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Dimethylzinc-Mediated Addition of Alkenylzirconocenes to α-Keto and α-Imino Esters

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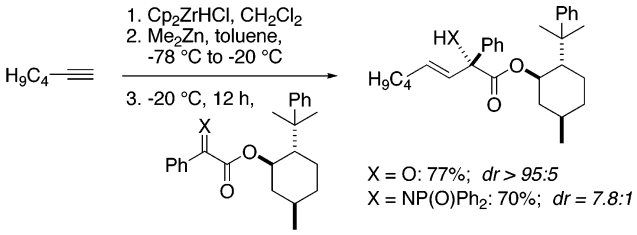
ABSTRACT



Hydrozirconation of alkynes followed by in situ transmetalation to dimethylzinc and 1,2-addition to activated ketones and *N*-diphenylphosphinoylimines leads to tertiary allylic alcohols and amines in high overall yield. With 8-phenylmenthol as the chiral auxiliary, *si*-face attack proceeds in good to excellent diastereoselectivities.

The addition of organometallic reagents to α-keto esters[1] provides access to 1,2-dioxygenated building blocks for organic synthesis.[2,3] The resulting tertiary α-hydroxy carboxylates serve as substructures for natural products and medicinal agents.[4] This approach is particularly valuable if the organometallic reagent is readily obtained from storable precursors and tolerates other commonly used functional groups. In contrast to the use of Grignard and lithium reagents, hydrozirconation of alkynes is relatively insensitive to the presence of many electrophilic functions, and the resulting organozirconocenes have been added to enones,[5,6] aldehydes,[7] epoxides,[8] esters,[9] isocyanates,[10] nitrones,[11] and imines.[12] As a continuation of our work on Zr→Zn transmetalations of alkenylzirconocenes and in situ additions to

(1) Kovacs, L. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 471.

(2) (a) Akiyama, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447. (b) Fuji, K.; Tanaka, K.; Ahn, M.; Mizuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 957. (c) Huang, D.-L.; Draper, R. W.; Lih, D. *Tetrahedron Lett.* **1994**, *35*, 661. (d) Tamai, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 439 and references therein.

(3) For lead references on the tactically related addition of enolates to α-keto esters, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860. (b) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1989**, 2069.

(4) See, for example: (a) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120−5121. (b) Senanayake, C. H.; Fang, Q. K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819.

(5) For reviews, see: (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. (b) Lipshutz, B. H.; Pfeiffer, S. S.; Tomioka, T.; Noson, K. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 110−148.

(6) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115. (b) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045. (c) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440. (d) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (e) Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935.

(7) (a) Wipf, P.; Xu, W. *Tetrahdron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205. (c) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (d) Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208. (e) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965.

(8) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825.

(9) (a) Wipf, P.; Xu, W. J. *J. Org. Chem.* **1993**, *58*, 5880. (b) Wipf, P.; Xu, W.; Takahashi, H.; Jahn, H.; Coish, P. D. G. *Pure Appl. Chem.* **1997**, *69*, 639.

(10) Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631.

(11) Pandya, S. U.; Garcon, C.; Chavant, P. Y.; Py, S.; Vallée, Y. *Chem. Commun.* **2001**, 1806.

(12) (a) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761. (b) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (c) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773. (d) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923.

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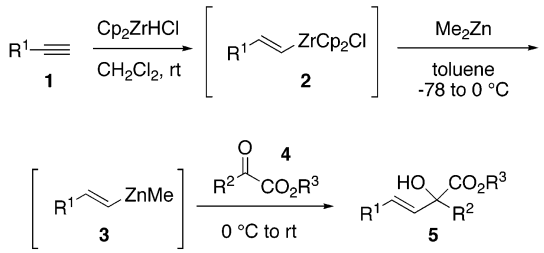
organic electrophiles,[13] we have now extended this methodology to the formation of functionalized tertiary allylic alcohols via addition to α-keto esters (Scheme 1).[14−16]

Scheme 1. Addition of Organozirconocenes to α-Keto Esters Mediated by Transmetalation to Dimethylzinc

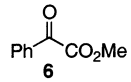
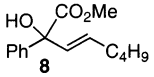
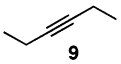
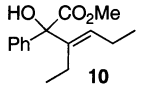
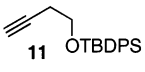
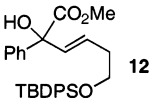
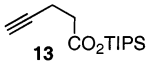
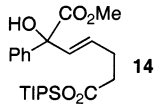
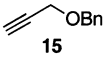
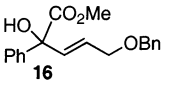
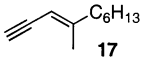
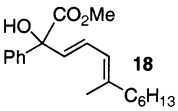
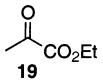
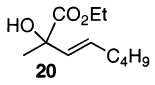
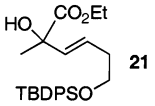
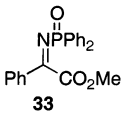
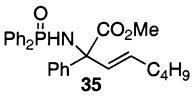
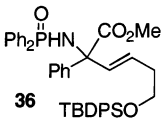


(*E*)-Alkenylzirconocenes **2** were readily obtained by hydrozirconation of alkynes **1** with Cp_2ZrHCl in CH_2Cl_2 at room temperature and, upon addition of a dimethylzinc solution in toluene, converted to the more nucleophilic alkenylzinc species **3**. After addition of α-keto esters **4** at 0 °C to the reaction mixture, tertiary allylic alcohols **5** were formed in 75−96% yield in 1−2 h upon warming to room temperature (Table 1).[17,18] In the absence of dimethylzinc, only traces of addition products were observed.

Ester functionalities were tolerated both in the substrate as well as in the alkyne component (entry 4). Silyl ethers (entries 3 and 8) and Lewis basic benzyl ethers (entry 5), internal alkynes (entry 2), and enynes (entry 6) all proceeded successfully through the 1,2-addition and afforded the expected α-hydroxy esters in high overall yields.

Since our initial attempts to affect an asymmetric addition to ketoester **6** in the presence of chiral ligands[7c,d,19] did not yield enantiomerically enriched products, we turned our attention to the readily available menthol derived α-keto esters **26** and **27**. There is encouraging literature precedent for the diastereoselective addition of organometallic reagents to chiral α-keto esters[20] and amides.[21] Treatment of benzoylformic acid **22** with α,α-dichloromethyl methyl ether[22] afforded 70% of acid chloride **23**, which could be converted in the presence of DMAP in CH_2Cl_2 to the menthyl ester **26**

Table 1. Preparation of Tertiary Allylic Alcohols and Amines from Alkynes and α-Keto or α-Imino Esters

entry	keto/imino ester	alkyne	product	yield [%][a]
1	 **6**	 **7**	 **8**	93
2	**6**	 **9**	 **10**	76
3	**6**	 **11**	 **12**	83
4	**6**	 **13**	 **14**	82
5	**6**	 **15**	 **16**	90
6	**6**	 **17**	 **18**	88
7	 **19**	**7**	 **20**	93
8	**19**	**11**	 **21**	75
9	 **33**	**7**	 **35**	92
10	**33**	**11**	 **36**	93

[a] Yields of isolated product based on α-keto/imino ester.

(13) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778.

(14) For representative examples for the addition of alkylzinc chloride, dialkylzinc, or trialkylzincate reagents to activated ketones, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Basavaiah, D.; Krishna, P. R. *Tetrahedron* **1995**, *51*, 12169. (c) Sugimura, H.; Watanabe, T. *Synlett* **1994**, 175.

(15) For recent examples of asymmetric additions of alkylzinc reagents to α-keto esters, see: (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781.

(16) For reports on the alkenylalane addition to activated carbonyl compounds and imines, see: (a) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Tetrahedron Lett.* **1999**, *40*, 627. (b) Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.

(17) **General Protocol.** To a suspension of Cp_2ZrHCl (0.24 g, 0.91 mmol) in dry CH_2Cl_2 (4.0 mL) was added **7** (0.11 mL, 0.91 mmol). The reaction mixture was stirred for 10 min at rt and evaporated in vacuo. A solution of the residue in dry toluene (4.0 mL) was cooled to −78 °C, treated with Me_2Zn (0.46 mL, 0.91 mmol), and warmed to 0 °C. After addition of **6** (87 μL, 0.61 mmol), the reaction mixture was warmed to rt, stirred for 2 h, quenched with saturated NH_4Cl, diluted with EtOAc, and filtered through Celite. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give **8** (0.14 g, 93%) as a colorless oil.

(18) Nonactivated ketones react only sluggishly under these reaction conditions.

(19) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197.

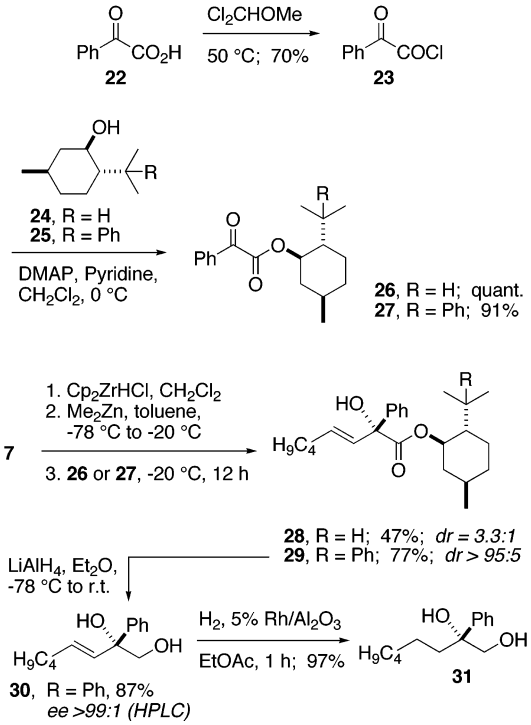
(20) (a) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988. (b) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417. (c) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(21) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009.

(22) Ottenheijm, H. C. J.; de Man, J. H. M. *Synthesis* **1975**, 163.

and the 8-phenylmenthyl[23] ester **27** in excellent yields (Scheme 2).

Scheme 2. Use of Chiral Esters in the 1,2-Addition Process and Assignment of Absolute Configuration by Conversion to the Known Diol **31**



Treatment of **26** and **27** at −20 °C with 1.5 equiv of the organometallic reagent derived from **7** afforded **28** and **29**, respectively. While the menthyl ester **26** provided **28** only in modest diastereoselectivity (3.3:1 by 500 MHz ^{1}H NMR), a single diastereoisomer was observed by ^{1}H NMR analysis in the formation of **29**. To quantify the diastereoselectivity of the addition process, the crude reaction mixture was subjected to $LiAlH_4$ reduction to afford diol **30** in 87% yield along with 92% of recovered **25**. Racemic diol **30** was readily separated by chiral HPLC (Chiralcel OD) and compared to material obtained from reduction of the 8-phenylmenthyl ester. Furthermore, hydrogenation of the allylic alcohol using H_2/Rh/Al_2O_3 gave the known[24] diol **31** in 97% yield (Scheme 2).[25]

According to the sign of the optical rotation of **31**, the addition proceeded with *si*-face attack via a π-stacked, chelated complex[20,21] to give the α-hydroxyester **29** in the (*R*)-configuration. On the basis of HF-6-31G* ab initio energy minimization, the chelated conformation shown in Figure 1 is at least 1.7 kcal/mol lower in energy than any alternative conformer, including monocoordinated structures

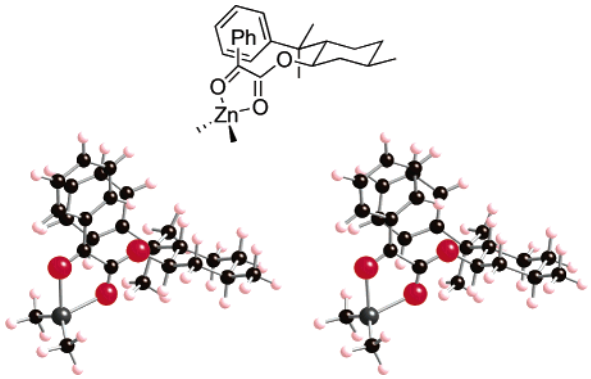


Figure 1. Stereoview of the lowest-energy Me_2Zn-chelated α-keto ester complex that can be used to rationalize the *si*-face selectivity of nucleophilic addition. The geometry was optimized at the Hartree−Fock 6-31G* level using the Spartan program.

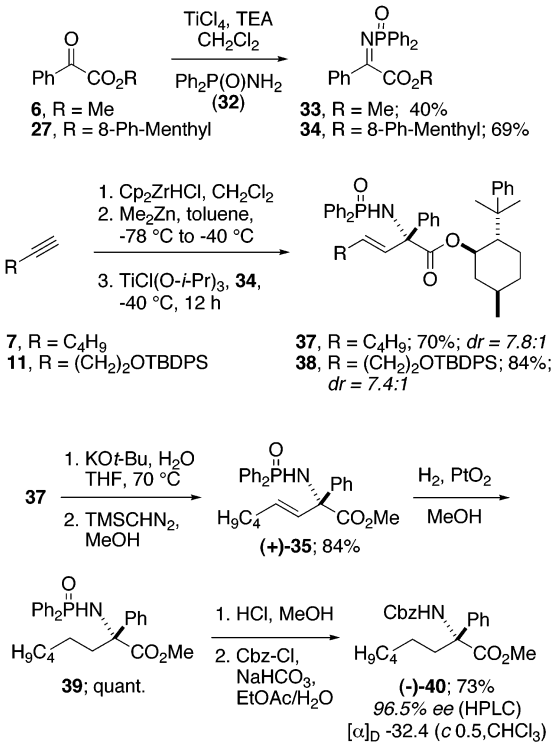
with the dipole-minimizing anti orientation of the carbonyl groups. The conformational rigidity rationalizes the outstanding facial selectivity observed in the nucleophilic addition to the 8-phenylmenthol ester, and this analysis is also in good agreement with Whitesell's π-stacking model for nucleophilic additions to esters with aryl auxiliaries.[20]

As a further extension of the scope of this methodology toward the preparation of α,α-disubstituted α-amino acid derivatives and 1,2-amino alcohols, we added alkenyl organometallics to α-*N*-diphenylphosphinoylimino esters (Scheme 3).[26] While the analogous *N*-tosylimines have been utilized previously,[27] this work represents the first report of nucleophilic additions to α-*N*-diphenylphosphinoylimino esters, which benefit from mild acidic deprotection conditions.[12]

Condensation of phosphonamide **32** with keto esters **6** and **27** in the presence of $TiCl_4$ and TEA afforded imino-esters **33** (40%) and **34** (69%), respectively.[28] Addition of 1.5 equiv of alkenylorganometallic reagent derived from alkynes **7** and **11** to imine **33** afforded allylic amides **35** (92%) and **36** (93%), respectively (Table 1). The analogous conversion of the chiral imino ester **34** at −20 °C afforded allylic amide **37** with modest diastereoselection (77%, dr = 5:1 by 600 MHz ^{1}H NMR). We envisioned that the stereoselectivity could be improved by precomplexing **34** with a Lewis acid. Indeed, after a quick survey of Lewis acids, precomplexation of **34** with 1 equiv of TiCl(O-*i*-Pr)$_3$ at −40 °C and treatment with 2 equiv of the alkenylorganometallics derived from alkynes **7** and **11** gave allylic amides **37** (70%; dr = 7.8:1) and **38** (84%; dr = 7.4:1), respectively. Saponification of the major isomer of **37** followed by methylation with $TMSCHN_2$ led to methyl ester (+)-**35** (84%). Hydrogenation (PtO_2, MeOH, quant), N-deprotection (HCl/MeOH), and Cbz-protection afforded (−)-**40** (73%). The configuration of this α,α-disubstituted α-amino acid derivative was assigned by comparison of the optical rotation of (−)-**40** with an

(23) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
(24) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978.
(25) Optical rotation $[\alpha]_D$ +2.15 (*c* 1.07, EtOH) was measured for **31**, which indicated an ee of >89% compared to the literature value[24] reported for this compound.
(26) Tye, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 275.
(27) Kulesza, A.; Jurczak, J. *Chirality* **2001**, *13*, 634.
(28) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.

Scheme 3. Formation of α,α-Disubstituted α-Amino Acids by Nucleophilic Addition to α-Imino Esters



authentic sample of (+)-**40** prepared independently using Seebach's methodology.[29,30]

In conclusion, the experimentally convenient protocol of in situ hydrozirconation−transmetalation to zinc can be extended to the 1,2-addition of vinyl organometallics to α-keto and α-imino esters. Functionalized tertiary allylic alcohols and amines are formed in good to excellent yields. The utility of this method has been further broadened by a highly diastereoselective variant using 8-phenylmenthol as a chiral auxiliary to afford chiral tertiary alcohols and α,α-disubstituted α-amino acids. The chiral auxiliary can be recovered and recycled in high yield. Further investigations into catalytic asymmetric additions to α-keto and α-imino esters will be reported in due course.

Acknowledgment. This work has been supported by a grant from the National Science Foundation (CHE-0078944).

Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR for **8**, **10**, **12**, **14**, **16**, **18**, **20**, **21**, **29**, **30**, **31**, and **33**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) (a) Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (b) O'Donnell, M. J.; Fang, Z.; Ma, X.; Huffman, J. C. *Heterocycles* **1997**, *46*, 617. (c) Ma, D.; Zhu, W. *J. Org. Chem.* **2001**, *66*, 348.

(30) Oxazolidinone **41** was alkylated with hexyl triflate at −78 °C followed by saponification with NaOMe/MeOH to give (+)-**40**.