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Switching Regioselectivity in the Allylation of Imines by N-Side Chain Tuning

Pierre-Olivier Delaye, Jean-Luc Vasse,* and Jan Szymoniak*

Institut de Chimie Moléculaire de Reims, CNRS (UMR 7312) and Université de Reims, 51687 Reims Cedex 2, France

jean-luc.vasse@univ-reims.fr; jan.szymoniak@univ-reims.fr

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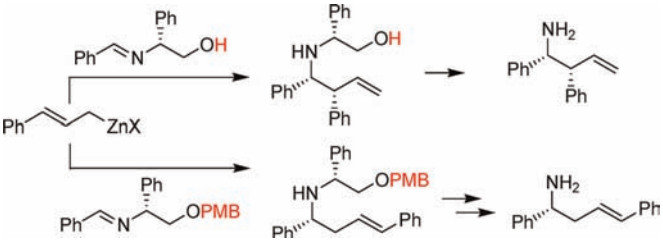
ABSTRACT



A spectacular inversion of α- to γ-regioselectivity in the allylzincation of imines can be achieved by fine-tuning of the N-side chain. This approach allows easy preparation of regioisomeric amines, in racemic as well as enantiopure forms. The usefulness of the method is illustrated by the parallel asymmetric syntheses of 2,3- and 2,5-diphenylpyrrolidines.

Owing to the fundamental role of the nitrogen atom in an abundance of biologically active molecules,[1] the development of regio- and stereoselective methods aimed at preparing amines is of constant interest.

In this context, the regiocontrolled addition (α- vs γ-selectivity) of substituted allylmetals to imines[2] is a major issue. Despite the extensive literature dealing with imine allylmetalation, only a few examples involving substituted allylic organometallics have been reported.[3] In particular, allylzincs bearing an electron-donating fragment are not common, due to the instability of the corresponding halide precursors. In this typical case, an alternative procedure involving allylzirconocenes, generated from allylic ethers,[4] followed by the transmetalation to zinc can be carried out.[5]

Moreover, the branched γ-adduct product, which is derived from a Zimmerman–Traxler-like transition state,[2,6] is generally observed. Therefore, synthetic methods selectively affording the α-regoisomer would be useful.

In this paper, we wish to report that nitrogen side chain tuning can induce a reversal of regioselectivity in the addition of aromatic allylzincs to imines.

The Taguchi–Hanzawa protocol[4b–d] was first applied to a series of allylic silyl ethers **1** to generate the corresponding zirconocenes. In a typical experiment, *n*-BuLi

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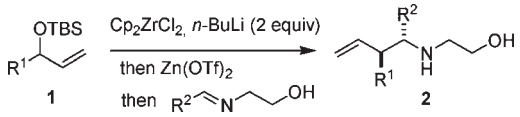
(5 mmol) was added to Cp_2ZrCl_2 (2.5 mmol) at −78 °C. Compound **1** (2.5 mmol) was next added, and the reaction mixture slowly warmed to 0 °C. Subsequent Zr→Zn transmetalation using $Zn(OTf)_2$ (2.5 mmol)[7] provided the allylzinc, which was allowed to react with an imine (1 mmol) derived from ethanolamine (Table 1).

This method allowed the addition of allyl fragments bearing different electron-donating moieties (Table 1, entries 2, 3, and 6) but could also be applied to other groups, such as phenyl (Table 1, entry 1), alkenyl (Table 1, entry 5), and alkyl (Table 1, entries 4 and 7) ones. This approach appears to be quite general, leading to the expected compounds **2a**−**g** in good yield. The *syn*/*anti* selectivity is typically moderate but could be improved with an imine derived from a chiral aminoalcohol.[2b,8]

Table 1. Allylation of Ethanolamine-Derived Imines

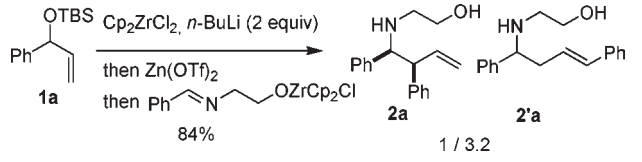


entry	R^1	R^2	**2** (yield)	dr
1	Ph	Ph	**2a** (83%)	4.2:1
2	3-furyl	Ph	**2b** (84%)	3.6:1
3	*N*-Boc-3-indolyl	Ph	**2c** (87%)	4:1
4	*i*-Pr	Ph	**2d** (72%)	2.6:1
5	Styryl	Ph	**2e** (70%)[a]	7:1
6	*N*-Boc-3-indolyl	CH_2OBn	**2f** (69%)	4.9:1
7	Ph-CH_2	Ph	**2g** (64%)	2.2:1

[a] The regioisomer was also formed and isolated in 17% yield.

Additionally, since 2 equiv of the allylzinc reagent were required for a complete reaction (one being consumed by the hydroxy group), we next decided to test an imine which was preliminarily deprotonated with a zirconocene hydride. Surprisingly, the linear adduct was obtained as the major compound in this case (Scheme 1).

Scheme 1



This regioselectivity reversal reflects an alternative mechanistic pathway and may be considered as a case of group tuning involving the O-$ZrCp_2Cl$ moiety. It was thus thought that the formation of the linear product could be favored by protecting the hydroxy group by a noncovalent-Zn-bonding function. This α-reactivity has been described in the literature with Cr[9] and allylsilane[10] but is rare with allylzincs.[11] This aspect was thus further studied using imines derived from 2-methoxyethylamine (Table 2). The experimental procedure, Barbier (Method A) or Taguchi−Hanzawa (Method B), was chosen according to the structure of the initial allylzinc derivatives.

A series of homoallylic amines were obtained in moderate to good yields. In the case of allylzincs bearing an aromatic (Table 2, entries 1−6) or a heteroaromatic (Table 2, entries 7−12) substituent, the nearly exclusive formation of the linear isomer was observed, irrespective of the method used. In the typical case of a dienylzinc reagent (Table 2, entry 13), the linear adduct remained the major product; however, the branched regioisomer was also observed. In contrast, variations were observed with alkyl-substituted allylzincs (Table 2, entries 14−16). Whereas the branched product was the major isomer (Table 2, entry 15), or even the unique reaction product (Table 2, entry 16) with primary R^1 alkyl groups, it was minor when R^1 = *i*-Pr (Table 2, entry 14).

The double bond in compounds **3** are almost all *E*-configurated, except when substituted with a heteroaromatic fragment. In most cases, the two isomers can be separated by simple column chromatography.

The opposite regioselectivity observed between conjugated and nonconjugated allylzinc derivatives might originate from the intrinsic reactivity of these two cases, which is likely to differ (Figure 1).

However, theses differences only appear with imines derived from an aminoether. In this case, the direct 1,2-addition at the α-position prevails leading to compounds **3**. This implies that the organometallic interacts differently depending on the imine side chain (Figure 1).

The nonracemic version was initiated by using an imine derived from phenylglycinol methyl ether. In this case, the regioselectivity is not α-exclusive but is still in favor of the linear product **3q** (8:1), which is obtained as a single diasteroisomer (Scheme 2).[12] The formation of **3q** is consistent with a chelation-controlled cinnamyl addition, with attack occurring at the more accessible re face (Scheme 2).

(7) Several Zn(II) sources were tested, and the best results were obtained with $Zn(OTf)_2$.

(8) For highly diastereoselective allylmetalation of an imine derived from an aminoalcohol, see: (a) Roy, U. K.; Roy, S. *Chem. Rev.* **2010**, *110*, 2472–2535. (b) Jang, T. S.; Ku, I. W.; Jang, M. S.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Org. Lett.* **2006**, *8*, 195–198. (c) Black, D. A; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 1991–1993. (d) Babu, S. A.; Yasuda, M.; Baba, A. *Org. Lett.* **2007**, *9*, 405–408. (e) Thirupathi, P.; Kim, S. S. *Tetrahedron* **2010**, *66*, 8623–8628.

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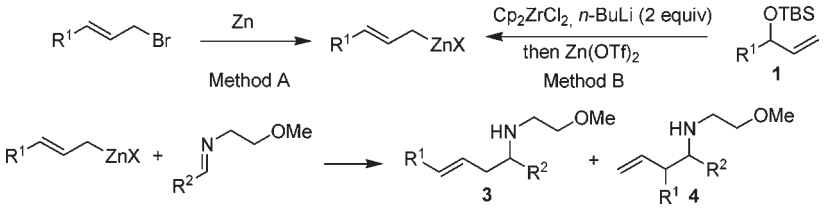
(12) The *R* configuration of the newly formed stereogenic center was deduced by analogy with **7** (vide infra, Scheme 5) which was converted into known compound **11** (vide infra, Scheme 6).

Table 2. Synthesis of Homoallylamines **3** vs **4**[a]



entry	R^1	R^2	method	**3**/**4**	**3** (yield)	*E*/*Z*	**4** (yield)	dr
1	Ph	Ph	B	>20:1	**3a** (98%)[b]	97:3		
2	Ph	3-pyridyl	A	16:1	**3b** (73%)[b]	96:4		
3	Ph	3-furyl	A	>20:1	**3c** (63%)[b]	98:2		
4	Ph	*i*-Bu	A	>20:1	**3d** (65%)[b]	95:5		
5	Ph	*n*-C_4H_9	A	>20:1	**3e** (50%)[b]	96:4		
6	Ph	styryl	A	>20:1	**3f** (67%)[b]	95:5		
7	3-furyl	Ph	B	>20:1	**3g** (97%)[b]	80:20		
8	2-thiophenyl	Ph	B	>20:1	**3h**[b] (82%)[c]	71:29		
9	benzothiophenyl	Ph	B	>20:1	**3i** (95%)[c]	63:37		
10	*N*-Boc-3-indolyl	Ph	B	>20:1	**3j** (84%)[d]	56/44		
11	*N*-Boc-3-indolyl	4-BrC_6H_4	B	>20:1	**3k** (83%)[d]	65:35		
12	*N*-Boc-3-indolyl	4-$MeOC_6H_4$	B	>20:1	**3l** (82%)[d]	62:38		
13	Styryl	Ph	B	9:1	**3m** (63%)[c]	85:15		
14	*i*-Pr	Ph	B	3:1	**3n** (42%)[c]	>95:5	**4n** (14%)[b]	9:1
15	CH_2Ph	3-furyl	A	1:6	**3o** (8%)	ND	**4o** (49%)[b]	1.5:1
16	*n*-C_4H_9	*n*-C_2H_5	A	<20:1			**4p** (53%)[b]	2:1

[a] Reaction conditions: Method A: Imine (2 mmol), bromide (2.2 mmol) and Zn (2.2 mmol) in THF (5 mL) at rt for 6 h. Method B: Cp_2ZrCl_2 (1.5 mmol), *n*-BuLi (3 mmol), THF −78 °C, 1 h; add **1** (1.5 mmol), then warm to 0 °C, 3 h; add $Zn(OTf)_2$ (1.5 mmol), 30 min, 0 °C; add Imine, rt, 10 h. [b] Yields of the major isomer isolated in the pure isomeric form. [c] Combined yield of unseparable isomers. [d] Combined yield of separable isomers

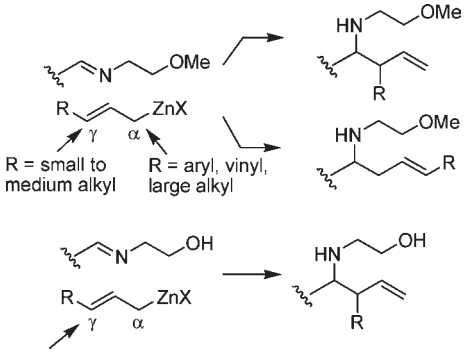
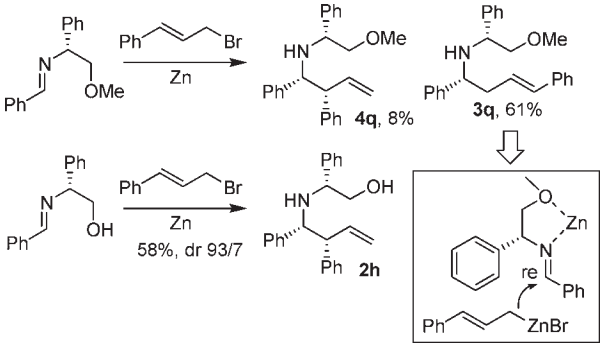


Figure 1. Reactivities of allylzincs toward imines.

Scheme 2. Stereoselective Cinnamylzinc Addition to Imine



In parallel, the analogous phenylglycinol-derived imine was subjected to the same reaction conditions to give the branched adduct **2h** as the major isomer (Scheme 2).

To take advantage of the selectivity reversal, regioisomeric primary homoallylic amines were prepared. First, amine **5** was obtained by adding $Pb(OAc)_4$ to **2h** (Scheme 3). This could also be applied to the linear regioisomer. In this case however, it was necessary to replace the OMe by a more labile protecting group. We thus chose the more suitable PMB phenylglycinol **6**[13] as chiral inducer. The imine, obtained by condensing **6** with benzaldehyde, was subjected to allylation and afforded **7** in good yield as well as regio- and diastereoselectivity. A simple acid treatment provided **8**, the regioisomer of **2h**. Finally, the amine **9** was obtained under oxidative conditions (Scheme 3).

Such regioisomeric amines have a significant potential in the field of heterocyclic synthesis. For example, amines **5** and **9** were converted to pyrrolidines (Scheme 4). First,

(13) For the preparation of **9** see Supporting Information.

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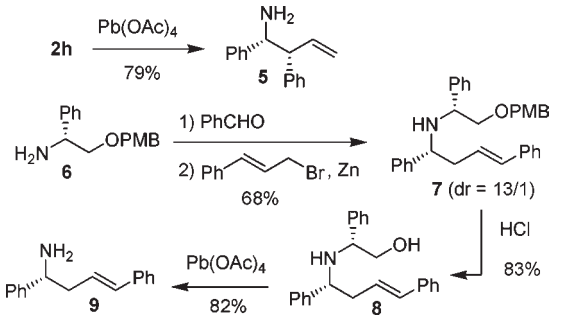
Scheme 3. Preparation of Regioisomeric Primary Amines



NTs-amine **10** underwent a iodoamination/deiodination sequence[14] to provide **11**[14b] as a 94:6 mixture of diastereomers. 2,3-Diphenylpyrrolidine **12** was then obtained by applying a hydrozirconation/iodation sequence to the temporarily trityl-protected amine **5**.[15]

In summary, a simple tuning of the imine lateral side chain combined with an easy removal of the N-side chain provides a selective access to regioisomeric primary amines. Moreover, the high stereoselectivity observed when using phenylglycinol and its OPMB analogue makes this reaction promising in terms of synthetic applications as illustrated by the synthesis of pyrrolidines.

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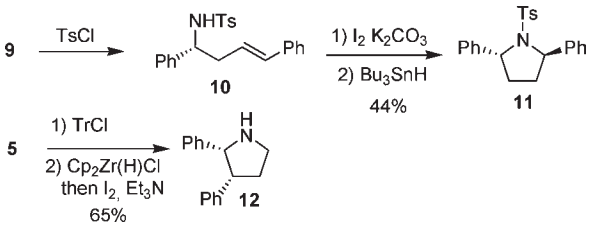
Scheme 4. Synthesis of Disubstituted Pyrrolidines



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Supporting Information Available. Experimental procedures, characterization, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.