Tandem Zirconocene Homologation–Aldimine Allylation

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ABSTRACT



Hydrozirconation of internal and terminal alkynes followed by in situ transmetalation to dimethylzinc and treatment with diiodomethane leads to chain extended allylic organometallics. Addition to *N*-phosphinoyl or *N*-sulfonyl aldimines provides homoallylic amines in 48–87% yield and 3:2 to >20:1 diastereometric ratios favoring *anti*-products.

The addition of organometallics to aldimines has mainly been limited to strongly basic reagents and/or activated imines. The increased reactivity of allyl organometallic reagents, however, is sufficient to overcome the inherent low electrophilicity of aldimines.¹ The homoallylic amines formed in this manner are important building blocks in organic synthesis.² Recently, a number of asymmetric catalysts for the allylation of aldimines have been developed.³ We now report a new method for the synthesis of homoallylic amines involving the three-component coupling of aldimines, diiodomethane, and alkenylzirconocenes, in the presence of dimethylzinc.

Organozirconium reagents participate in many carbon– heteroatom and carbon–carbon bond forming processes.⁴ A particularly attractive aspect of these early transition metal derivatives is their ease of preparation by hydrometalation of readily available alkenes and alkynes.⁵ Recently, we have discovered a three-component condensation of alkenylzirconocenes, *N*-diphenylphosphinoylimines, and dihalomethanes that provides a highly diastereoselective access to amino cyclopropanes (Scheme 1).⁶

Interestingly, the order of addition of reactants proved to be crucial for product formation. While optimizing the imine addition/cyclopropanation process, we discovered that ad-



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⁽²⁾ For example, see: (a) Enders, D.; Schankat, J.; Klatt, M. Synlett 1994,
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^{(3) (}a) Nakamura, H.; Nakamura, K.; Yamamoto, Y. J. Am. Chem. Soc. **1998**, *120*, 4242. (b) Nakamura, K.; Nakamura, H.; Yamamoto, Y. J. Org. Chem. **1999**, 64, 2614. (c) Fang, F.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. J. Org. Chem. **1999**, 64, 4844. (d) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. Angew. Chem., Int. Ed. **2001**, 40, 1896.

dition of CH_2I_2 to the reaction mixture prior to imine 2 led to a switch from cyclopropylamine 4 to the homoallylic amine 5, in 58% yield and 5:1 diastereoselectivity, favoring the *anti*-isomer 5a (Scheme 2).⁷ The yield was slightly



increased by lowering the temperature, but the effect on diastereoselectivity was minimal.⁸ No reversal of stereoselectivity occurred upon addition of BF₃•OEt₂, in contrast to the allylation of aldehydes with allylzirconium reagents.⁹

The reaction scope is illustrated in Table 1.¹⁰ Some functional groups on the alkyne segment, such as silyl ethers (entry 3), did not interfere with the reaction; however, the use of silyl esters or internal alkynes resulted in both lower yield and reduced diastereoselectivity (entries 4 and 2). Electron-donating and -withdrawing groups on the aldimine were tolerated and had no effect on product ratios (entries 5 and 6). *N*-Tosylimines such as **16** were also suitable substrates but provided decreased diastereoselectivity (entry 7). However, while the formation of *N*-diphenylphosphinoylimines from enolizable aldehydes is elusive,⁶ the corresponding alkyl sulfonylimines are readily formed.¹¹ Treatment of hydrocinnamyl tosylimine **18** with the vinyl zirconocene derived from alkyne **8** provided the homoallylated product **19a** in excellent diastereoselectivity (entry 8).

The assignment of the relative stereochemistry of these addition products was first based on the coupling constant

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(7) In the absence of CH_2I_2 , no homoallylic amine product was observed. CH_2CI_2 alone is not sufficient to induce the reaction, in contrast to observations made in ref 6.

(8) In refluxing CH_2Cl_2 , the diastereometic ratio is 83:17, at room temperature the ratio is 85:15, and at 0 °C the ratio is 86:14.

(11) Chemla, F.; Hebbe, V.; Normant, J.-F. Synthesis 2000, 75.

analysis of lactams **20a** and **20b**, formed by hydrolysis and cyclization of phosphinoylamines **11a** and **11b**, respectively, and later confirmed by an X-ray analysis of **20a** (Scheme 3). ¹H coupling constants were characteristic for 1,2-diaxial



and gauche relationships in the major and minor addition products and were in good agreement with literature values. 12,13

We are rationalizing the formation of homoallylic products by the homologation mechanism shown in Figure 1. First,



Figure 1. Proposed mechanism.

hydrozirconation of 1-hexyne followed by transmetalation with Me₂Zn affords vinylzinc intermediate 21.^{14,15} Rapid reaction of 21 with CH₂I₂ is expected to give, after [1,2]-shift,¹⁶ allylic zinc 22, which adds to aldimine 2 to form the

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⁽⁹⁾ Yamamoto, Y.; Saito, Y.; Maruyama, K. J. Organomet. Chem. 1985, 292, 311.

⁽¹⁰⁾ **Typical Procedure.** A suspension of 195 mg (0.756 mmol) of Cp₂-ZrHCl in 2 mL of CH₂Cl₂ was treated at room temperature with 95.0 μ L (0.827 mmol) of 1-hexyne. After 2 min, the yellow solution was cooled to -78 °C, treated with 375 μ L (0.750 mmol) of Me₂Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with 100 μ L (1.24 mmol) of CH₂I₂, stirred for 2 min, and treated with a solution of 76.0 mg (0.249 mmol) of imine **2** in 1 mL of CH₂Cl₂. The reaction mixture was stirred at room temperature for 12 h, quenched with saturated NH₄Cl, diluted with EtOAc and saturated NaHCO₃, filtered through a pad of Florisil, and concentrated in vacuo. The residue was chromatographed on deactivated SiO₂ (1:9, hexanes/EtOAc containing 1% Et₃N) to yield 71 mg (71%) of **5a** and **5b** as an 85:15 (separable) mixture of diastereomers.

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615. (b) Ramage, R.; Hapton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. J. Chem. Soc., Perkin Trans. 1 1984, 1357. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. Tetrahedron Lett. 1993, 34, 5831.

⁽¹³⁾ On the basis of the assignments of **11a** and **11b**, all other major products were identified as *anti* on the basis of the characteristic upfield shift in the ¹H NMR spectra for the substituted vinyl proton, relative to the corresponding proton of the *syn* isomer. The assignment of **7a** is still tentative.

⁽¹⁴⁾ In the absence of Me_2Zn , no imine addition products are formed. (15) Et_2Zn can be used in place of Me_2Zn ; however, although the selectivity for the formation of **5a** increased to ca. 10:1, the yield dropped to 47%.

⁽¹⁶⁾ For precedence for this type of rearrangement, see: (a) Charette, A. B.; Marcoux, J.-F. J. Am. Chem. Soc. **1996**, 118, 4539. (b) McWilliams, J. C.; Armstrong, J. D.; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. J. Am. Chem. Soc. **1996**, 118, 11970. (c) Sidduri, A.; Rozema, M. J.; Knochel, P. J. Org. Chem. **1993**, 58, 2694. (d) Shibli, A.; Varghese, J. P.; Knochel, P.; Marek, I. Synlett **2001**, 818.

entry	alkyne	aldimine	homoallylic amide ^a	yield ^b	diastereoselectivity ^c
1	==−C₄H ₉ 1	NP(O)Ph ₂ Ph H 2	NHP(O)Ph ₂ Ph 5a	71%	85:15
.2	C ₂ H ₅ − = C ₂ H ₅ 6	2	$\begin{array}{c} NHP(O)Ph_2\\ Ph & C_2H_5\\ C_2H_5 & \mathbf{7a} \end{array}$	49%	75:25
3	──(CH ₂) ₂ OBDPS 8	2	Ph Ph 9a	72%	85:15
4	==(CH ₂)₂CO₂TIPS 10	2	Ph HP(O)Ph ₂ CO ₂ TIPS 11a	48%	62:38
5	8	NP(O)Ph ₂ (p-MeO ₂ C)Ph H 12	MeO ₂ C	69%	85:15
6	1	NP(O)Ph ₂ (p-MeO)Ph H 14	MeO MeO MeO MeO	79%	83:17
7	8	Ph H 16	Ph Ph 17a	81%	60:40
8	8	Ph H 18	Ph 19a NHTS OBDPS	87%	>95:5

Lable 1 Three Component Coupling of This neb, Thanning, and Cit/1	Table 1.	Three-Component	Coupling of	Alkynes,	Aldimines,	and	CH ₂ I ₂
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^a Only major isomer shown. ^b Yields of isolated products based on imines. ^c Based on integration of ¹H NMR spectrum of the crude reaction mixture.

observed homoallylic amide **5a**.¹⁷ A closed transition state is likely for this reaction,¹ and minimization of allylic strain explains the preference for *anti*-configuration of the product, but alternative open or boatlike transition states cannot be completely excluded.¹⁸ Indirect support for a preferred cyclic transition state comes from the dependence of the diastereoselectivity on the nature of the pseudoaxial imine substituent: the bulkier aromatic aldimines significantly erode *anti*-selectivity versus an aliphatic chain (Table 1, entries 7 and 8). We assume that the allylic zinc species **22** is (*E*)configured; however, metallotropic rearrangements typical for lithium, magnesium, zinc, or indium crotylorganometallics could contribute to erosion of diastereoselectivity. Attempts to prepare the analogous homoallylic alcohols by replacing aldimines with aldehyde substrates have thus far failed, and furthermore, efforts to prepare 7 using a $B \rightarrow Zn$ transmetalation¹⁹ in place of our $Zr \rightarrow Zn$ transmetalation strategy²⁰ have also failed. In either case, only allylic products were formed, and thus both the aldimine and a zirconocene complex may be involved in the formation of the reactive allylic metal species.

While exploring alternative methods to prepare internal akenyl zirconium reagents, we applied Takahashi's protocol for the oxidative insertion of $Cp_2Zr(n-Bu)_2$ into 2-bromopropene (Scheme 4).²¹ Under standard conditions,¹⁰ the homoallylic amide **24** was formed in 75% yield, thus establishing a variant of this reaction for the preparation and homologation of zirconocenes that are regioisomeric to the products of hydrozirconation of terminal alkynes. Interestingly, when

⁽¹⁷⁾ For the allylation of imines with zinc reagents, see: Jones, P.; Knochel, P. J. Org. Chem. **1999**, 64, 186.

⁽¹⁸⁾ See, for example: Lu, W.; Chan, T. H. J. Org. Chem. 2001, 66, 3467 and references therein.

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 CH_2I_2 was left out of this reaction mixture, a homoallylated product was formed nonetheless. We isolated phosphinoylamide **25** in 45% yield in addition to 16% of the expected vinyl addition product **26**.

Although a 1:1 ratio of $Cp_2Zr(n-Bu)_2$ and 2-bromopropene was used in the latter reaction, it is feasible but unprecedented that vinylzirconocene **23** inserts into unreacted bromooalkene and ring expands to a zirconacyclopent-3-ene. The latter species, prepared via a completely different approach, is known to allylate aldehydes in high efficiency and regioselectivity.²² A mechanistic rationalization of the reaction course leading to **25** is further complicated by the observation that Me₂Zn is required for product formation in this transformation as well.²³ In conclusion, we have developed a preparatively convenient three-component coupling between vinylzirconium reagents, aldimines, and CH_2I_2 for the synthesis of homoallylic amines in good yield and modest to high diastereoselectivities. This new reaction complements our protocols for the direct formation of amino cyclopropanes and allylic amines.⁶ An intriguing general characteristic of this chemistry is that diverse products are obtained from simple starting materials, and distinct reaction manifolds mainly depend on the order of addition of reagents and require the presence of both zirconocene and zinc organometallics in the reaction mixture. Studies toward enantioselective variants of zirconocene-mediated aldimine additions as well as toward the elucidation of the mechanism for formation of the rogue homoallylic amine **25** will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds 5, 7, 9, 11–13, 15, 17–20, and 24–26. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽²²⁾ Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Nakamura, A. Chem. Lett. 1981, 671.

⁽²³⁾ If the reaction mixture is stirred for 5 min prior to the addition of imine 2, the ratio of 25:26 is 1:1; if stirring time is extended to 2 h, the ratio increases to 3:1. If no Me₂Zn is added, no addition to the imine is observed.