

In conclusion, we have developed a highly regio- and diastereoselective benzylation of acyclic fluorinated allylic carbonates under mild conditions using rhodium(III) chloride as the pre-catalyst. This protocol offers a direct approach to the installation of a privileged ternary benzyl scaffold, which is ubiquitous in medicinal chemistry. The current method is a rare example of the direct catalytic cross-coupling of a simple and electronically unbiased toluene nucleophiles without the necessity of modifying or pre-activating the aryl scaffold. The ability to employ various sterically diverse and functionalized allylic carbonates, along with a variety of benzyl nucleophiles, makes this an attractive method. Notably, the configurational fluxionality of the rhodium-allyl intermediate facilitated the development of a diastereoselective variant for the construction of vicinal acyclic stereocenters, and contiguous ternary/quaternary stereogenic centers in a cyclic system. Overall, the associated challenges with catalytic cross-couplings of benzyl nucleophiles, coupled with the practicality of the pre-catalyst, make this an important addition in this area.

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Conflict of interest

The authors declare no competing financial interest.

Keywords: allylic substitution • benzylzinc nucleophile • hard nucleophile • regio- and diastereoselective • rhodium(III) chloride

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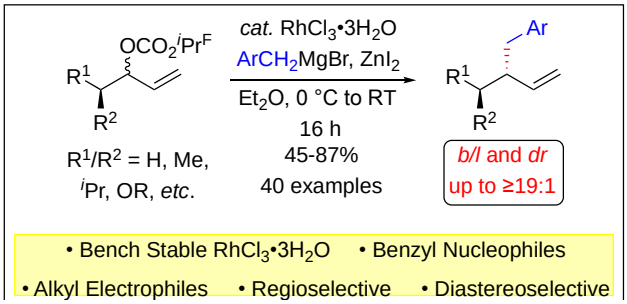

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