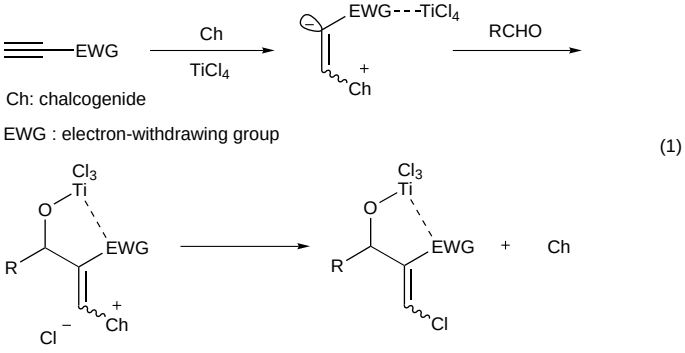
A Convenient Synthesis of α-Halomethylene Aldols or β-Halo-α-(hydroxyalkyl)acrylates Using the Chalcogeno-Baylis–Hillman Reaction**

Tadashi Kataoka,* Hironori Kinoshita, Sayaka Kinoshita, Tatsunori Iwamura, and Shin-ichi Watanabe

The Baylis–Hillman reaction is an efficient carbon–carbon bond-forming reaction that has become of major interest recently.[1] In the course of our studies into the reactions of alkynyl or alkenyl selenonium salts with sodium benzenesulfinate in an alcohol,[2] the chalcogenide-catalyzed Baylis–Hillman reaction was identified as the reverse reaction. After various attempts to find a good catalyst, we developed a reaction catalyzed by chalcogenides and $TiCl_4$, known as the chalcogeno-Baylis–Hillman reaction.[3] This reaction has some merits, namely, that it is complete within an hour[4] and can be applicable to thioesters[5] and ketoesters,[6] for which the Baylis–Hillman reaction gives unsatisfactory results. Dimethyl sulfide, cyclic chalcogenides, and bifunctional chalcogenides are used as the catalysts of the reactions.[4, 7, 8] Asymmetric synthesis using this procedure was attempted, although the enantiomeric excess of the products was not satisfactory.[8]

Most recently, we obtained α-chloromethyl aldols, the hydrogen chloride adducts of the Baylis–Hillman products, after purification of the raw products by column chromatography.[9] An examination of the mechanism of this reaction showed us that the chloride ion generated in the reaction process acts as an important nucleophile. Also, vinyl selenonium salts react with halide ions to give vinyl halides[10] through similar reaction pathways to the reactions of selenonium salts with alkoxides.[2] The outcome of these studies gave rise to the idea that acetylenic compounds should undergo the chalcogeno-Baylis–Hillman reaction [Eq. (1)]. The Baylis–Hillman reaction of active alkynes with aldehydes cannot proceed from the mechanistic viewpoint of the reaction. Therefore, β-branched acrylates, for example, are usually prepared from the reactions of α-metallated acrylates with aldehydes.[11, 12]

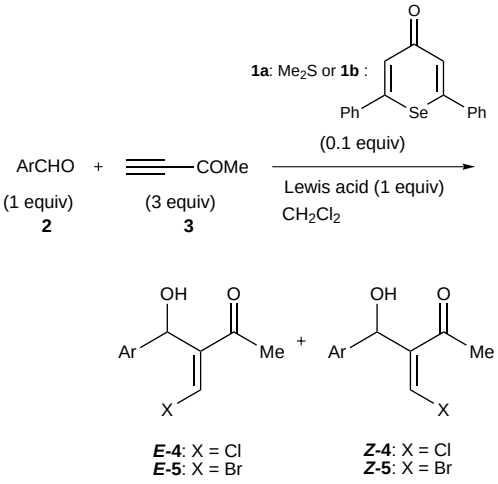


(1)

In this communication, we describe the chalcogeno-Baylis–Hillman reaction of active alkynes with aldehydes giving α-halomethylene aldols or β-halo-α-(hydroxyalkyl)acrylates. The products are highly functionalized by the four groups, that is, the carbon–halogen bond, the conjugated carbon–carbon double bond, the hydroxy group, and the carbonyl group, and can subsequently be transformed into a variety of useful compounds.[13]

Reactions of 3-butyn-2-one (**3**) with some benzaldehydes **2** were conducted [Eq. (2)], and the results are shown in Table 1. The reaction of **3** with *p*-nitrobenzaldehyde (**2a**) proceeded in the presence of dimethyl sulfide (**1a**, 0.1 equiv) and $TiCl_4$ (1 equiv) at 0 °C for 2 h to give the α-chloromethylene aldol **4a** in 86% yield (Entry 1). The product contained the *E* isomer only, and its geometry was determined by NOE enhancement of the ^{1}H NMR spectrum. Reactions with other aldehydes, **2b**–**d**, gave adducts **4b**–**d**, respectively, in high yields (Entries 3–5). The reaction using 2,6-diphenylselenopyran-4-one (**1b**) was slower than that using dimethyl sulfide (**1a**)—achieving a satisfactory result took 5 h at room temperature. Interestingly, the reaction proceeded without chalcogenide to give the product **4a** in 84% yield in an isomer ratio $E:Z = 1:1$ (Entry 7). This finding showed that

Table 1. Reactions of 3-Butyn-2-one (**3**) with Aldehydes (**2**).[a]



(2)

Entry	Ar (ArCHO)	Catalyst	Product	Yield [%]	*E*:*Z* Ratio
1	*p*-$NO_2C_6H_4$ (**2a**)	**1a**/$TiCl_4$	**4a**	86%	*E* only
2	*p*-$NO_2C_6H_4$ (**2a**)	**1b**/$TiCl_4$	**4a**	89%	*E* only
3	*p*-$CF_3C_6H_4$ (**2b**)	**1a**/$TiCl_4$	**4b**	73%	*E* only
4	*p*-ClC_6H_4 (**2c**)	**1a**/$TiCl_4$	**4c**	73%	*E* only
5	*p*-FC_6H_4 (**2d**)	**1a**/$TiCl_4$	**4d**	89%	*E* only
6	*p*-$NO_2C_6H_4$ (**2a**)	**1a**/$TiBr_4$	**5a**	63%	*E* only
7	*p*-$NO_2C_6H_4$ (**2a**)	$TiCl_4$	**4a**	84%	1:1
8	*p*-$NO_2C_6H_4$ (**2a**)	$TiBr_4$	**5a**	49%	*E* only

[a] All reactions were performed at 0 °C for two hours with the exception of the reaction in entry 2, which took place at room temperature for five hours.

[*] Prof. Dr. T. Kataoka, H. Kinoshita, S. Kinoshita, Dr. T. Iwamura, S.-i. Watanabe
Gifu Pharmaceutical University
6-1 Mitahora-higashi 5-chome, Gifu 502-8585 (Japan)
Fax: (+81) 58-237-5979
E-mail: kataoka@gifu-pu.ac.jp

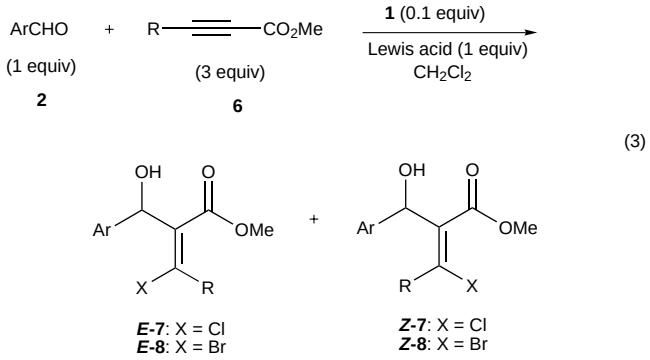
[**] This work was supported in part by a Grant-in-Aid for Scientific Research (Priority Areas Nos. 10133244 and 11120247) from the Ministry of Education, Science, Sports, and Culture, Japan.

  0044-8249/00/11213-2448 $ 17.50+.50/0

the chloride ion generated from $TiCl_4$ acted as a nucleophile, but the isomer ratios between the products of entries 1 and 7 were quite different. Very recently, Li and co-workers reported a $TiCl_4$-mediated Baylis–Hillman reaction.[14] The reaction with $TiBr_4$ afforded the α-bromomethylene aldol **5a** in 49% yield (Entry 8).

Next, reactions of alkyne carboxylic acid esters with aromatic aldehydes were examined [Eq. (3)]. The results are summarized in Table 2. The reaction of methyl propiolate (**6a**) with *p*-nitrobenzaldehyde (**2a**) at room temperature for

Table 2. Reactions of Alkyne Carboxylic Acid Esters (**6**) with Aldehydes (**2**).[a]



(3)

Entry	Ar (ArCHO)	R (Ester)	Catalyst	t [h]	Product	Yield [%]	E:Z Ratio
1	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1a**/$TiCl_4$	24	**7a**	53	1:4
2	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1a**/$TiCl_4$	41	**7a**	70	1:6
3	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1a**/$TiCl_4$	64	**7a**	75	1:7
4	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1a**/$TiCl_4$[b]	50	**7a**	34	1:3
5	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1b**/$TiCl_4$	24	**7a**	5	ND[c]
6	*p*-$CF_3C_6H_4$ (**2b**)	H (**6a**)	**1a**/$TiCl_4$	50	**7b**	36	1:1.6
7	*p*-ClC_6H_4 (**2c**)	H (**6a**)	**1a**/$TiCl_4$	50	**7c**	47	1:7
8	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	**1a**/$TiCl_4$	50	**8**	37	1:2
9	*p*-$NO_2C_6H_4$ (**2a**)	Me (**6b**)	**1a**/$TiCl_4$	50	**7d**	25	1:1
10	*p*-$NO_2C_6H_4$ (**2a**)	CO_2Me (**6c**)	**1a**/$TiCl_4$	50	**7e**	31	*Z* only
11	*p*-$NO_2C_6H_4$ (**2a**)	H (**6a**)	$TiCl_4$	50	–[d]	–[d]	–[d]

[a] All reactions were performed at room temperature. [b] One equivalent of **1a** was used, rather than a catalytic quantity. [c] ND = not determined. [d] No reaction took place.

24 h produced adduct **7a** in 53% yield with a ratio of E:Z = 1:4 (Entry 1). Prolonged reaction time increased the yield (Entry 3), but use of one equivalent of **1a**, rather than a catalytic quantity, decreased it (Entry 4). The reaction using 2,6-diphenylselenopyran-4-one (**1b**) as a Lewis base afforded the product **7a** in only 5% yield (Entry 5). Use of $TiBr_4$ as a Lewis acid gave β-bromoacrylate **8** in low yield. Similarly, *p*-trifluoromethyl- and *p*-chlorobenzaldehydes **2b** and **2c** gave the products **7b** and **7c**, respectively, in low yields (Entries 6 and 7). The reaction catalyzed by only $TiCl_4$ did not afford the product **7a** (Entry 11). These results indicate that **6a** was less reactive than 3-butyn-2-one (**3**) and also that dimethyl sulfide (**1a**) worked as an important catalyst for the reactions. The isomer distribution was *Z* isomer predominant and opposite to that obtained with ketone **3**. β-Substituted alkyne carboxylate **6b** and dimethyl acetylenedicarboxylate **6c** provided the adducts **7d** and **7e** in 25% and 31% yields, respectively (Entries 9 and 10).

In summary, we have described the chalcogeno-Baylis-Hillman reaction of active alkynes as an efficient synthetic method for α-halomethylene aldols or β-halo-α-(hydroxybenzyl)acrylates. The asymmetric synthesis and application of this chemistry in the synthesis of bioactive compounds are currently under investigation.

Experimental Section

4a: *p*-Nitrobenzaldehyde (**2a**; 76 mg, 0.5 mmol) and methyl sulfide (**1a**; 3 mg, 0.05 mmol) were added to a solution of 3-butyn-2-one (**3**; 102 mg, 1.5 mmol) in anhydrous dichloromethane (1.5 mL). $TiCl_4$ (55 μL, 0.5 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h and then quenched by addition of saturated aqueous $NaHCO_3$ solution (1.5 mL). The inorganic precipitate was removed by filtration through celite, and the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel with hexane/ethyl acetate (1/1) to give (*E*)-4-chloro-3-[1-hydroxy-1-(4-nitrophenyl)methyl]-3-buten-2-one ((***E***)-**4a**) in 86% yield. (***E***)-**4a**: m.p. 117 °C (from hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3), 4.41 (d, J = 11 Hz, 1H, OH), 6.01 (d, J = 11 Hz, 1H, benzylic H), 7.56 (s, 1H, vinyl H), 7.55 and 8.19 (each d, J = 8.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$; * denotes two overlapping signals): δ = 26.9, 70.1, 123.7*, 126.0*, 136.9, 142.5, 147.3, 148.9, 197.9; elemental analysis calcd (%) for $C_{11}H_{10}ClNO_4$: C 51.68, H 3.94, N 5.48; found: C 51.66, H 3.99, 5.47.

The (***Z***)-**4a** isomer was also obtained from the reaction of **2a** with **3** in the presence of $TiCl_4$. (***Z***)-**4a**: m.p. 113–114 °C (from hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3H, CH_3), 3.42 (d, J = 6 Hz, 1H, OH), 5.62 (d, J = 6 Hz, 1H, benzylic H), 6.81 (s, 1H, vinylic H), 7.55 and 8.23 (each d, J = 8.5 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$; * denotes two overlapping signals): δ = 32.2, 73.7, 123.7*, 127.1*, 132.1, 142.7, 147.5, 147.9, 200.6; elemental analysis calcd (%) for $C_{11}H_{10}ClNO_4$: C 51.68, H 3.94, N 5.48; found: C 51.86, H 4.03, N 5.38.

Received: January 11, 2000 [Z 14524]

[1] K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; A. B. Baylis, M. E. D. Hillman (Celanese Corp.), German Patent, **1972**, 2155113 [*Chem. Abstr.* **1972**, *77*, 34174q]; H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1983**, *95*, 795–796; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795–796; J. Rabe, H. M. R. Hoffmann, *Angew. Chem.* **1983**, *95*, 796–797; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 796–797; for reviews, see: S. E. Drewes, G. H. P. Roos, *Tetrahedron* **1988**, *44*, 4653–4670; D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062; E. Ciganek in *Organic Reactions, Vol. 51* (Ed.: L. A. Paquette), John Wiley & Sons, Inc., New York, **1997**, pp. 201–350.

[2] T. Kataoka, Y. Banno, S. Watanabe, T. Iwamura, H. Shimizu, *Tetrahedron Lett.* **1997**, *38*, 1809–1812; S. Watanabe, K. Yamamoto, Y. Itagaki, T. Kataoka, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2053–2055.

[3] T. Kataoka, T. Iwama, S. Tsujiyama, *Chem. Commun*. **1998**, 197–198.

[4] T. Kataoka, T. Iwama, S. Tsujiyama, T. Iwamura, S. Watanabe, *Tetrahedron* **1998**, *54*, 11813–11824.

[5] T. Kataoka, T. Iwama, H. Kinoshita, S. Tsujiyama, Y. Tsurukami, T. Iwamura, S. Watanabe, *Synlett* **1999**, 197–198.

[6] D. Basavaiah, K. Muthukumaran, B. Sreenivasulu, *Synlett* **1999**, 1249–1250.

[7] T. Iwama, H. Kinoshita, T. Kataoka, *Tetrahedron Lett*. **1999**, *40*, 3741–3744.

[8] T. Kataoka, T. Iwama, S. Tsujiyama, K. Kanematsu, T. Iwamura, S. Watanabe, *Chem. Lett*. **1999**, 257–258; T. Iwama, S. Tsujiyama, H. Kinoshita, K. Kanematsu, Y. Tsurukami, T. Iwamura, S. Watanabe, T. Kataoka, *Chem. Pharm. Bull.* **1999**, *47*, 956–961.

[9] T. Kataoka, H. Kinoshita, T. Iwama, S. Tsujiyama, T. Iwamura, S. Watanabe, O. Muraoka, G. Tanabe, *Tetrahedron*, submitted.

[10] T. Kataoka, S. Watanabe, unpublished results.

[11] Copper: J. P. Marino, R. J. Linderman, *J. Org. Chem.* **1981**, *46*, 3696–3702; J. P. Marino, R. J. Linderman, *J. Org. Chem.* **1983**, *48*, 4621–

4628; H.-X. Wei, S. Willis, G. Li, *Tetrahedron Lett.* **1998**, *39*, 8203–8206.
[12] Aluminum: Y. Genisson, C. Massardier, I. Gautier-Luneau, A. E. Greene, *J. Chem. Soc. Perkin. Trans. 1* **1996**, 2869–2872; P. V. Ramachandran, M. V. R. Reddy, M. T. Rudd, J. R. de Alaniz, *Tetrahedron Lett*. **1998**, *39*, 8791–8794; G. Li, H.-X. Wei, B. R. Whittlesey, N. N. Batrice, *J. Org. Chem.* **1999**, *64*, 1061–1064; P. V. Ramachandran, M. V. R. Reddy, M. T. Rudd, J. R. de Alaniz, *Tetrahedron Lett*. **1999**, *40*, 627–630.
[13] V. J. Lee in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 125; A. B. Smith, S. N. Kilenyi, *Tetrahedron Lett*. **1985**, *26*, 4419–4422; R. C. Larock, K. Narayanan, S. S. Hershberger, *J. Org. Chem*. **1983**, *48*, 4377–4380.
[14] G. Li, H.-X Wei, J. J. Gao, T. D. Caputo, *Tetrahedron Lett.* **2000**, *41*, 1–5.

Base-Specific Minor Groove Site Binding in Metallo-Nucleobase Polymers**

Michelle A. Shipman, Clayton Price, Mark R. J. Elsegood, William Clegg, and Andrew Houlton*

The use of metal–ligand bond formation to generate extended molecular assemblies is now a well established aspect of supramolecular chemistry.[1] Recently this approach has been combined with the use of organic ligands which possess hydrogen-bonding functionalities in an effort to further introduce directional interactions for structure building.[1, 2] Nucleobases are a useful set of building blocks for forming such structures through a combination of these interactions, and this has been demonstrated in particular in the work of Lippert.[3] Here we report crystal and molecular structures of two nucleobase coordination polymers containing adenine and guanine. These were formed from reactions of Cu^{II} ions with the respective purine bases derivatized with an alkyldiamine tether.[4] Analysis of the resulting polymers reveals a base-specific metal ion binding to the minor groove site N3, with coordination observed only with adenine, and formation of a polynucleotide analogue in the case of guanine.

Aqueous solutions containing equimolar equivalents of $Cu(NO_3)_2$ and the appropriate nucleobase–alkyldiamine (ethylenediamine-N9-ethylguanine, G-Et-en, and ethylenediamine-N9-ethyladenine, A-Et-en) as the hydrochloride salt showed evidence for the formation of Cu:L complexes in the UV/Vis spectra (characteristic band at $\lambda = 650$ nm).[5] This was also supported by electrospray mass spectrometry data with both solutions indicating the presence of the appropriate $[CuL(NO_3)]^+$ cation (m/z: 362, L = Et-G-en; 346, L = Et-A-en). Slow evaporation of these solutions yielded crystals suitable for single crystal X-ray analyses.[6]

Compound **1**, $[Cu(Et\text{-}N7\text{-}G\text{-}en)(H_2O)_2][NO_3]Cl \cdot (H_2O)_x$, is a coordination polymer in which the metal ion adopts a square pyramidal configuration with a {3N:2O} coordination sphere (Figure 1). The three nitrogen donor atoms are provided by the diamine function of one ligand and the N7 of the guanine from a second ligand. The extended structure contains stacked guanine bases which are rotated by 90° and inclined at 9.6° with respect to the nearest neighbor (related by a crystallographic fourfold screw axis). The 6-membered rings of the purine heterocycles in the stack lie above one another at a separation of approximately 3.157 Å. Figure 2a shows the bond density representation of the polymer chain to highlight the polymer shape. The helical arrangement has a pitch of 12.627 Å (the unit cell c-axis) and the copper ions spiral around the outside of the helical structure with a distance of 6.984 Å between adjacent metal ions in the backbone. Interestingly, this is close to the intrastrand P···P distance observed in duplex B-DNA (approximately 6.7 Å).[7]

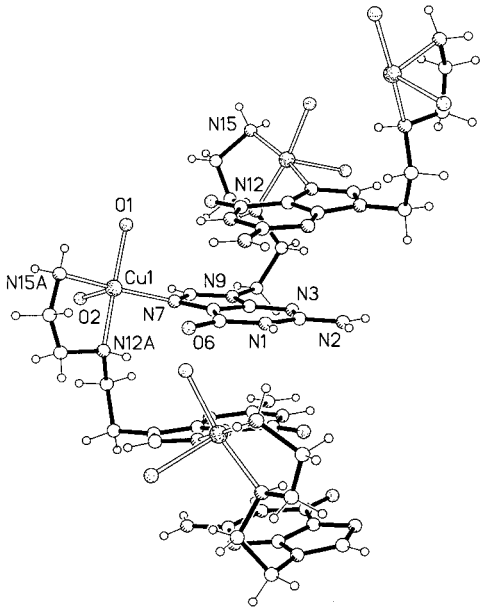


Figure 1. Polymeric chain in **1** formed by coordination through N7 and the diamine function. Metal–ligand bond lengths: Cu-O1 2.012(5), Cu-O2 2.315(7), Cu-N7 1.992(7), Cu-N12A 2.027(6), Cu-N15A 1.977(8) Å. The nucleobase lies at an angle of 70.9° to the plane formed by basal donor atoms (N7/O1/N12A/N15A), with the copper ion lying 0.208 Å above this plane. Each of the guanine residues is hydrogen bonded to uncoordinated nitrate anions ($O4NO_3^-\cdots$ N2 2.873 and $O3NO_3^-\cdots$ N1 2.874 Å).

In fact, **1** may be considered as a cationic polyguaninyl analogue and bears relevance to several aspects of DNA chemistry. For instance, antisense technology requires a means to enhance the binding between target and probe strands.[8] Cationic oligonucleotides based on metal ion linkages, as in **1**, may be an effective approach to this problem.

The analogous adenine complex, $[CuCl(Et\text{-}A\text{-}en)][NO_3] \cdot H_2O$ (**2**), is also polymeric with square pyramidal Cu^{II} ions and a {4N:Cl} donor set of ligands. However, the individual polymer chains exhibit a markedly different topology relative

[*] Dr. A. Houlton, M. A. Shipman, Dr. C. Price, Dr. M. R. J. Elsegood, Prof. W. Clegg
Department of Chemistry
University of Newcastle upon Tyne
Newcastle upon Tyne, NE1 7RU (UK)
Fax: (+44) 191-222-6929
E-mail: andrew.houlton@ncl.ac.uk

[**] This work was financially supported by the EPSRC and the BBSRC. The EPSRC mass spectrometry service at the University of Wales, Swansea, is acknowledged.

  0044-8249/00/11213-2450 $ 17.50+.50/0