CHEMCOMM Communication
www.rsc.org/chemcomm

Highly diastereoselective additions of methoxyallene and acetylenes to chiral α-keto amides†

So Won Youn, Yong Hae Kim,* Jeong-Wook Hwang and Youngkyu Do*

Center for Molecular Design & Synthesis, School of Molecular Science, Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon, 305-701, Korea. E-mail: kimyh@mail.kaist.ac.kr

Received (in Cambridge, UK) 9th January 2001, Accepted 24th April 2001
First published as an Advance Article on the web 15th May 2001

α-Keto amides bearing (*S*)-indoline chiral auxiliaries reacted with lithiated methoxyallene or lithium acetylides to produce the corresponding dihydrofuranones 7 through formation of the tertiary α-hydroxy allenes, or tertiary α-hydroxy acetylenes, respectively, at −78 °C with high diastereoselectivities (up to > 99% de).

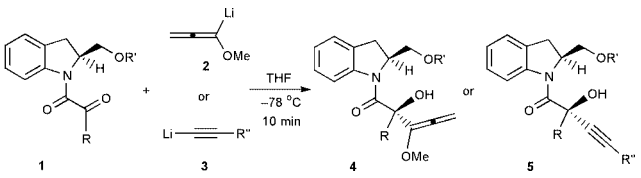
A number of diastereoselective nucleophilic additions of organometallic reagents to α-keto amides[1] bearing appropriate chiral auxiliaries have been reported as useful methods for the synthesis of optically active tertiary α-hydroxy acid derivatives, which are valuable for the asymmetric syntheses of medicinal agents and natural products.[2] Creating a tertiary alcohol center in which the stereochemistry can be controlled by a defined chiral environment in the addition of organometallic reagents to ketones still represents a significant challenge.[3]

Lithiated methoxyallene[4–6] is a promising nucleophile because the products produced by its addition to carbonyl compounds[7–8] can be converted into a variety of interesting compounds such as enones[9] or dihydrofuran derivatives.[10] In particular chiral propargylic alcohols[11] are useful intermediates in the synthesis of natural products.[2,12] Although a number of stereoselective additions of acetylides to aldehydes[11a–c] have been reported, asymmetric addition of acetylides to ketones to produce chiral tertiary alcohols is little known.[11d,e] A highly enantioselective addition of cyclopropanylacetylide to aryltrifluoromethyl ketone as a special substrate has been reported as the first example.[11d,e] However, a general method to prepare chiral tertiary α-hydroxy acetylenes has not yet been reported.

Recently, we reported that chiral α-keto amides derived from (*S*)-indoline-2-carboxylic acid resulted in high stereoselectivity in stereocontrolled additions of organometallics[1b] and allylation.[1c] On the supposition that these chiral α-keto amides might be good chiral auxiliaries, we examined the diastereoselective additions of lithiated methoxyallene **2** and lithium acetylides **3** to various chiral α-keto amides **1**.

The lithiated methoxyallene **2** was generated by treatment of methoxyallene (2.5 eq.) with *n*-BuLi (2.0 eq.) in THF at −78 °C for 30 min.[7b] Lithium acetylide **3** was prepared by addition of *n*-BuLi (1.5 eq.) to a solution of acetylene (1.7 eq.) in THF at 0 °C, followed by cooling to −78 °C after 30 min.[11a] Lithiated methoxyallene or lithium acetylide was reacted with α-keto amides at −78 °C in THF. Since the allene adducts **4** are generally labile[7b,c] so giving low yields (Table 1), the crude product **4** was reacted to obtain **6** without purification. Two equivalents of **2** were added to **1** at −78 °C in THF. The reaction mixture was stirred for 10 min at −78 °C and then quenched with distilled water. Extraction with CH_2Cl_2, drying over $MgSO_4$, and concentration gave crude product **4**, which was treated with a solution of *t*-BuOK (0.5 eq.) in DMSO at 50 °C. The reaction mixture was stirred for 1 h and then quenched with H_2O. Extraction with Et_2O, drying over $MgSO_4$, and concentration gave the crude residue, which was purified by column chromatography on SiO_2 to give dihydrofuran derivatives **6** which were treated with 5% HCl and extracted with diethyl ether and EtOAc at pH 11. The combined organic layers were dried over $MgSO_4$ and concentrated to give dihydrofuranones **7**. The results obtained are summarized in Table 2.

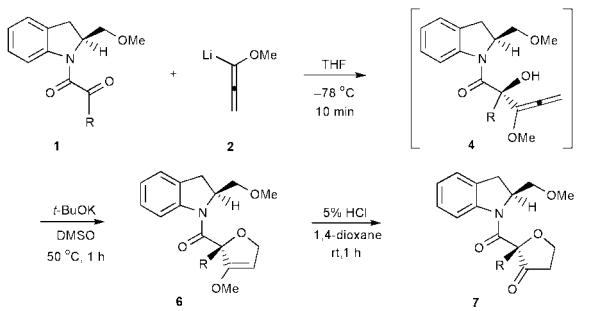
Table 1 Diastereoselective additions of lithiated methoxyallene **2** and lithium acetylides **3** to chiral α-keto amides **1**



Run	Substrate	R	R′	R″	Product	Yield (%)[a]	dr[b]
1	**1a**	Me	Me	—	**4a**	42	99:1
2	**1b**	Et	Me	—	**4b**	54	94:6
3	**1c**	*n*-Hex	Me	—	**4c**	45	98:2
4	**1d**	Ph	Me	—	**4d**	56	96:4
5	**1e**	Me	$SiMe_2Bu$-*t*	—	**4e**	32	80:20
6	**1f**	Ph	$SiMe_2Bu$-*t*	—	**4f**	33	83:17
7	**1a**	Me	Me	Ph	**5a**	71	98:2
8	**1b**	Et	Me	Ph	**5b**	91	94:6
9	**1d**	Ph	Me	Ph	**5c**	53	95:5
10	**1e**	Me	$SiMe_2Bu$-*t*	Ph	**5d**	62	99:1
11	**1a**	Me	Me	CH_2OMe	**5e**	72	99:1
12	**1a**	Me	Me	*n*-Bu	**5f**	88	99:1
13	**1a**	Me	Me	$SiMe_3$	**5g**[c]	66	> 99:1

[a] Isolated yields. [b] Determined by HPLC (Daicel chiral OD column). [c] R″ = H : $SiMe_3$ was removed.

Table 2 Transformation of crude products **4** to dihydrofuran derivatives **6** and 3(2*H*)-dihydrofuranones **7**



		6		**7**	
Run	R	Yield (%)[a,b]	dr[c]	Yield (%)[a]	dr[c]
1	Me **(1a)**	33 **(6a)**	> 99:1	80 **(7a)**	> 99:1
2	Et **(1b)**	41 **(6b)**	> 99:1	76 **(7b)**	> 99:1
3	*n*-Hex **(1c)**	35 **(6c)**	> 99:1	75 **(7c)**	> 99:1
4	Ph **(1d)**	44 **(6d)**	> 99:1	78 **(7d)**	> 99:1

[a] Isolated yields. [b] Overall yields from **1**. [c] Determined by ^1H NMR.

† Electronic supplementary information (ESI) available: synthesis and spectroscopic data for **4b**, **5g**, **6b** and **7b**. See http://www.rsc.org/suppdata/cc/b1/b100355k/

 DOI: 10.1039/b100355k

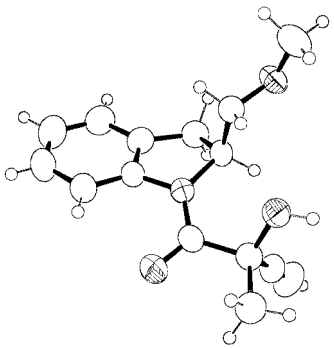
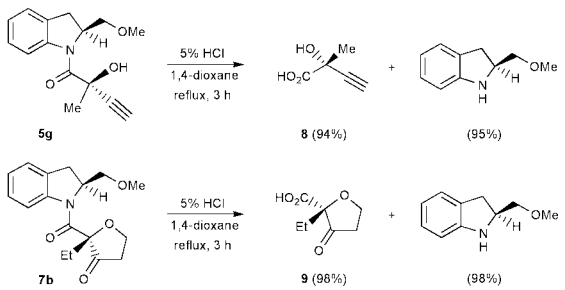


Fig. 1 X-Ray structure of **5g**.

The purified products **4**, **5** and **6** were identified by ^{1}H, ^{13}C NMR,[7b–d] IR and MS. The ratios of diastereomers were determined by HPLC using a chiral OD column. The absolute configuration of **5g** was determined by comparison of the specific rotation of **8** ($[\alpha]_D^{25}$ −40.2°, *c* = 1.7, acetone) with the literature value[13] ($[\alpha]_D^{24}$ −41.0°, c = 10, acetone) and its structure determined by X-ray analysis (Fig. 1).[14] The ratios of diastereomers were unaltered during the process. Compound **8** has been found in plant growth regulators[2e] and highly enantiomeric excess synthesis of **8** has not been reported previously.

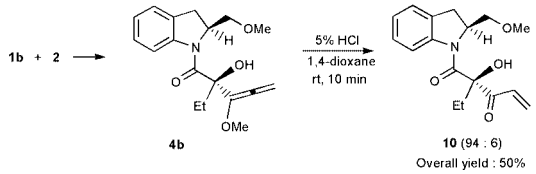
Enol ethers of 2,5-dihydrofuran derivatives **6** were readily hydrolyzed by HCl solution (H_2O:1,4-dioxane = 10:1) to provide the corresponding 3(2*H*)-dihydrofuranones **7** in good yields (75–80%), which are interesting intermediates as analogues of muscarone.[15b] Their structural element appears in other biologically active compounds[15] and their transformation to certain deoxy sugar derivatives can be performed. The indoline α-keto amides have a great advantage in terms of cleavage of the amide bond to give chiral products and recover the indoline chiral auxiliary.[1b,c,16] The cleavage of the amide bond of indoline amides is much easier than that of alkyl amides such as proline amides. For instance, the chiral products **5g** or **7b** were readily hydrolyzed with 5% HCl in 1,4-dioxane under reflux for 3 h to give the corresponding 2-hydroxy-2-methylbut-3-ynoic acid **8** or 2-ethyl-3(2*H*)-dihydrofuranone-2-carboxylic acid **9** in 94–98% yields, respectively, as shown in Scheme 1. The chiral auxiliary was recovered in 95–98% yield without loss of optical purity. Earlier work[11d,e] on asymmetric addition of acetylide to a ketone (not a chiral auxiliary) gave one chiral tertiary alcohol from a specific ketone leading to one compound. Our method, however, provides a general methodology to produce chiral tertiary α-hydroxy carboxylic acid acetylenes.



Scheme 1

Conversion of the hydroxyalkylated allenes into the α,β-unsaturated ketones under acidic conditions is also a useful reaction.[9] It is noteworthy that treatment of **4b** with 5% HCl provided enone **10** within 10 min at 25 °C as shown in Scheme 2. The ratio of diastereomers was also unaltered during hydrolysis. The enone moiety may be an interesting precursor for Michael-type additions or cycloadditions.[17]

In summary, it has been demonstrated that the reaction of α-keto amides derived from (*S*)-indoline-2-carboxylic acid with lithiated methoxyallene or lithium acetylide can provide useful



Scheme 2

intermediates, chiral tertiary α-hydroxy acid derivatives with high diastereoselectivities.

Notes and references

1 (*a*) K. Soai and M. Ishizaki, *J. Org. Chem.*, 1986, **51**, 3290; (*b*) Y. H. Kim, I. S. Byun and J. Y. Choi, *Tetrahedron: Asymmetry*, 1995, **6**, 1025; (*c*) Y. H. Kim and S. H. Kim, *Tetrahedron Lett.*, 1995, **36**, 6895; (*d*) C. H. Senanayake, K. Fang, P. Grover, R. P. Bakale, C. P. Vandenbossch and S. A. Wald, *Tetrahedron Lett.*, 1999, **40**, 819, and references therein.

2 (*a*) S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, New York, 1983, ch. 2; (*b*) D. W. McPherson and F. F. Knapp, *J. Org. Chem.*, 1996, **61**, 8335; (*c*) Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, 1993, **115**, 8451; (*d*) A. V. R. Rao, J. S. Yadav and M. Valluri, *Tetrahedron Lett.*, 1994, **35**, 3613; (*e*) W. L. White, K. L. Ricciardelli and M. K. Chaguturu, *US Pat.*, 4704161.

3 T. Akiyama, K. Ishikawa and S. Ozaki, *Synlett*, 1994, 275; D. A. Evans, M. C. Kozlowski, S. C. Burgey and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1997, **119**, 7893; J. L. Wood, B. M. Stoltz, H. J. Dietrich, D. A. Pflum and D. T. Petsch, *J. Am. Chem. Soc.*, 1997, **119**, 9641; P. I. Dosa and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 445.

4 F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, 1985, **50**, 5308.

5 S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 916.

6 For recent reviews of the chemistry of alkoxyallenes, see: R. Zimmer, *Synthesis*, 1993, 165; P. v. R. Schleyer, C. Lambert and E. U. Würthwein, *J. Org. Chem.*, 1993, **58**, 6377.

7 (*a*) D. Gange and P. Magnus, *J. Am. Chem. Soc.*, 1978, **100**, 7746; (*b*) S. W. Goldstein, L. E. Overman and M. H. Rabinowitz, *J. Org. Chem.*, 1992, **57**, 1179; (*c*) S. Hormuth and H.-U. Reissig, *J. Org. Chem.*, 1994, **59**, 67; (*d*) W. Schade and H.-U. Reissig, *Synlett*, 1999, 632.

8 P. Rochet, J.-M. Vatèle and J. Goré, *Synlett*, 1993, 105; T. Arnold, B. Orschel and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1033.

9 S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1968, **87**, 1179.

10 S. Hoff, L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1969, **88**, 609.

11 (*a*) T. Mukaiyama and K. Suzuki, *Chem. Lett.*, 1980, 255; (*b*) G. M. R. Tombo, E. Didier and B. Loubinoux, *Synlett*, 1990, 547; (*c*) E. J. Corey and K. A. Cimprich, *J. Am. Chem. Soc.*, 1994, **116**, 3151; (*d*) A. S. Thompson, E. G. Corley, M. F. Huntington and E. J. J. Grabowski, *Tetrahedron Lett.*, 1995, **36**, 8937; (*e*) L. Tan, C. Chen, R. D. Tillyer, E. J. J. Grabowski and P. J. Reider, *Angew. Chem., Int. Ed.*, 1999, **38**, 711; (*f*) D. A. Evans, D. P. Halstead and B. D. Allison, *Tetrahedron Lett.*, 1999, **40**, 4461; (*g*) Z. Li, V. Upadhyay, A. E. DeCamp, L. Di Michele and P. J. Reider, *Synthesis*, 1999, 1453; (*h*) D. E. Frantz, R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806.

12 K. C. Nicolaou and S. E. Webber, *J. Am. Chem. Soc.*, 1984, **106**, 5734; E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto and Y. Hamada, *Tetrahedron Lett.*, 1986, **27**, 2199; W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, 1994, **116**, 6457; D. Vourloumis, K. D. Kim, J. L. Petersen and P. A. Magriotis, *J. Org. Chem.*, 1996, **61**, 4848.

13 D. Dugat, M. Verny and R. Vessière, *Tetrahedron*, 1971, **27**, 1715.

14 *Crystal data* for **5g**: $C_{15}H_{17}NO_3$: M_r = 259.3, orthorhombic, space group $P2_12_12_1$, a = 10.300(2), b = 10.536(2), c = 25.810(6) Å, V = 2800.9(11) Å^3, Z = 8, D_c = 1.230 g cm^{-3}, $F(000)$ = 1104, μ(Mo-Kα) = 0.086 mm^{-1}, R_1 = 0.0333, wR_2 = 0.0404 for 2661 reflections ($F_o > 4\sigma(F_o)$). (Note two independent molecules which have the same configuration are contained in the unit cell of the crystal of **5g**.) The absolute configuration could not be determined (Flack parameter: –0.43 (76)). CCDC 156841. See http://www.rsc.org/suppdata/cc/b1/b100355k/ for crystallographic data in .cif or other electronic format.

15 (*a*) J. E. Semple and M. M. Joullié, *Heterocycles*, 1980, **14**, 1825; (*b*) M. DeAmici, C. Dallanoce, C. DeMicheli, E. Grana, A. Barbieri, H. Ladinsky, G. Schiavi and T. Zonta, *J. Med. Chem.*, 1992, **35**, 1915.

16 S. M. Kim, I. S. Byun and Y. H. Kim, *Angew. Chem., Int. Ed.*, 2000, **39**, 728.

17 For examples: W. Choy, L. A. Reed and S. Masamune, *J. Org. Chem.*, 1983, **48**, 1139.