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Dimethylzinc-Mediated Additions of Alkenylzirconocenes to Aldimines. New Methodologies for Allylic Amine and *C*-Cyclopropylalkylamine Syntheses

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Abstract: Hydrozirconation of alkynes with zirconocene hydrochloride followed by in situ transmetalation to dimethylzinc provides access to reactive alkenyl organometallic reagents from readily available precursors. Upon addition of imines, 1,2-attack leads to synthetically useful allylic amine building blocks. In the presence of CH_2I_2 or CH_2Cl_2, the *N*-metalated allylic amide intermediate is cyclopropanated and *C*-cyclopropylalkylamines are formed in high yield and excellent diastereoselectivities favoring the anti products. The use of enynes as starting materials for this domino reaction provides conjugated biscyclopropanes and thus allows the stereoselective formation of five new carbon−carbon bonds. A transition state that explains the need for both zirconocene complex and alkyl zinc in the cyclopropanation reaction is proposed.

Introduction

The formation of chiral secondary alcohols through the enantioselective addition of organozinc reagents to aldehydes in the presence of amino alcohols is one of the most widely studied reactions in organic synthesis and asymmetric catalysis.[1] The corresponding nucleophilic addition to aldimines is not nearly as developed, partly due to the diminished electrophilicity and the softer Lewis base character of imines compared to carbonyl groups.[2] Soai et al. showed that the diphenylphosphinoyl group could be used to activate aldimines toward enantioselective alkylation with dialkylzinc reagents in the presence of stoichiometric quantities of *N*,*N*-dialkylnorephedrines.[3] Several alternative chiral amino alcohols have subsequently been developed that can be used as ligands for this reaction.[4] Other activated imines such as *N*-(amidobenzyl)benzotriazoles,[5] nitrones,[6] *N*-arylimines,[7] and *N*-tosylimines[8] can also be alkylated with dialkylzincs under the appropriate reaction conditions, and alkylation of selected *N*-alkyl aldimines with triorganozincates has been reported,[9] as has alkynylation of *N*-benzyl nitrones with zinc alkyne complexes.[10] As an extension of our studies on the use of zirconocenes for the preparation of allylic alcohols,[11,12] we became interested in the synthesis of allylic amines **4** by addition of vinylzinc reagents **2**, prepared in situ by the hydrozirconation[13] of alkynes followed by transmetalation with dimethylzinc,[14] to aldimines **3** (Scheme 1).[15]

Interestingly, when CH_2Cl_2 was used as the solvent for this reaction in place of tetrahydrofuran (THF) or toluene, *C*-cyclopropylalkylamines **5** were obtained instead (Scheme 2, path a). The latter products were obtained as well if CH_2Cl_2 or CH_2I_2 were added to a solution of **2** and **3** in toluene. Furthermore, switching the order of addition of reaction components and adding imine **3** last led to a new reaction dichotomy in the formation of homoallylic amine products **6** (Scheme 2, path b).[16] We now report a study of the scope and limitations of using the hydrozirconation−transmetalation−imine addition sequence for the preparation of allylic amines and *C*-cyclopropylalkylamines.[17]

Results and Discussion

Preparation of Allylic Amides. Our initial goal was to prepare allylic amides **4** in one pot in a single solvent system.

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(10) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.
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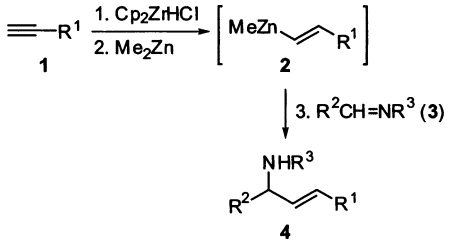
Scheme 1



Scheme 2

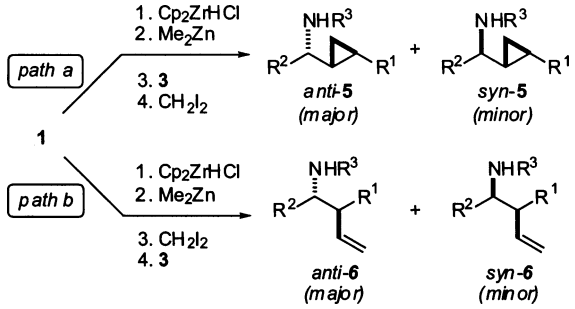
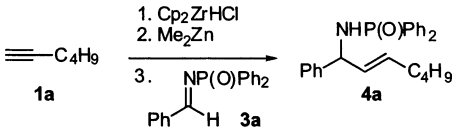


Table 1. Reaction Optimization for Allylic Amide Formation



entry	solvent	**1a**/Cp_2ZrHCl(equiv)	Me_2Zn(equiv)	temp (°C)	time (h)	yield[a] (%)
1	CH_2Cl_2	1.5	1.5	room temp	18	41
2	CH_2Cl_2	1.5	1.5	reflux	1	54
3	CH_2Cl_2	3.0	3.0	reflux	16	11
4	THF	1.5	1.5	room temp	35	54
5	THF	2.0	2.0	40	1	65
6	toluene[b]	1.5	1.5	room temp	2	76
7	toluene	1.5	1.5	room temp	4	59
8	toluene	1.5	1.5[c]	room temp	6	26
9	toluene[b]	1.5	0	room temp	4	0
10	toluene[b]	1.5	0.2	room temp	16	72

[a] Yields of isolated products based on **3a**. [b] Hydrozirconation was performed in CH_2Cl_2, which was subsequently removed in vacuo and replaced with toluene. [c] Et_2Zn was used in place of Me_2Zn.

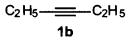
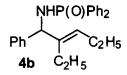
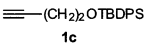
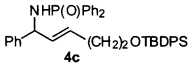
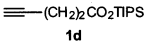
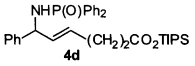
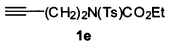
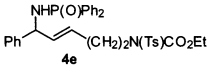
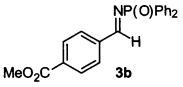
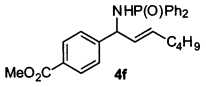
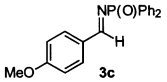
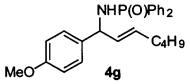
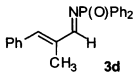
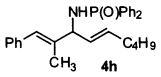
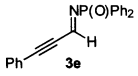
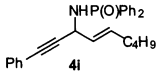
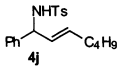
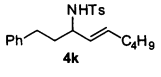
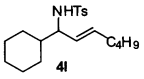
Even though toluene is the solvent of choice for the asymmetric synthesis of allylic alcohols[12] and for diethylzinc additions to *N*-diphenylphosphinoylimines,[18] we first used CH_2Cl_2 and THF since hydrozirconation is much faster in these two solvents than in toluene.[19] While the reaction was successful, yields of the desired allylic amide **4a** did not exceed 54 and 65% in CH_2Cl_2 and THF, respectively (Table 1, entries 1−5). In CH_2Cl_2, the maximum yield was obtained when the reaction was performed at reflux with 1.5 equiv of alkyne, zirconocene hydrochloride, and dimethylzinc (entry 2). Doubling the amount of these three reagents had a detrimental effect on the yield of **4a** (entry 3), due to formation of the *C*-cyclopropylalkylamide (vide infra). In THF, the highest yield was obtained when the reaction was performed at 40 °C (entry 5). A higher and more reproducible yield was achieved at room temperature in toluene. For small-scale reactions, the alkyne was hydrozirconated in CH_2Cl_2 (<10 min reaction time at 25 °C), and the solvent was then switched to toluene prior to transmetalation with dimethylzinc (entry 6). Alternatively, hydrozirconation in toluene avoided the need for a solvent switch by maintaining a single solvent for the entire one-pot reaction (entry 7), but led to a significant increase in the hydrozirconation time (>60 min at 40 °C). The use of diethylzinc in place of dimethylzinc resulted in a much lower isolated yield of **4a** (entry 8). No addition to the imine was observed in any solvent in the absence of the dialkylzinc additive (entry 9); however, as was found for the allylic alcohol synthesis,[20] substoichiometric quantities of dimethylzinc could be used to affect the same transformation, though the reaction time was increased (entry 10).

Using the optimal reaction conditions reported in Table 1, entry 6, the reaction scope was further investigated (Table 2). The isolated yields of all but one of the allylic amides were in the range of 60−90%. Only the electron-rich *p*-methoxy substituted imine **3c** led to a lower yield (entry 7). The symmetrical internal alkyne **1b** was used to form trisubstituted double bonds (entry 2). Functional groups such as silyl ethers (entry 3), silyl esters (entry 4), and sulfonamides and carbamates (entry 5) were tolerated on the alkyne segment. However, sterically very hindered alkynes such as trimethylsilylacetylene were hydrozirconated but not further converted to allylic amides under these conditions. In remarkable contrast to diethylzinc additions to *N*-diphenylphosphinoylimines,[4d] electron-withdrawing groups on the benzaldimine did not affect the reaction yield (entry 6), whereas the presence of electron-donating groups significantly reduced the amount of isolated compound, possibly due to the instability of the desired product (entry 7). Addition to α,β-unsaturated aldimine **3d** and alkynylimine **3e** afforded allylic amides **4h**,**i** (entries 8 and 9); however, we have been unable to synthesize *N*-diphenylphosphinoyl aldimine substrates derived from enolizable aldehydes.[21] In contrast, *N*-tosylalkylimines **3g,h** were readily available[22] and proved to be excellent substrates for this reaction (entries 11 and 12). Similarly, *N*-tosylbenzaldimine **3f** was converted to the allylic sulfonamide **4j** in high yield (entry 10).

Synthesis of *C*-Cyclopropylalkylamides. While optimizing the alkyne hydrozirconation−transmetalation−aldimine addition reaction sequence, we discovered a novel three-component cyclopropane synthesis. When the imine addition step was performed in CH_2Cl_2 at reflux in the presence of 3 equiv of both the vinylzirconocene and dimethylzinc (Table 1, entry 3), the *C*-cyclopropylmethylamide *anti*-**5a** was formed in 58% yield, in addition to 11% of the expected allylic amide **4a** (Scheme 3). A single diastereomer, later found to have the anti stereochemistry by X-ray analysis of benzamide *anti*-**8a**, was observed by ^1H NMR analysis of the crude reaction mixture. When the reaction was performed in CD_2Cl_2 at reflux, the geminal bis-deuterated cyclopropane *anti*-**5b** was formed, thus confirming that the chlorinated solvent served as the origin of the extra carbon in the product. To the best of our knowledge, this is the first example of a preparative cyclopropanation in which CH_2Cl_2 serves as the carbene precursor.[23] Moreover, we found that it was not necessary to use CH_2Cl_2 as the solvent; performing this reaction in toluene at room temperature in the presence of 10 equiv of CH_2Cl_2 as an additive resulted in a

(17) For a preliminary communication of this work, see: Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122.
(18) Soai, K.; Suzuki, T.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1994**, 317.
(19) Wipf, P.; Takahashi, H.; Zhuang, N. *Pure Appl. Chem.* **1998**, *70*, 1077.
(20) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639.
(21) See also Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.
(22) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

Table 2. Addition of in Situ Prepared Alkenylorganometallics to Aldimines. Reaction Scope of Allylic Amide Formations

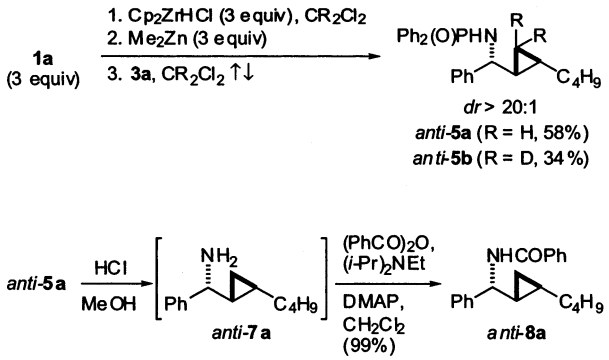
Entry	Alkyne	Aldimine	Allylic amide[a]	Yield[b]
1	**1a**	**3a**	**4a**	76%
2	 **1b**	**3a**	 **4b**	72%
3	 **1c**	**3a**	 **4c**	73%
4	 **1d**	**3a**	 **4d**	65%
5	 **1e**	**3a**	 **4e**	59%
6	**1a**	 **3b**	 **4f**	84%
7	**1a**	 **3c**	 **4g**	35%
8	**1a**	 **3d**	 **4h**	72%
9	**1a**	 **3e**	 **4i**	85%
10	**1a**	 **3f**	 **4j**	80%
11	**1a**	 **3g**	 **4k**	90%
12	**1a**	 **3h**	 **4l**	81%

[a] Reaction conditions: (i) 1.5 equiv of Cp_2ZrHCl, 1.5 equiv of alkyne **1**, CH_2Cl_2, room temp, 10 min; (ii) 1.5 equiv of Me_2Zn, toluene, −78 °C, 5 min; (iii) 1.0 equiv of aldimine **3**, toluene, room temp, 2−5 h. [b] Yields of isolated products are based on aldimines **3**.

43% yield of *anti*-**5a** (in addition to 26% of isolated **4a**) after 36 h reaction time.

To increase the yield and the relative rate of cyclopropanation, we added CH_2I_2 to the reaction mixture. The isolated yield of *anti*-**5a** increased to 74%. Using these optimized conditions, a broad range of functionalized *C*-cyclopropylalkylamides were obtained in 45−85% yield (Table 3). Furthermore, we found that addition of 1 equiv of benzyl alcohol had a significant

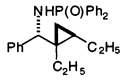
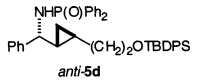
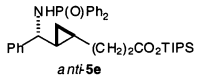
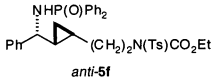
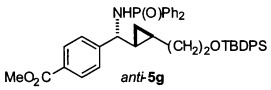
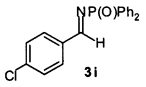
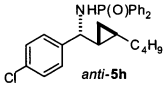
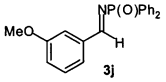
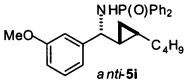
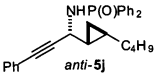
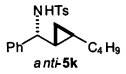
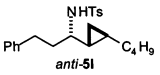
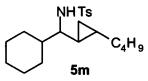
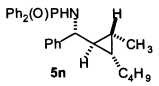
Scheme 3



positive effect on the isolated yield of *anti*-**5a** (entry 2), possibly due to the replacement of the potentially reactive methyl ligand on zirconium with an alkoxide group (vide infra).[15a,b] The trisubstituted cyclopropane *anti*-**5c** was formed in 46% yield

(23) While both CH_2I_2 and CH_2Br_2 are routinely utilized in the Simmons−Smith reaction, CH_2Cl_2 is generally considered unreactive in a wide range of modifications of this method: (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (b) LeGoff, E. *J. Org. Chem.* **1964**, *29*, 2048. (c) Maeda, T.; Tada, H.; Yasuda, K.; Okawara, R. *J. Organomet. Chem.* **1971**, *27*, 13. (d) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**. *46*, 892. (e) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. It has, however, been reported that a mixture of alkene and methylene chloride reacts with heated zinc film at low pressure to give traces of cyclopropane products: (f) Fauveau, C.; Gault, Y.; Gault, F. G. *Tetrahedron Lett.* **1967**, 3149.

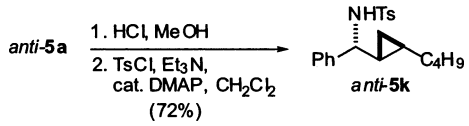
Table 3. Three-Component *C*-Cyclopropylalkylamide Synthesis

Entry	Alkyne	Aldimine	Allylic amide[a,b]	Yield[c]	*dr*
1	**1a**	**3a**	*anti*-**5a**	74%	97:3[d]
2	**1a**	**3a**	*anti*-**5a**	91%[e]	>95:5[f]
3	**1b**	**3a**	 *anti*-**5c**	46%	96:4[d]
4	**1c**	**3a**	 *anti*-**5d**	68%	98:2[d]
5	**1d**	**3a**	 *anti*-**5e**	71%	>95:5[f]
6	**1e**	**3a**	 *anti*-**5f**	45%	>95:5[f]
7	**1c**	**3b**	 *anti*-**5g**	84%	>95:5[f]
8	**1a**	 **3i**	 *anti*-**5h**	65%	>95:5[f]
9	**1a**	 **3j**	 *anti*-**5i**	51%	>95:5[f]
10	**1a**	**3e**	 *anti*-**5j**	60%	>95:5[f]
11	**1a**	**3f**	 *anti*-**5k**	66%	96:4[f]
12	**1a**	**3g**	 *anti*-**5l**	67%	87:13[f]
13	**1a**	**3h**	 **5m**	62%[g]	40:60[f]
14	**1a**	**3a**	 **5n**	52%[h,i]	>95:5[f]

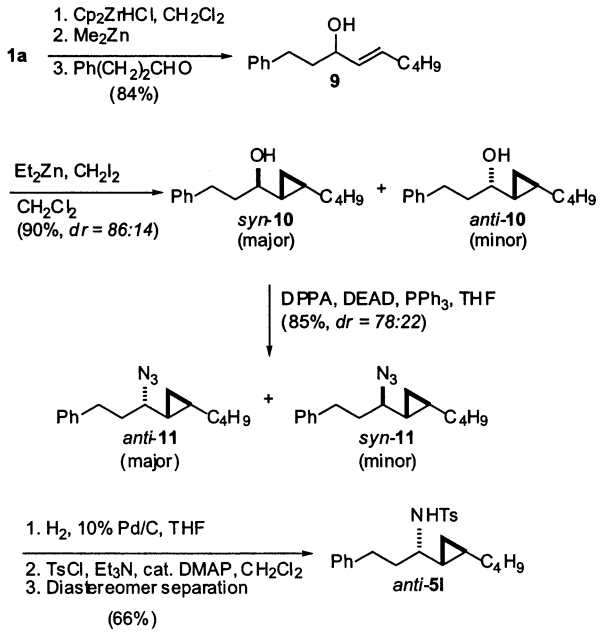
[a] Only the major stereoisomer is shown. [b] Reaction conditions: (i) 3 equiv of Cp_2ZrHCl, 3 equiv of alkyne **1**, CH_2Cl_2, room temp, 10 min; (ii) 3 equiv of Me_2Zn, CH_2Cl_2, −78 °C, 5 min; (iii) 1 equiv of aldimine **3**, CH_2Cl_2, reflux, 1−2 h; (iv) 5 equiv of CH_2I_2, CH_2Cl_2, reflux, 2−12 h. [c] Yields of isolated products are based on aldimine **3**. [d] Determined by HPLC analysis of the crude reaction mixture. [e] 1 equiv of $PhCH_2OH$ was added to the reaction mixture. [f] Determined by ^1H NMR analysis of the crude reaction mixture. [g] Additional Me_2Zn (3 equiv) and CH_2I_2 (10 equiv) were added to the reaction mixture. [h] Et_2Zn (6 equiv) and CH_3CHI_2 (12 equiv) were added to the reaction mixture. [i] Hydrozirconation was performed in THF, and the solvent was exchanged with $ClCH_2CH_2Cl$ for the remainder of the reaction.

using internal alkyne **1b** (entry 3). Functional groups tolerated on the alkyne segment included silyl ethers (entry 4), silyl esters (entry 5), sulfonamides, and carbamates (entry 6). Both electron-rich and electron-deficient benzaldimines were effective substrates (entries 7−9). Alkynylimine **3e** afforded *anti*-**5j** in 60% yield (entry 10), and, as with all benzaldimine substrates, only one diastereomer was observed by ^1H NMR analysis of the crude reaction mixture. The α,β-unsaturated aldimine **3d** was not an effective substrate, since a complex mixture of bis-cyclopropane and mono-cyclopropane products was formed under the general reaction conditions. As observed for the formation of allylic amides, *N*-tosylaldimine **3f** was nearly as effective as *N*-phosphinoylimine **3a** (entry 11). A diminished anti:syn diastereomeric ratio (dr) of 87:13 was observed when alkylimine **3g** was used (entry 12), and the more bulky aldimine **3h** further eroded the dr to 40:60 (entry 13). This reaction was the most sluggish and required addition of further equivalents of dimethylzinc to the reaction mixture in order to achieve high conversion. Also, unlike Scheme 3, no trace of **5m** was formed if the reaction was performed in CH_2Cl_2 at reflux in the absence

Scheme 4



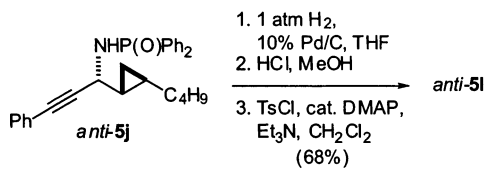
Scheme 5



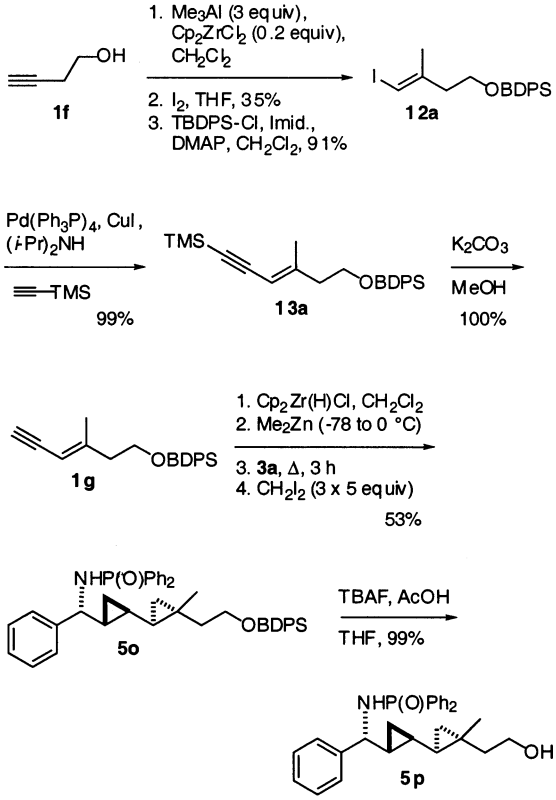
of added CH_2I_2. Finally, this methodology could also be extended to the synthesis of trisubstituted cyclopropanes by replacing CH_2I_2 with CH_3CHI_2 (entry 14); however, the use of $(CH_3)_2CI_2$[24] afforded only trace amounts of the desired tetrasubstituted cyclopropane. With diiodoalkanes as carbenoid precursors, the hydrozirconation had to be performed in a solvent other than CH_2Cl_2 in order to avoid formation of *anti*-**5a** as the major product.

The anti configuration was observed for the major diastereomer of all *C*-cyclopropylalkylamides but **5m**. The stereochemistry of *anti*-**5b**, *anti*-**5c**, *anti*-**5d**, *anti*-**5e**, *anti*-**5f**, *anti*-**5g**, *anti*-**5h**, and *anti*-**5i** was assigned by analogy to *anti*-**5a**. Deprotection[25] and *N*-tosylation of *anti*-**5a** afforded *anti*-**5k**, confirming an identical relative configuration for the major diastereomers of both *N*-phosphinoyl and *N*-sulfonyl amides (Scheme 4). The relative configuration of *C*-cyclopropylalkylamide *anti*-**5l** was determined chemically (Scheme 5). Allylic alcohol **9** was prepared using our Zr−Zn transmetalation, aldehyde addition methodology.[11] An alcohol-directed Simmons−Smith cyclopropanation of **9** with $Zn(CH_2I)_2$ [26] afforded **10** as an 86:14 mixture of easily separable diastereomers.[27] Mitsunobu substitution of the secondary alcohol in *syn*-**10** with DPPA[28] in the presence of DEAD and triphenylphosphine gave an 78:22 mixture of diastereomeric azides.[29] Reduction of the mixtures of epimeric azides **11** with H_2 and Pd on carbon followed by *N*-tosylation and epimer separation by chromatography on SiO_2 afforded *anti*-**5l** in 66% overall yield. Finally, the relative configuration of *anti*-**5j** was similarly determined chemically by reduction, deprotection, and tosylation to give *anti*-**5l** (Scheme 6).

Scheme 6



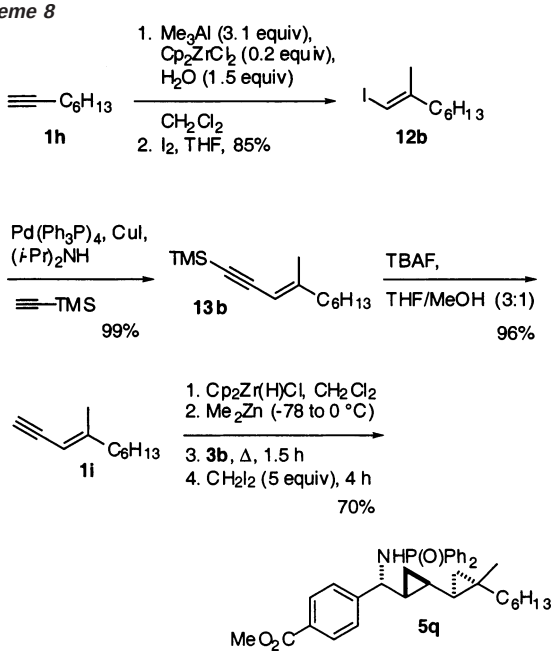
Scheme 7



An important extension of this new methodology was achieved by the conversion of enynes **1g** and **1i** to the corresponding biscyclopropanes **5o** and **5q** (Schemes 7 and 8). While the second cyclopropanation required more forcing conditions and addition of an excess of CH_2I_2,[30] a single diastereomeric product with a total of five new C,C-bonds was found in both reaction mixtures. Starting enyne **1g** was obtained by carboalumination[31] of alkyne **1f** followed by iodination of the intermediate vinyl alane, *O*-silylation, and Sonogashira coupling[32] with trimethylsilane (TMS)−acetylene followed by *C*-desilylation in basic methanol.[33] Enyne **1i** was obtained

(24) Charette, A. B.; Wilb, N. *Synlett* **2002**, 176.
(25) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.
(26) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592.
(27) Compound *syn*-**10** was expected to be the major diastereomer based upon extensive precedence by, among others: (a) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966. (b) Harada, S.; Kowase, N.; Tabuchi, N.; Taguchi, T.; Dobashi, Y.; Dobashi, A.; Hanzawa, Y. *Tetrahedron* **1998**, *54*, 753.
(28) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977.
(29) The structural assignment of the major epimer of the azide displacement as the S_N2 product, *anti*-**11**, was confirmed by subjecting *anti*-**10** to analogous Mitsunobu reaction conditions. A 15:85 mixture of diastereomers favoring the epimer, *syn*-**11**, was isolated in the latter conversion.
(30) The reduced cyclopropanation rate for the distal double bond can readily be explained by the greater distance between the N-ligated zinc carbenoid specied and the alkene in the transition-state structures (cf. Scheme 9). Due to the long N−Zn and Zn−C bonds (ca. 2 Å), intramolecular delivery is still feasible, however.
(31) Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1.

Scheme 8



analogously by water-accelerated carboalumination[34] of **1h** via vinyl iodide **12b**.[35] Since neither biscyclopropane **5o** nor **5q** was sufficiently crystalline for X-ray structure determination, the silyl protective group of **5o** was cleaved with tetrabutylammonium fluoride (TBAF) and the anti−anti configuration of biscyclopropane **5p** was elucidated by X-ray analysis. The one-pot conversion of enynes to these *C*-biscyclopropylalkylamides represents a highly stereoselective and efficient approach for the synthesis of conjugated oligocyclopropanes. Traditionally, multistep pathways have been required for the assembly of these structurally intriguing natural and unnatural building blocks.[36]

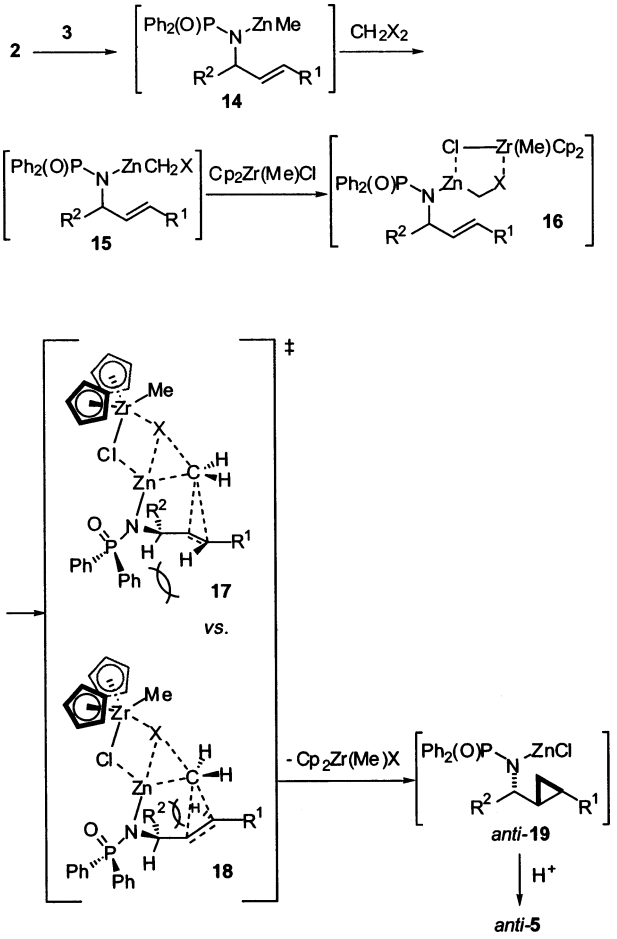
Mechanistic Proposal. In all cases, allylic amide formation clearly preceded the appearance of cyclopropanated product, therefore indicating that a metalated derivative of **4** was the reactive substrate for carbene transfer onto the alkene moiety. When the reaction mixture was quenched prematurely (with no added CH_2I_2), a low conversion to **5** was observed. After 1 h at reflux, for example, the isolated yield of *anti*-**5a** dropped to 29%, along with a corresponding increase in the yield of **4a** to 43%. In contrast, after 16 h at reflux, a 58% yield of *anti*-**5a** and a 11% yield of **4a** was observed. An alternative mechanism for this transformation, i.e., the generation of a cyclopropylzinc species,[37] followed by nucleophilic addition to imine, was rendered unlikely by these observations. Furthermore, the cyclopropylzinc reagent derived from 1-hexyne via hydrozirconation, transmetalation to zinc, and cyclopropanation was found to be completely unreactive toward aldimine **3f**.

While there is ample precedence for the formation of *syn*-diasteromers by directed Simmons−Smith-type cyclopropanations,[38] we were, at first, surprised at the exceptionally high anti selectivity in the formation of *C*-cyclopropylalkylamides **5**. In addition, the activation of CH_2Cl_2 as a zinc carbenoid source was quite unprecedented, and, moreover, the presence of zirconocene proved to be crucial for an efficient cyclopropanation. Under otherwise analogous conditions but using vinyl alanes or vinyl boranes as substrates and subjecting them to one-pot Al→Zn[39] or B→Zn[40] transmetalation processes, only allylic amides **4** were isolated after addition of aldimine **3a** to the reaction mixture in CH_2Cl_2 at reflux. Even in the presence of 5 equiv of CH_2I_2, no cyclopropanated product was detected in the boron-based reaction, whereas a low yield of cyclopropyl amide **5** was generated from the vinyl zinc species obtained by transmetalation of the corresponding vinyl alane. Furthermore, if an organozirconocene complex was not present in the reaction mixture, excess dimethylzinc in CH_2Cl_2 at reflux temperatures did not convert allylic amide **4a** into cyclopropane **5a**. Even after addition of Cp_2ZrCl_2, allylic amide **4a** was recovered quantitatively. Interestingly, subjecting **4a** to standard Simmons−Smith cyclopropanation conditions afforded **5a** in good yield, but in a lower anti:syn ratio of 71:29, thus clearly confirming that the zirconocene complex was involved both in the generation of the active cyclopropanating agent and in the stereoselectivity-determining step of the zinc carbenoid addition. Furthermore, if **4a** was added to the reaction mixture used for preparation of *anti*-**5k** (Table 2, entry 10), *anti*-**5a** was isolated in >20:1 dr. If the same transformation was attempted in the absence of added CH_2I_2, the conversion of **4a** to *anti*-**5a** was found to be significantly higher than the ratio of *anti*-**5k** to **4j**. Accordingly, cyclopropanation of phosphinoylamides was accelerated vs sulfonylamide substrates.[41] The importance of an intramolecular activating group was also supported by the observation that addition of an unactivated alkene (CH_2═CH-$(CH_2)_2$OBDPS) or even alcohol **9** to the reaction mixture did not yield cyclopropanated derivatives of these alkenes. It is therefore unlikely that this cyclopropanation is an intermolecular process mediated by a mixed phosphinoylamide methylzinc reagent.[42] The lack of reactivity of allylic alcohol **9** toward further conversion to cyclopropane also explained why we had not observed this process previously in our addition reactions to aldehydes.[11,12]

While mechanistic details of the multicomponent zirconocene/zinc aldimine addition−cyclopropanation process remain somewhat obscure, we propose a stepwise process that is in agreement with all experimental observations (Scheme 9). After transmetalation of alkenylzirconocene to dimethylzinc, addition to aldimine **3** affords *N*-metalated allylic amide intermediate **14**. Insertion of zinc into dihalomethane forms the halomethylzinc species **15**.[27,43] This carbon−halogen bond insertion might be facilitated by the presence of the nitrogen ligand on zinc, the zirconocene complex, or both.[27b,44] The zirconocene formed in the transmetalation reaction serves the role of a Lewis acid activator for zinc carbenoid formation by complexing the

(32) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 203−229.
(33) Bick, S.; Zimmermann, S.; Meuer, H.; Sheldrick, W. S.; Welzel, P. *Tetrahedron* **1993**, *49*, 2457.
(34) (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068. (b) Ribe, S.; Wipf, P. *J. Chem. Soc., Chem. Commun.* **2001**, 299.
(35) Iwasawa, N.; Maeyama, K. *J. Org. Chem.* **1997**, *62*, 1918.
(36) (a) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (c) Barrett, A. G. M.; Tuestin, G. J. *J. Chem. Soc., Chem. Commun.* **1995**, 355.
(37) Yachi, K.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2515.
(38) See Scheme 5 and refs 23e and 27, as well as: Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.
(39) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719.
(40) Srebnick, M. *Tetrahedron Lett.* **1991**, *32*, 2449.
(41) (a) Russ, P.; Ezzitouni, A.; Marquez, V. E. *Tetrahedron Lett.* **1997**, *38*, 723. (b) Momose, T.; Nishio, T.; Kirihara, M. *Tetrahedron Lett.* **2002**, *37*, 4987.
(42) See, for example: Charette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139.
(43) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

Scheme 9



halogen atom of the halomethyl zinc species **16** and increasing electron density on zinc by providing a bridging chloride ligand.[45] Of the two feasible transition states **17** and **18**,[45a,46] the former suffers from large steric interactions between the diphenylphosphinoyl substituent and the alkene moiety. In contrast, **18** is subjected to the 1,3-allylic strain interaction that is usually responsible for high syn selectivity,[27] but the steric strain around the bulky diphenylphosphinoyl group is now relieved. Transition-state **18** provides the major isomer, *anti*-**19**. The high level of anti selectivity is also consistent with diastereoselectivities observed in the Simmons−Smith cyclopropanation of allylic ethers.[47]

Conclusions

The sequential hydrozirconation−transmetalation−imine addition of alkynes establishes an efficient new route for the preparation of synthetically useful allylic amine building blocks. In the presence of CH_2I_2 or CH_2Cl_2, the *N*-metalated allylic amide is cyclopropanated in situ, and high yields of *C*-cyclopropylalkylamines are isolated in excellent diastereoselectivities. If CH_2Cl_2 is used as a reaction solvent, this process can be considered a domino reaction[48] that provides a total of three new carbon−carbon bonds and a synthetically valuable structural motif in a single step.[49] The use of enynes as starting materials expands this chemistry further and results in the stereoselective formation of five new C,C-bonds. In addition to dimethylzinc, the presence of zirconocene is crucial for realizing these transformations,[14] and a mechanistic hypothesis that takes advantage of the dual Lewis acidic and halide bridging properties of the zirconocene complex is consistent with all experimental observations and the high anti selectivity observed for the cyclopropane products. Further studies of the novel reactivity patterns of zirconocene/zinc complexes as well as the development of an enantioselective version of this reaction are continuing in our laboratories.

Experimental Section.

***N*-(1-Phenylhept-2-enyl)-P,P-diphenylphosphinamide (4a). General Protocol A.** A suspension of 208 mg (0.807 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated at room temperature with 105 μL (0.914 mmol) of 1-hexyne, stirred for 5 min, and concentrated in vacuo. A solution of the resulting yellow solid in 2 mL of toluene was cooled to −78 °C, treated with 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, and cannulated into a suspension of 155 mg (0.508 mmol) of imine **3a** in 2 mL of toluene. The reaction mixture was stirred at room temperature for 2 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated in vacuo. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 151 mg (76%) of **4a** as a colorless solid: mp 139−140 °C (EtOAc/hexane); IR (KBr) 3127, 2952, 2922, 2859, 1456, 1437, 1194, 1182, 1121, 1109 cm^{-1}; ^1H NMR δ 8.00−7.93 (m, 2 H), 7.89−7.82 (m, 2 H), 7.55−7.23 (m, 11 H), 5.69 (ddt, 1 H, J = 15.3, 6.2, 1.2 Hz), 5.53 (dtd, 1 H, J = 15.3, 6.6, 1.1 Hz), 4.83 (td, 1 H, J = 9.4, 6.4 Hz), 3.34 (dd, 1 H, J = 9.4, 6.2 Hz), 2.01 (q, 2 H, J = 6.4 Hz), 1.34−1.26 (m, 4 H), 0.90 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 143.03, 142.96, 133.73, 133.39, 132.45, 132.29, 132.17, 132.06, 132.01, 131.67, 128.44, 128.37, 128.21, 127.10, 126.92, 56.87, 31.77, 31.12, 22.19, 13.88; EIMS *m*/*z* 389 (M^+, 15), 332 (19), 306 (25), 216 (98), 201 (92), 188 (100), 172 (35), 143 (55), 129 (87), 115 (35), 91 (33); HRMS (EI) *m*/*z* calcd for $C_{25}H_{28}NOP$ 389.1909, found 389.1906.

Preparation of *anti*-5a in the Presence of CH_2I_2. General Protocol B. A suspension of 390 mg (1.51 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated at room temperature with 190 μL (1.65 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to −78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with a solution of 153 mg (0.501 mmol) of imine **3a** in 2 mL of CH_2Cl_2, and heated to reflux for 1 h. The reaction mixture was cooled to room temperature, treated with 200 μL (2.48 mmol) of CH_2I_2, heated to reflux for a further 2 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated in vacuo. The residue was chromatographed on deactivated SiO_2 (1:9,

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hexanes/EtOAc containing 1% Et_3N) to yield 149 mg (74%) of *anti*-**5a** [dr = 97:3 (HPLC)] as a colorless solid.

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Supporting Information Available: Comprehensive experimental protocols and spectroscopic data, ^1H and ^{13}C NMR spectra for **4b**−**l,** *anti*-**5b**, *anti*-**5e**, *anti*-**5j**, *anti*-**5k**, *anti*-**5l**, and **5m**−**q** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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