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Synthesis of Homoallylic Amines by Hydrozirconation–Imine Addition of Allenes

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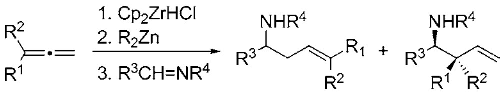
ABSTRACT



Hydrozirconation of allenes followed by in situ transmetalation to dialkylzinc leads to the formation of an allylic zinc species that, upon addition of aldimines to the reaction mixture, provides homoallylic amines in 64–85% yield.

Hydrozirconation of allenes is an efficient method for generating allylzirconocenes.[1] These reagents provide good yields and diastereoselectivities in the allylation of aldehydes and ketones. Recently, allylzirconocene alkoxides derived from zirconocene(II)−alkene complexes have also been used in aldimine allylations providing syn homoallylic amines in good to excellent yields.[2,3] Hydrozirconation of silyl- or stannyl-substituted allenes gives rise to bimetallic species that could potentially serve as dianion equivalents, but in general the addition of these species to aldehydes and ketones has led to Peterson-type elimination and has therefore been limited to 1,3-diene synthesis.[4,5] Selective transmetalation of zirconium offers a strategy to expand the chemistry of allene hydrozirconation products;[6] for example, Pi and Huang have shown that transmetalation of allylzirconocenes to copper(I) salts provides a useful reagent for addition to enones.[5]

Our previous approach to homoallylic amines involved the cascade zirconocene homologation−aldimine addition reaction with diiodomethane.[7] Mechanistically, this multicomponent strategy was limited to the preparation of terminal vinyl-substituted homoallylic amines. These compounds are important building blocks in organic synthesis, and numerous methods for generating both racemic and enantiomerically enriched homoallylic amines have been developed.[8] In contrast, few protocols for the generation of silylated homoallylic amines are available.[9] Since applications of silicon-containing substrates in cross-coupling reactions[10] and allylation processes[11] are increasing in number, we were interested in extending our zirconocene methodology toward the formation of homoallylic amines bearing vinylic or allylic

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(1) (a) Chino, M.; Matsumoto, T.; Suzuki, K. *Synlett* **1994**, *5*, 359. (b) Suzuki, S.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483. (c) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 2793. For a recent review of the chemistry of allenes, see: Brummond, K. M.; Chen, H. *Modern Allene Chem.* **2004**, *2*, 1041.

(2) Oshima, K.; Shinokubo, H.; Yorimitsu, H.; Fujita, K. *J. Org. Chem.* **2004**, *69*, 3302.

(3) For other applications of allylzirconocenes, see: (a) Hanzawa, Y.; Kiyono, H.; Taguchi, T. *Heterocycles* **2004**, *62*, 297. (b) Paquette, L. A.; Kang, H.-J. *Tetrahedron* **2004**, *60*, 1353. (c) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1999**, *40*, 2793. (d) Yamanoi, S.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1998**, *39*, 9727.

(4) Maeta, H.; Hasegawa, T.; Suzuki, K. *Synlett* **1993**, 341.

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(8) For reviews, see: (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 975−1006. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Risch, N.; Arend, M. In *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21b, pp 1894−1907. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(9) For recent syntheses, see: (a) Kadouri-Puchot, C.; Bertin, B.; Comesse, S. *Tetrahedron Lett.* **2004**, *45*, 3807. (b) Furman, B.; Dziedzic, M. *Tetrahedron Lett.* **2003**, *44*, 8249. (c) Dobbs, A. P.; Guesné, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880. (d) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127.

(10) (a) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. (b) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 163−216. (c) Tsuji, J. In *Palladium Reagents and Catalysts*; J. Wiley & Sons: Chichester, UK, 2004; pp 338−351.

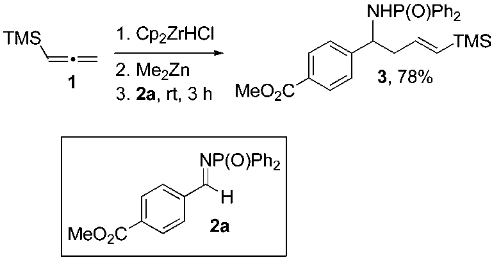
(11) (a) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, *15*, 3173. (b) Barbero, A.; Pulido, F. J. *Acc. Chem. Res.* **2004**, *37*, 817. (c) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

10.1021/ol051266j CCC: $30.25

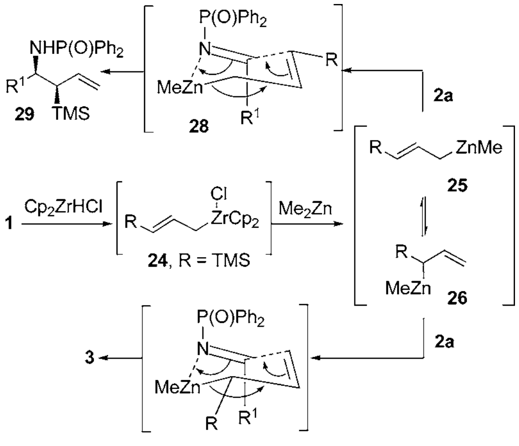
silicon functionalities, and we envisioned that hydrozirconation of readily available allenylsilanes[12] would be a suitable way to generate reactive organometallic intermediates for this purpose.

Treatment of allene **1** with zirconocene hydrochloride[13] at −78 °C followed by briefly warming to room temperature, recooling to −78 °C, and addition of dimethylzinc and aldimine **2a** led to the (*E*)-vinylsilane **3** in 78% yield (Scheme 1).[14] The scope of this reaction is illustrated in Table 1.[15] TMS-, TBS-, and Bu_3Sn-substituted allylzinc species reacted with both the aromatic aldimine **2a** and the in situ-generated aldimine **2b**[16] and provided the corresponding vinylsilanes and vinylstannanes in high yields (entries 1−3, 6, 7). In contrast, the (*E*)-allylzirconocene obtained from hydrozirconation of **6** adds to carbonyl compounds in the absence of Me_2Zn to give *anti*-β-alkoxystannanes, which eliminate spontaneously to the corresponding 4-monosubstituted dienes.[4] Other allenes that did not possess silicon or tin substituents also performed well in this reaction; however, these substrates provided the terminal alkene products typical of allylations of imines or aldehydes (entries 4, 5, 8),[17] in agreement with our previous results.[7] Interestingly, 1-methyl-1-trimethylsilyl allene **15** led exclusively to allylsilane upon reaction with aldimine **2b**. The increased steric hindrance associated with the 1,1-disubstitution was most likely responsible for this reversal in selectivity, since the analogous effect was also observed for the dimethylated allene **17** in entry 10. Trisubstituted allenes such as **19** did not yield any product upon addition to aldimines **2a** or **2b**. This lack of reactivity was attributed to the formation of side products during the hydrozirconation step. Both aromatic (**2a**) and aliphatic (**2b**) *N*-phosphinyl aldimines as well as the more reactive tosyl aldimine **20**[18] were efficient electrophiles. All products were diastereomerically pure by NMR analysis, and the relative configurations of compounds **9** and **16** were confirmed by X-ray structure analysis.

Scheme 1



We propose a cyclic transition state for vinylsilane formation (Figure 1). Hydrozirconation of the allenylsilane **1** leads regioselectively to allylzirconocene **24**.[1] Upon transmetalation to dimethylzinc, two allylic zinc intermediates are formed. The terminal zinc species **25** and the internal zinc reagent **26** are in rapid equilibrium,[19] with **25** reacting to give the terminal alkene **29** (not observed) and **26** leading to the vinylsilane **3** (observed product). An alternative reaction pathway would involve a direct 1,2-addition of allylzinc reagent **25** to the aldimine without allylic inversion to give product **3**. However, the exclusive formation of the vinylsilane with the TMS-substituted zinc species, in contrast to the formation of a mixture of both vinylic and allylic products from the *tert*-butyl-substituted allene, supports the allylic inversion pathway. With 1,1-disubstituted substrates such as **15**, the steric strain should position the metal away from the substituents, thereby producing exclusively the terminal vinyl group in the product through allylic inversion.[20]



27, R^1 = (*p*-MeO_2C)Ph; R = TMS

Figure 1. Proposed mechanism for homoallylic amine formation.

We were able to extend this methodology toward chiral auxiliary-controlled addition to *N*-*tert*-butanesulfinyl imi-

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[12] Pornet, J. In *Organometallics: Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds*; Fleming, I., Ed.; G. Thieme Verlag: Stuttgart, 2002; Vol. 4, pp 669−683.

[13] (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Wipf, P.; Kendall, C. *Top. Organomet. Chem.* **2004**, *8*, 1.

[14] When the reaction was performed in the absence of Me_2Zn, no product was formed, even upon heating to 90 °C for 6 h. Et_2Zn performed equally well in all reported examples.

[15] **Typical Procedure.** A solution of 23.2 mg (0.207 mmol) of allene **1** in 1 mL of CH_2Cl_2 was treated at −78 °C with 53.4 mg (0.207 mmol) of Cp_2ZrHCl and allowed to warm to room temperature over 20 min. After approximately 90% of the CH_2Cl_2 was removed under reduced pressure, 1 mL of toluene was added. The resulting red solution was cooled to −78 °C and treated with 104 μL (0.207 mmol) of Me_2Zn (2.0 M in toluene) and 50.0 mg (0.138 mmol) of imine **2a**. The reaction mixture was warmed to room temperature and stirred for 3 h, quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (three times), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (7:3, EtOAc−hexanes) to yield 51.6 mg (78%) of **3** as a colorless solid.

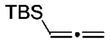
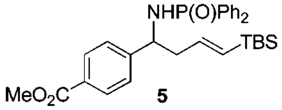
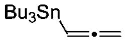
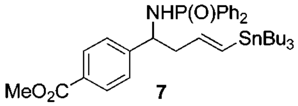
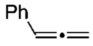
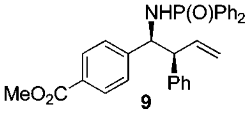
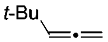
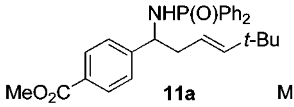
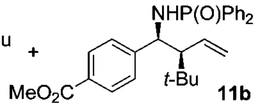
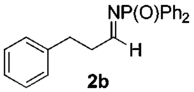
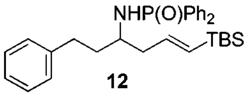
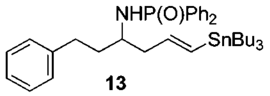
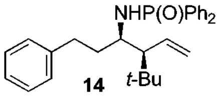
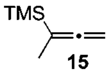
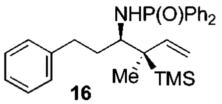
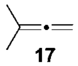
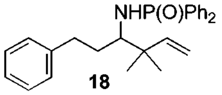
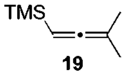
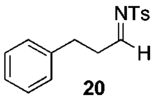
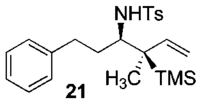
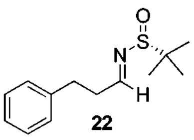
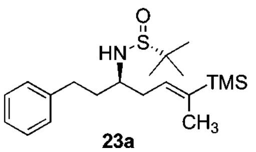
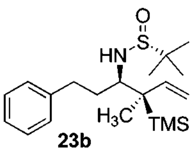
[16] Although *N*-phosphinylalkylamides are difficult to synthesize under standard imine formation conditions, a versatile method for in situ generation has been developed: Charette, A. B.; Boezio, A. A.; Côté, A. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5405.

[17] Allylzinc additions to aldimines: (a) Miginiac, L.; Courtois, G. *J. Organomet. Chem.* **1989**, *376*, 235. (b) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489. (c) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186. (d) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530. (e) Dalmolen, J.; Van der Sluis, M.; Nieuwenhuijzen, J. W.; Meetsma, A.; De Lange, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Eur. J. Org. Chem.* **2004**, 1544.

[18] Chemla, F.; Hebbe, V.; Normant, J.-F. *Synlett* **2000**, 75.

[19] Review: Marek, I.; Normant, J.-F. *Chem. Rev.* **1996**, *96*, 3241.

Table 1. Scope of Hydrozirconation−Imine Addition of Allenes

entry	allene	aldimine[a]	homoallylic amide	Yield[b]
1	**1**	**2a**	**3**	78%
2	 **4**	**2a**	 **5**	80%
3	 **6**	**2a**	 **7**	81%
4	 **8**	**2a**	 **9**	83%[c]
5	 **10**	**2a**	 **11a** +  **11b**	64%[d]
6	**4**	 **2b**	 **12**	79%
7	**6**	**2b**	 **13**	79%
8	**10**	**2b**	 **14**	80%[c]
9	 **15**	**2b**	 **16**	81%[c]
10	 **17**	**2b**	 **18**	76%
11	 **19**	**2a** *or* **2b**	no reaction	--
12	**15**	 **20**	 **21**	85%[c]
13	**15**	 **22**	 **23a** +  **23b**	**23a**: 36%[c] **23b**: 45%[e]

[a] Aldimines **2b** and **20** were formed in situ.[16,18] [b] Yields of isolated products based on imines. [c] Dr > 95:5. [d] Ratio of **11a** and **11b** formed was 1.5:1. [e] A single diastereomer was observed by ^{1}H NMR, and a dr = 96:4 was found by chiral HPLC analysis (Chiralpak AD-H column).

nes.[21] A yield of 81% and a 1:1.3 ratio of vinylsilane **23a** to allylic silane **23b** was obtained when allenylsilane **15** was added to sulfinyl imine **22** (entry 13). The allylic silane **23b** was formed with a dr > 95:5. Attempts to improve the regioselectivity of this addition by changing the solvent, adding metal salts, or modifying the substituents on the sulfinyl imine proved to be unsuccessful. The mixture of **23a** and **23b** was separated by chromatography on SiO_2, and the vinylsilane geometry was assigned through NOE analysis (see Supporting Information).

Further unoptimized catalytic asymmetric additions of **4** to **2a** in the presence of 15 mol % (−)-MIB[22] as a chiral ligand gave allylic amine **5** in a low 33% ee. We are continuing our studies to identify a more suitable chiral ligand for this process.

In conclusion, we have developed a new synthesis of homoallylic amines with vinylic and allylic silane and stannane substituents, employing both aromatic and aliphatic aldimines. All reaction products were obtained as single diastereomers, and an extension of this reaction to a chiral auxiliary-controlled process has been achieved through the use of *N-tert*-butanesulfinyl imines. The allylzinc species that are obtained by in situ transmetalation demonstrate a unique reactivity and regioselectivity in imine additions that differentiates them from their allylzirconocene precursors. Further explorations of the use of chiral ligands and synthetic applications of the functionalized silanes will be reported in due course.

Acknowledgment. This work has been supported by the National Science Foundation (CHE-0315205). We thank Dr. Steve Geib (University of Pittsburgh) for X-ray crystallographic analyses of **9** and **16**.

Supporting Information Available: Experimental procedures and spectral data for compounds **3**, **5**, **7**, **9**, **11a**, **11b**, **12**−**14**, **16**, **18**, **21**, **23a**, and **23b** and CIF files for **9** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In the hydroboration of allenylsilanes, steric hindrance appears to favor positioning the boron at the less substituted allylic site. This chemistry has proven to be an effective method for the synthesis of allylsilanes possessing a homoallylic alcohol functionality: Roush, W. R.; Micalizio, G. C.; Heo, J.-N. *Org. Lett.* **2003**, *5*, 1693 and references therein.

(21) For a recent review, see: Ellman, J.; Owens, T.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(22) Nugent, W. A. *Chem. Commun.* **1999**, 1369.