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Diastereodivergent Addition of Allenylzincs to Aryl Glyoxylates

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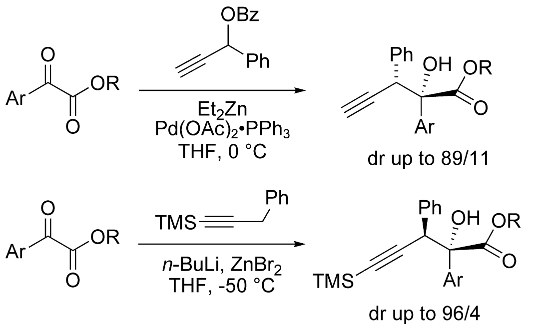
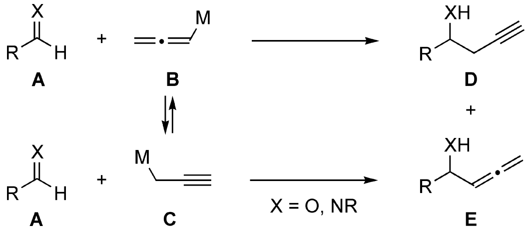
ABSTRACT



A diastereodivergent addition of allenylzincs to aryl glyoxylates was observed depending on the method used for the preparation of the allenylzinc reagent. The allenylzincs were prepared from propargylic benzoates in the presence of a palladium catalyst or by metalation of alkynes.

The addition of allenylmetals to aldehydes and imines has been used extensively to synthesize homopropargylic alcohols and amines, respectively.[1] When aldehydes or imines **A** are treated with allenylmetals, a mixture of homopropargylic and allenic products **D** and **E** is observed, due to an equilibrium between allenylmetal of type **B** and propargylmetal **C** (Scheme 1). The ratio between **D** and **E** depends on the metal. It is worth noting that the addition of allenylzincs to aldehydes proceeds with high regioselectivity to afford homopropargylic alcohols.

Scheme 1. Addition of Allenyl/Propargylmetals to Imines and Aldehydes



Whereas α-ketoesters have been frequently transformed to the corresponding α-hydroxyesters when treated with organometallic reagents, the addition of allenylmetals to α-ketoesters has been rarely studied.[2] Here, we would like to report that tertiary homopropargylic alcohols of type **H** can be obtained in good yields from aryl glyoxylates **F** by addition of 3-phenylallenylzinc **G** generated either from propargylic benzoate using $Pd(OAc)_2•PPh_3/Et_2Zn$ or by metalation of 1-(trimethylsilyl)-3-phenylprop-1-yne (Scheme

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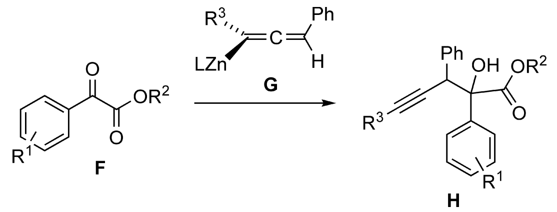
(1) (a) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 2, 81. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Marshall, J. A. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2006; Vol. 1, 421. (d) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153.

10.1021/ol900494g CCC: $40.75

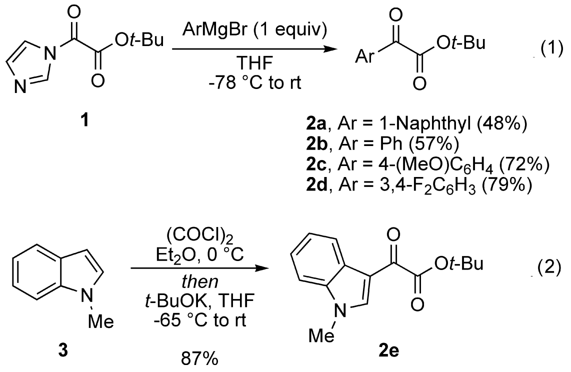
2). Furthermore, depending on the experimental conditions used for the generation of allenylzinc **G**, a divergent diastereoselectivity was observed in providing compound **H**.

Scheme 2. Addition of 3-Phenylallenylzincs to Aryl Glyoxylates



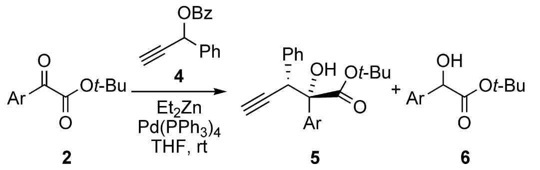
Aryl glyoxylates **2a**−**d** were synthesized by addition of Grignard reagents to (imidazoyl)glyoxylate **1**.[3] The aryl glyoxylates **2a**−**d** were isolated in 48−79% yields (Scheme 3, eq 1). Glyoxylate **2e** was obtained by nucleophilic attack of *N*-methylindole **3** to oxalyl chloride, followed by the transformation of the acyl chloride intermediate to *tert*-butyl ester **2e** by addition of *t*-BuOK (Scheme 3, eq 2).

Scheme 3. Synthesis of Aryl Glyoxylates



The addition of an allenylzinc to compounds **2a**−**e** was then examined. The preparation of 3-phenylallenylzinc of type **G** (R^3 = H) has been described by Tamaru *et al.* from benzoate **4** (1.2 equiv) by treatment with Pd(PPh$_3$)$_4$ (5 mol %) in the presence of diethylzinc (3.6 equiv).[4] Following this procedure, the addition of the allenylzinc, generated from **4**, to aryl glyoxylates **2a** and **2b** provided compounds **5a** (54%) and **5b** (65%) with a diastereomeric ratio of 75/25 and 89/11, respectively. The moderate yields of **5** were due to the reduction of aryl glyoxylates **2** by diethylzinc, leading to 2-aryl-2-hydroxyacetates **6** as significant byproducts (29% and 16%) (Table 1).[5] It is worth mentioning that decreasing the quantity of diethylzinc or the temperature to 0 °C did not provide better yields in **5**, and these latter conditions did not prevent the formation of compound **6**.

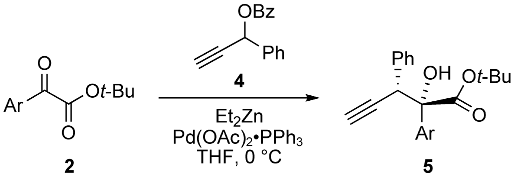
Table 1. Reactivity of Allenylzinc Prepared from **4** Using Pd(PPh$_3$)$_4$/Et$_2$Zn



2	Ar	**5** (dr, yield %)			**6** (yield %)
2a	1-naphthyl	**5a**	75/25	54	29
2b	Ph	**5b**	89/11	65	16

The addition of the allenylzinc, generated from propargylic benzoate **4** according to the procedure described by Marshall *et al.*,[6] to aryl glyoxylates **2** was then examined. Thus, the addition of the allenylzinc generated by treatment of propargylic benzoate **4** (3 equiv) with Pd(OAc)$_2$·PPh$_3$ in a 1:1 ratio (10 mol %) and diethylzinc (6 equiv) to compounds **2a**−**c** and **2e** afforded the corresponding homopropargylic alcohols **5a**−**c** and **5e** in good yields (68−88%) with diastereomeric ratios ranging from 85/15 to 89/11. We have to point out that no traces of the reduction products **6** were detected by using these conditions (Table 2).[7] However, treatment of aryl glyoxylate **2d** led to a complex mixture of products.

Table 2. Reactivity of Allenylzinc Prepared from **4** Using Pd(OAc)$_2$·PPh$_3$/Et$_2$Zn



Ar	**5**	dr	yield (%)
1-naphthyl	**5a**	87/13	88
Ph	**5b**	85/15	80
4-(MeO)C$_6$H$_4$	**5c**	89/11	86
3-*N*-Me-indolyl	**5e**	87/13	68

As allenylzincs can also be formed by metalation of alkynes, compound **7** was first treated with *n*-BuLi, and then

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(2) (a) Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Org. Chem.* **1986**, *51*, 886. (b) McPherson, D. W.; Lambert, C. R.; Jahn, K.; Sood, V.; McRee, R. C.; Zeeberg, B.; Reba, R. C.; Knapp, F. F., Jr. *J. Med. Chem.* **1995**, *38*, 3908. (c) Clive, D. L. J.; Zhou, Y.; Pires de Lima, D. *Chem. Commun.* **1996**, 1463. (d) McCluskey, A.; Muderawan, I. W.; Muntari; Young, D. J. *J. Org. Chem.* **2001**, *66*, 7811.

(3) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211.

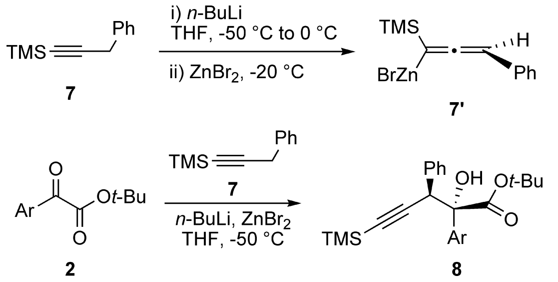
(4) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878.

(5) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249.

(6) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

a transmetalation was achieved using zinc bromide to produce the desired 3-phenylallenylzinc **7′**, which was then added to glyoxylates **2a**−**e**.[8] The desired α-hydroxyesters **8** were isolated, but a dramatic change in the diastereoselectivity was observed as the major isomer obtained under these conditions corresponds to the minor isomer obtained by using the conditions developed by Tamaru *et al*. or Marshall *et al*. Compounds **8** were obtained in good yields (80−99%) and with diastereomeric ratios ranging from 64/36 (Ar = 3,4-$F_2C_6H_3$) to 88/12 (Ar = 1-naphthyl) (Table 3). Desilylation of compounds **8** (K_2CO_3, MeOH, rt) and comparison of the spectral data of the resulting desilylated alkynes with those of **5** showed that compounds **5** and **8** had the opposite relative stereochemistry.

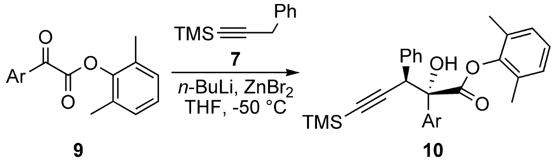
Table 3. Reactivity of Allenylzinc Generated by Metalation of **7**



Ar	8	dr	yield (%)
1-naphthyl	**8a**	88/12	88
Ph	**8b**	65/35	92
4-(MeO)C_6H_4	**8c**	71/29	95
3,4-$F_2C_6H_3$	**8d**	64/36	80
3-*N*-Me-indolyl	**8e**	73/27	99

It is worth noting that for the addition of 3-phenylallenylzinc, generated by metalation of **7**, to ethyl 2-(naphthalen-1-yl)-glyoxylate resulted in a poor diastereoselectivity as a diastereomeric ratio of 1/1 was observed. The diastereoselectivity was therefore sensitive to the steric hindrance of the ester group. Bulky 2,6-dimethylphenyl esters **9a**−**c** were then examined. These latter compounds were obtained by hydrolysis of *tert*-butyl esters **2a**−**c** and esterification of the resulting carboxylic acids with 2,6-dimethylphenol (DCC, DMAP, CH_2Cl_2, rt).[9] Treatment of **9a**−**c** with the allenylzinc generated by metalation of **7** (*n*-Buli, $ZnBr_2$) led to homopropargylic alcohols **10a**−**c** in good yields and with diastereomeric ratios from 78/22 to 96/4 (Table 4). As expected, the diastereomeric ratios were better with 2,6-dimethylphenyl esters **9** than with *tert*-butyl esters **2**.

Table 4. Addition of Allenylzinc **7′** to 2,6-Dimethylphenyl Aryl Glyoxylates

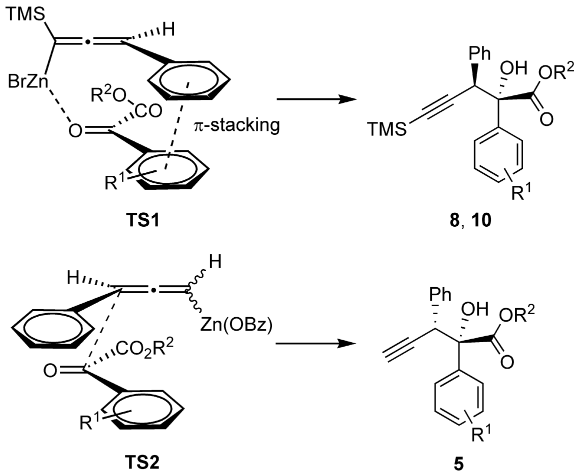


Ar	10	dr[a]	yield (%)
1-naphthyl	**10a**	96/4 (88/12)	85
Ph	**10b**	78/22 (65/35)	82
4-(MeO)C_6H_4	**10c**	92/8 (71/29)	63

[a] dr in parentheses refer to the corresponding *tert*-butyl ester **8**.

In order to explain the divergent diastereoselectivity in the propargylation of aryl glyoxylates, two different transition states can be proposed. When the allenylzinc reagent is prepared by metalation of alkyne **7**, a coordination of allenylzinc bromide to the ketone and a stabilizing π-stacking interaction between the aromatic groups can take place in a cyclic transition state **TS1** leading to compounds **8** and **10** (Scheme 4).[1,10] In **TS1**, an increase of the steric hindrance of the ester group would increase the diastereoselectivity which is in accordance with the obtained experimental

Scheme 4. Proposed Transition States



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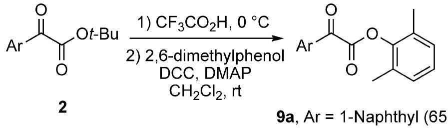
(7) The relative configuration of compound **5b** was unambiguously ascertained by its transformation into (2*S**,3*R**)-2,3-diphenylpent-4-ene-1,2-diol which has been described in the literature: (a) Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442. The relative configuration of the other compounds **5a**, **5c**, and **5e** was assigned by analogy.

(8) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553.

(9) Synthesis of 2,6-dimethylphenyl glyoxylates **9**:



9a, Ar = 1-Naphthyl (65%)
9b, Ar = Ph (57%)
9c, Ar = 4-(MeO)C_6H_4 (93%)

(10) (a) Saniere-Karila, M.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1973**, 3371. (b) Favre, E.; Gaudemar, M. *J. Organomet. Chem.* **1975**, *92*, 17.

results. On the other hand, an open transition state **TS2** could account for the diastereoselectivity observed in compounds **5**, issued from the addition of the allenylzinc generated with $Pd(OAc)_2 \cdot PPh_3/Et_2Zn$ to aryl glyoxylates **2**.[11]

Depending on the conditions used to generate the allenylzincs, the addition of these latter to aryl glyoxylates produced diastereomeric tertiary homopropargylic alcohols. The use of these allenylzincs to synthesize biologically active compounds is under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] For examples of open transition states with allenylzincs, see: (a) Bernaud, F.; Vrancken, E.; Mangeney, P. *Synlett* **2004**, 1080. (b) Ferreira, F.; Denichoux, A.; Chemla, F.; Bejjani, J. *Synlett* **2004**, 2051.