J|A|C|S COMMUNICATIONS

Published on Web 06/05/2009

Unlocking Ylide Reactivity in the Metal-Catalyzed Allylic Substitution Reaction: Stereospecific Construction of Primary Allylic Amines with Aza-Ylides

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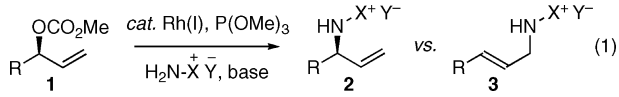
The transition metal catalyzed allylic amination reaction represents a powerful method for the asymmetric construction of stereogenic C−N bonds that are present in secondary metabolites and medicinally important agents.[1,2] Nonetheless, the development of this process into a general cross-coupling reaction has been impeded by the ability to control regioselectivity in the union of unsymmetrical acyclic allylic alcohol derivatives with the requisite nitrogen pronucleophiles.[1,2] Although a variety of transition metal complexes now provide enantiomerically enriched acyclic secondary allylic amines in a highly regioselective manner with more conventional nitrogen pronucleophiles, the examination of charge-separated derivatives has not been forthcoming.[1−6] We envisioned that ylides would provide ideal partners for this transformation given their low basicity and would thus provide a new class of nucleophiles for this venerable process. Herein, we now describe the regio- and enantiospecific rhodium-catalyzed allylic amination of chiral nonracemic secondary allylic carbonates **1**, using the aza-ylide derived from 1-aminopyridinium iodide, for the construction of secondary allylic pyridinium salts **2** (eq 1).



A critical feature with the metal-catalyzed allylic substitution reaction is the mechanistic dichotomy created by the nucleophile, which can significantly alter the regio- and stereochemical outcome of this process.[2] With this detail in mind, we elected to examine the merit of aza-ylides as stabilized nitrogen nucleophiles for the regio- and stereospecific rhodium-catalyzed allylic amination, since it was envisioned that the nucleophilicity of the ylide could be tailored through the judicious choice of the stabilizing group (Figure 1).[7,8] For example, phosphonium and sulfonium ylides are field and resonance stabilized, whereas the ammonium and pyridinium derivatives are only field stabilized.[8] Hence, the latter should be considerably more reactive in this process since they are less stabilized and therefore more nucleophilic.

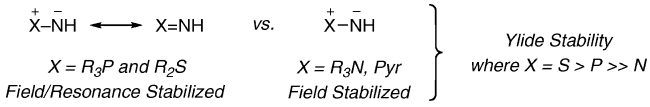


Figure 1. Relative stability of various ylides based on field and resonance stabilization.

Table 1 outlines the preliminary evaluation of the proposed allylic amination with an aza-ylide. We envisioned that the stabilizing group would be the most important contributing factor for the ylide contrary to our previous studies, which demonstrated that the alkali metal salt of the pronucleophile was critical for attaining high yield and regioselectivity.[3,8] Treatment of the allylic carbonate ***rac*-1a** (R = $Ph(CH_2)_2$) with the aza-ylide derived from 1-aminopyridinium iodide in the presence of Wilkinson's catalyst modified with trimethyl phosphite furnished secondary allylic pyridinium iodide ***rac*-2a** in 71% yield, with ≥19:1 regioselectivity (entry 1). This contrasts the results with the phosphonium and sulfonium aza-ylides, which proved completely unreactive under analogous conditions (entries 2/3). As anticipated, the nature of the alkali metal does not affect the selectivity; however, the sodium and potassium derivatives provide some recovered allylic carbonate ***rac*-1a** (entry 1 vs 4/5). Further studies examined the effect of inorganic and tertiary amine bases, in which potassium carbonate[9] afforded a similar yield of ***rac*-2a**, whereas 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was less efficient, albeit with complete conversion (entry 6/7). The lower yield for the reactions that consume all the allylic carbonate was ascribed to the formation of methoxide from the fragmentation of the methyl carbonate-leaving group, which can presumable generate the aza-ylide of ***rac*-2a**. Gratifyingly, quenching the reaction with acetic acid and lithium iodide furnished the secondary allylic amino pyridinium salt ***rac*-2a** in an improved 89% yield with analogous selectivity (entry 8).[10]

Table 1. Optimization of the Regioselective Rhodium-Catalyzed Allylic Amination Reaction using Aza-ylides (eq 1; ***rac*-1a** R = $Ph(CH_2)_2$)[a]

	$H_2N-X^+Y^-$					
entry	X =	Y =	base	additive	ratio of ***rac*-2a/3a**[b,c]	yield (%)[d]
1	NC_5H_5	I	LiHMDS	−	≥19: 1	71
2	PPh_3	Br	"	−	−	NR
3	SPh_2	Cl	"	−	−	NR
4	NC_5H_5	"	NaHMDS	−	≥19: 1	68[e]
5	"	"	KHMDS	−	"	65[e]
6	"	"	K_2CO_3	−	"	68[e]
7	"	"	DBU	−	"	39
8	***NC_5H_5***	***I***	***LiHMDS***	***LiI/AcOH***	***≥19: 1***	***89***

[a] All reactions were carried out on a 0.25 mmol reaction scale using 10 mol% $RhCl(PPh_3)_3$ *modified* with 40 mol% $P(OMe)_3$ and 1.1 equiv of the anion of the pyridinium salt in MeCN/THF (1.5:1) at room temperature. [b] Regioselectivity was determined by 500 MHz ^1H NMR on the crude reaction mixtures. [c] The linear product **3a** was prepared independently *via* Pd(0) catalysis. [d] Isolated yields. [e] Recovered **rac-1a** (5−10%).

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 8) to a variety of racemic secondary allylic carbonates (*vide infra*). The regioselectivity in the allylic alkylation is tolerant of a wide array of allylic alcohol derivatives. For example, linear and branched alkyl substituents afford excellent regiocontrol (Table 2, entries 1−5 and 6−9), in which the branching is inconsequential in terms of regioselectivity contrary to our previous work with *N*-alkyl sulfonamides.[3] Additional studies demonstrated that benzyl and *tert*-butyldimethylsilyl protected hydroxymethyl and ethyl derivatives also provide excellent selectivity (entries 10−13), as did the aryl substituents (entries 14 and 15).

10.1021/ja9041302 CCC: $40.75

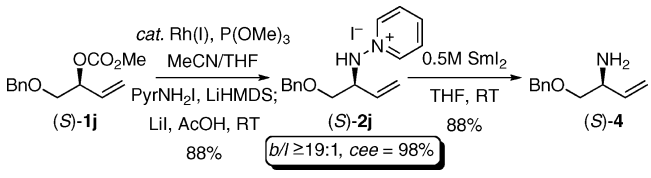
Table 2. Scope of the Regioselective Rhodium-Catalyzed Allylic Amination Reaction with the 1-Aminopyridinium Ylide (eq 1; ***rac*-1** X = NC_5H_5, Y = I)[a]

entry	allylic carbonate ***rac*-1** R_2 =		ratio of ***rac*-2/3**[b,c]	yield (%)[d]
1	$Ph(CH_2)_2$	**a**	≥19:1	89
2	Me	**b**	≥19:1	76
3	^{n}Pr	**c**	≥19:1	87
4	^{n}Bu	**d**	≥19:1	87
5	CH_2=$CH(CH_2)_2$	**e**	≥19:1	73
6	^{i}Pr	**f**	≥19:1	79
7	^{c}Hex	**g**	≥19:1	75
8	^{i}Bu	**h**	≥19:1	86
9	$PhCH_2$	**i**	≥19:1	78
10	$BnOCH_2$	**j**	≥19:1	88
11	$BnO(CH_2)_2$	**k**	≥19:1	84
12	$TBSOCH_2$	**l**	≥19:1	84
13	$TBSO(CH_2)_2$	**m**	≥19:1	86
14	Ph	**n**	≥19:1	81
15	Npth	**o**	≥19:1	89

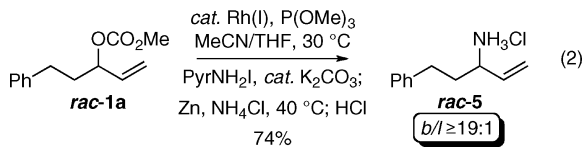
[a] All reactions were carried out on a 0.25 mmol reaction scale. [b] Regioselectivities were determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixtures. [c] The linear products **3** were prepared independently *via* Pd(0) catalysis. [d] Isolated yields.

Additional studies examined the mechanistic course of the allylic amination in the context of the stereospecificity. Treatment of the allylic carbonate (*S*)-**1j** (98% *ee*) with the aza-ylide under the optimized reaction conditions furnished the chiral nonracemic secondary allylic pyridinium salt (*S*)-**2j** in 88% yield, with retention of absolute configuration in accord with our previous studies with soft nucleophiles (*b*/*l* ≥ 19:1, 98% *cee*).[11] Reductive cleavage of the pyridinium salt (*S*)-**2j** with samarium diiodide furnished the enantiomerically enriched primary allylic amine (*S*)-**4** in 88% yield.[12]

Scheme 1. Stereospecific Allylic Amination and N−N Bond Cleavage



Finally, the synthetic utility of this process was further illustrated with the development of a novel one-pot protocol using 1-aminopyridinium iodide as a novel ammonia equivalent.[13] Based on our preliminary work with weak inorganic bases we envisioned that the allylic amination could be promoted with catalytic base, which would provide an opportunity to affect the *in situ* reductive cleavage to the primary amine. Gratifyingly, treatment of the allylic carbonate ***rac*-1a** under the analogous reaction conditions, *albeit using catalytic potassium carbonate at 30 °C*, followed by the *in situ* reductive cleavage using Zn/NH_4Cl, furnished the allylic amine hydrochloride salt ***rac*-5** in 74% overall yield (*b*/*l* ≥ 19:1).[14]



In conclusion, we have developed a regio- and enantiospecific rhodium-catalyzed allylic amination reaction using the aza-ylide derived from 1-aminopyridinium iodide. This investigation demonstrates the importance of the ylide-stabilizing group for obtaining the desired nucleophilicity and the ability to utilize the aza-ylide as a commercially available ammonia equivalent, which serves to illustrate the synthetic potential of this nucleophile for the preparation of primary allylic amines. Overall, this work provides an opportunity to investigate the utility of this new class of nucleophiles in related metal-catalyzed reactions.

Acknowledgment. Dedicated to Prof. Philip D. Magnus, FRS on the occasion of his 65th birthday. We sincerely thank the NIH (GM58877) for generous financial support. We also thank Prof. Jeffrey N. Johnston for helpful discussions pertaining to the isolation of primary amines. Finally we would like to acknowledge the *Royal Society* for a *Wolfson Research Merit Award* (P.A.E.) and the University of Liverpool for a *Postgraduate Research Studentship* (E.A.C.).

Supporting Information Available: Experimental procedures and spectral data for ***rac*-2a-o**, (*S*)-**4**, and ***rac*-5** (PDF). X-ray crystallographic file in CIF format for ***rac*-2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA9041302