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Regioselective and Enantiospecific Rhodium-Catalyzed Allylic Amination with *N*-(Arylsulfonyl)anilines

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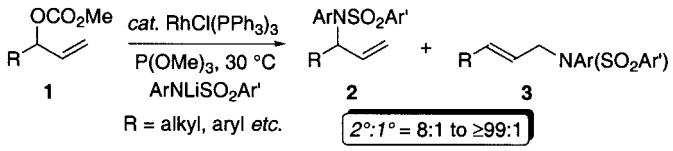
ABSTRACT



The regioselective and enantiospecific rhodium-catalyzed allylic amination of secondary allylic carbonates 1 with *N*-(arylsulfonyl)anilines provides a convenient process for the construction of arylamines 2. This method, in conjunction with ring-closing metathesis and radical cyclization reactions, allows the direct construction of biologically relevant pharmacophores as exemplified by the construction of dihydroquinoline and dihydrobenzo[*b*]indoline derivatives.

The importance of *N*-substituted arylamines in biologically important molecules, particularly pharmaceuticals and agrochemicals, has provided the impetus for recent developments in the transition metal-catalyzed cross-coupling of aryl halides and *pseudo*-halides with amines.[1,2] This strategy now provides one of the most direct and versatile methods for the construction of this important structural motif. Despite the significant accomplishments in this area, we envisioned an alternative approach to *N*-substituted arylamines in which anilines serve as the nucleophilic component in a metal-catalyzed allylic substitution reaction.[3,4] Recent work demonstrated that the rhodium-catalyzed amination of allylic epoxides using anilines furnished the requisite amino alcohol derivatives with excellent regio- and diastereoselectivity.[5] However, the ability to regioselectively alkylate *unsymmetrical* acyclic allylic alcohol derivatives with anilines, to afford *secondary* products, has not been forthcoming.[4]

In a program directed toward controlling regioselectivity in metal-catalyzed allylic substitution reactions, we have demonstrated that rhodium-catalyzed allylic substitutions proceed with excellent regioselectivity and retention of

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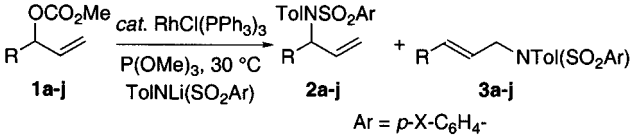
absolute configuration *via* the proposed intermediacy of a distorted π-allyl or *enyl* ($\sigma + \pi$) organorhodium intermediate.[6,7] Herein, we now describe the regioselective rhodium-catalyzed allylic amination of *unsymmetrical* acyclic secondary carbonates **1a**−**j** with the lithium anion of *N*-arylsulfonyl anilines to afford the *N*-arylsulfonyl allylic anilines **2/3a**−**j** in excellent yield, favoring the secondary products **2a**−**j** (Scheme 1).

Scheme 1. Regioselective Rhodium-Catalyzed Allylic Amination with *N*-Arylsulfonyl Anilines



Preliminary studies demonstrated that the lithium counterion was optimum for good selectivity, in accord with or previous studies.[7c] Treatment of the allylic carbonate **1f** with the lithium salt of *N*-arylsulfonyltoluidine (Ar; X = Me) and Wilkinson's catalyst *modified* with trimethyl phosphite at 30 °C, furnished the corresponding alkylation products **2f/3f** in 97% yield, with 70:1 regioselectivity favoring **2f** (Scheme 1).

The electronic influence of the arylsulfonamide was also examined with the expectation that this may alter the nucleophilicity and thus influence the selectivity. Interestingly, the *para*-substituent has minimal influence on the regioselectivity (for **1f**, 2°:1° Ar; X = NO_2 ≥ 99:1; MeO = 90:1; Me = 70:1). The *N*-4-methoxybenzenesulfonyl toluidine (MbsNHTol; X = MeO) was utilized for convenience as we expected the nitro group may interfere in subsequent synthetic applications (*vide infra*). Finally, the enantiospecific rhodium-catalyzed allylic amination was examined to determine the stereochemical course of this transformation. Treatment of the enantiomerically enriched allylic carbonate (*R*)-**1f** (≥ 99% ee) under the standard reaction protocol furnished the *N*-arylsulfonyl allylic aniline (*R*)-**2f** in 93% yield (*X* = MeO; *2°:1°* = 90:1) with 98% cee, consistent with a double inversion process, analogous to earlier studies.[7,8]

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(8) The retention of absolute configuration in the rhodium-catalyzed allylic amination was assigned by the comparison of (*R*)-**2f** prepared from (*R*)-**1f** (Scheme 1) with (*S*)-**2f** prepared via Mitsunobu inversion of the allylic alcohol (*R*)-**1f** ′ with *N*-4-methoxybenzenesulfonyl toluidine.

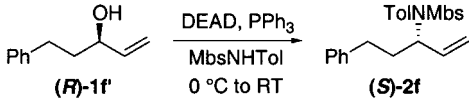


Table 1. Scope of the Regioselective Rhodium-Catalyzed Allylic Amination of **1a**−**j** with TolN(Li)Mbs

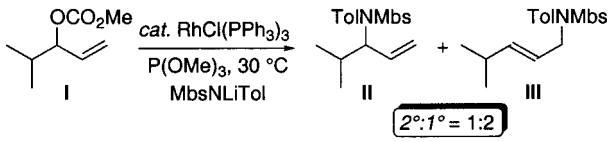
	allylic carbonate **1**[a]			
entry	R =		ratio of **2/3**[b,c]	yield (%)[d]
1	Me	**a**	≥99:1	96
2	CH_2=$CH(CH_2)_3$	**b**	46:1	91
3	$(CH_3)_2CHCH_2$	**c**	12:1	94
4	$(CH_3)_2CH(CH_2)_2$	**d**	27:1	89
5	$PhCH_2$	**e**	20:1	86
6	$PhCH_2CH_2$	**f**	90:1	93
7	$TBSOCH_2$	**g**	23:1	83
8	$BnOCH_2$	**h**	8:1	85
9	Ph	**i**	47:1	94
10	Npth	**j**	41:1	96

[a] All allylic amination reactions were carried out on a 0.5 mmol reaction scale.[9] [b] Ratios of regioisomers were determined by HPLC on crude reaction mixtures. [c] The primary products were prepared independently *via* Pd(0) catalysis.[3] [d] Isolated yields.

Table 1 summarizes the application of this transformation to a variety of racemic *secondary* allylic carbonates **1a**−**j**. *The excellent selectivity obtained for this type of substitution provides an important advance in the synthesis of* N-*(arylsulfonyl)anilines using the metal-catalyzed allylic amination reaction.* The allylic alcohol derivatives examined demonstrate a high degree of tolerance for linear and branched alkyl substituents, provided the branching is not at the α-position with respect to the leaving group (entries 1−6).[10] The allylic amination also tolerates hydroxymethyl groups, where the silicon-protecting group is presumably able to reduce the proximal ligation of the ether oxygen to the metal center (entry 7 vs 8).[11] Aryl substituents also furnish the allylic anilines with excellent regioselectivity (entries 9 and 10).

(9) **Representative Experimental Procedure:** Trimethyl phosphite (24 μL, 0.20 mmol) was added directly to a red solution of Wilkinson's catalyst (46 mg, 0.05 mmol) in anhydrous THF (2.0 mL) at 30 °C, under an atmosphere of argon. The catalyst was allowed to form over ca. 20 min, resulting in a light yellow homogeneous solution. Lithium hexamethyldisilyl azide (950 μL, 0.95 mmol, 1.0 M solution in THF) was added to *N*-4-methoxysulfonyltoluidine (277 mg, 1.0 mmol) in a mixture of anhydrous THF/DMF (2.5 mL; 1.5/1) and the anion allowed to form over ca. 15 min, before being added to the preformed catalyst via Teflon cannula rinsing with anhydrous THF (2 × 0.25 mL). The optically active allylic carbonate (*R*)-**1f** (110 mg, 0.5 mmol; ≥99% ee by capillary GLC analysis) was then added via a tared 100 μL syringe, to the preformed rhodium catalyst and nucleophile, and the resulting reaction mixture was stirred at 30 °C for ca. 1 h (TLC control). The reaction mixture was then partitioned between diethyl ether and a saturated aqueous $NaHCO_3$ solution. The organic layers were combined, washed with a saturated aqueous NaCl solution, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil (2°:1° = 90:1 by crude HPLC). Purification by flash chromatography (eluting with a 10−15% ethyl acetate in hexane gradient) furnished the allyl arylamine (*R*)-**2f/3f** (196 mg, 93%) as a colorless oil; cee = 98% by HPLC analysis.[7c]

(10) Although β-branching is tolerated, α-branching leads to significantly reduced *secondary* selectivity. The allylic amination of the isopropyl derived allylic carbonate **I** furnished the allylic amination products **II/III** as a 1:2 mixture favoring the *primary* product **III**.



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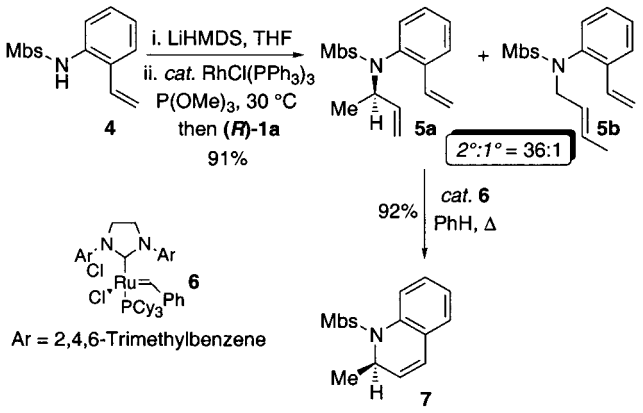
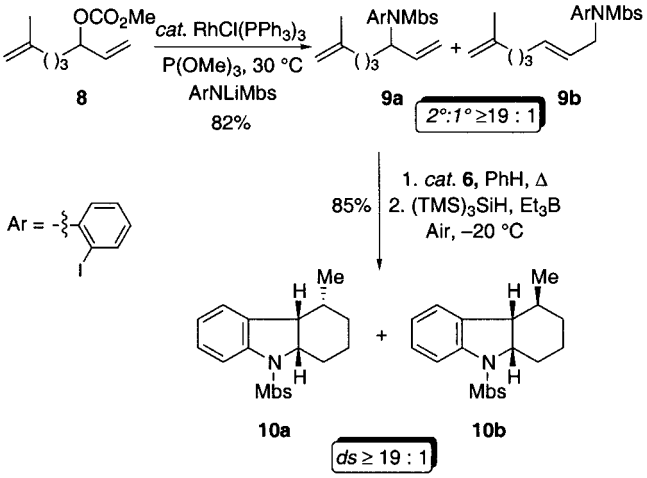
Scheme 2. Rhodium-Catalyzed Allylic Amination/ Ring-Closing Metathesis Approach to Dihydroquinolines



Scheme 3. Rhodium-Catalyzed Allylic Amination/ Ring-Closing Metathesis Followed by Radical Cyclization; Approach to Dihydrobenzo[*b*]indolines



The *N*-protected allylic anilines also provide versatile synthons for target directed synthesis, as outlined above. Scheme 2 outlines the application of this strategy to the construction of enantiomerically enriched dihydroquinolines. The rhodium-catalyzed allylic amination of (*R*)-**1a** (95% ee) with the lithium anion of *N*-(4-methoxybenzenesulfonyl)-2-vinyl aniline furnished the corresponding allyl aniline **5a/b** in 91% yield (98% cee),[7c] as a 36:1 mixture of regioisomers favoring **5a**, illustrating tolerance for *ortho*-substitution.[7e] The diene **5a** was then subjected to ring-closing metathesis with Grubbs' catalyst **6** to afford the dihydroquinoline **7** in 92% yield.[12,13]

The preparation of substituted dihydrobenzo[*b*]indoline derivatives remains an important synthetic undertaking. The combination of the allylic amination, in conjunction with ring-closing metathesis and a free radical cyclization, provides a convenient approach to the dihydrobenzo[*b*]-indoline skeleton, as illustrated in Scheme 3. The rhodium-catalyzed allylic amination of **8** with the lithium anion of 2-iodo-(*N*-4-methoxybenzenesulfonyl)aniline furnished the corresponding *N*-(arylsulfonyl)aniline **9a/b** in 82% yield, as a ≥19:1 mixture of regioisomers favoring **9a** (by 400 MHz NMR). The diene **9a** was then subjected to ring-closing metathesis with **6**[12,13] and treated with tris(trimethylsilyl)-silane[14] and triethylborane at −20 °C, in the presence of air, to furnish the dihydrobenzo[*b*]indoline derivatives **10a/b** in 85% yield, as a ≥19:1 mixture of diastereoisomers in favor of **10a** (by 400 MHz NMR),[15] in which the stereochemical assignment was confirmed through NOE experiments.

In conclusion, we have developed a regioselective and enantiospecific rhodium-catalyzed allylic amination reaction with *N*-(arylsulfonyl)anilines, which tolerates linear and branched alkyl, aryl, and heteroatom substituents. Furthermore, this study also demonstrates that *o*-substituted anilines serve as excellent nucleophiles to allow the expeditious construction of biologically relevant pharmacophores, as exemplified by the synthesis of the dihydroquinoline and dihydrobenzo[*b*]indoline derivatives.

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Supporting Information Available: Spectral data for **2a**−**j**, **5a**, **7**, **9a**, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a related approach to dihydrobenzo[*b*]indoline derivatives, see: Patro, B.; Murphy, J. A. *Org. Lett.* **2000**, *2*, 3599.