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Pinacol Coupling Reaction of *β*-Halo-α,*β*-unsaturated Aldehydes Promoted by TiI_4

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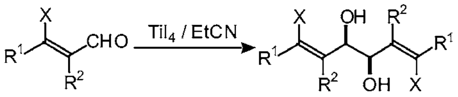
ABSTRACT



The pinacol reaction of *β*-halogenated α,*β*-unsaturated aldehydes was promoted by titanium tetraiodide to give coupling products in good yields with high *dl*-selectivity. Subsequent reduction with H_2/Pd–C gave saturated *vic*-diols in good yields. Heck coupling reaction enabled the displacement of halogens with vinyl groups without the loss of stereochemical integrities.

A number of 1,2-diols have been utilized as useful synthons for the synthesis of biologically important compounds such as HIV protease inhibitors and natural products,[1] and several approaches to their syntheses have been described. Among them, the pinacol coupling reaction constitutes one of the most straightforward methods.[2] Recently, high diastereoselectivity, catalytic use of active species, and cross-coupling have been attained in such reactions.[3] Use of low-valent metals such as titanium,[4] zirconium,[5] vanadium,[6] samarium,[7] and so on is, in principle, needed for promoting the pinacol coupling, because, for a majority of cases, the reaction proceeds via a single-electron-transfer mechanism.

We have been interested in the reaction using titanium tetraiodide, which possesses good reducing ability for various substrates, including ketones, imines, and sulfoxides,[8] and we have already reported that the pinacol coupling of aromatic aldehydes is conducted under the influence of titanium tetraiodide. However, the titanium tetraiodide could not sufficiently promote the pinacol coupling reaction of

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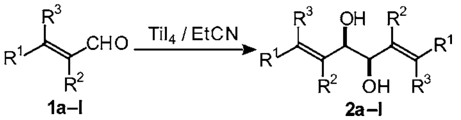
aliphatic aldehydes due to its mild reducing ability.[9] Many useful 1,2-diols are aliphatic; therefore, precursors for aliphatic derivatives were sought. After screening a series of substrates, we have found that α,β-unsaturated aldehydes possessing a halogen serve as excellent substrates for pinacol coupling, and the subsequent hydrogenation furnished saturated 1,2-diols in good overall yields. Herein we report the pinacol coupling of β-halo α,β-unsaturated aldehydes promoted by titanium tetraiodide. The results of the pinacol coupling reaction of α,β-unsaturated aldehydes are summarized in Table 1.[10]

Table 1. Pinacol Coupling Reaction of α,β-Unsaturated Aldehyde

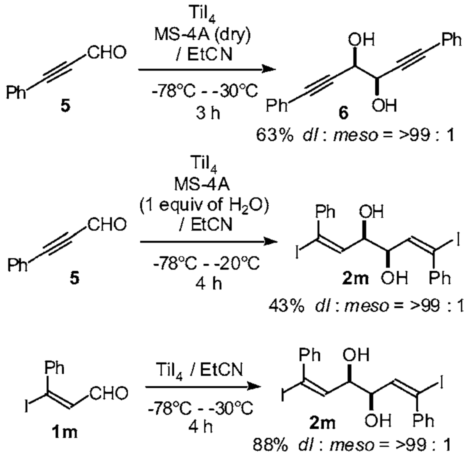


entry	R¹	R²	R³	temp (°C)	time (h)	yield (%)[a]	*dl*:*meso*[b]
1: **a**	Ph	H	H	from −78 to −20	2.5	83	>99:1
2: **b**	Ph	H	Cl	from −78 to −70	0.5	87	>99:1
3: **c**	Ph	H	Br	from −78 to −50	1.5	85	>99:1
4: **d**	Ph	H	I	from −78 to −20	4.0	88	>99:1
5: **e**	Ph	Br	H	from −78 to 0	6.5	68	>99:1
6: **f**	*n*-Pr	H	H	from −78 to −10	3.5	16	>99:1
7: **g**	*n*-Pr	H	Br	from −78 to −20	2.5	82	>99:1
8: **h**	*n*-Pr	H	I	from −78 to 0	5.0	72	>99:1
9: **i**	*t*-Bu	H	H	from −78 to rt	20	0	
10: **j**	*t*-Bu	H	Cl	from −78 to rt	10	57	93:7
11: **k**	$-(CH_2)_4-$		H	from −78 to rt	24	0	
12: **l**	$-(CH_2)_4-$		Cl	from −78 to rt	22.5	32	97:3

[a] Isolated yield. [b] Determined by ^1H NMR. See, refs 4h and 12.

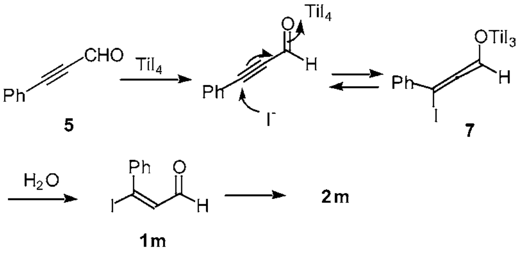
The coupling reaction of cinnamaldehyde gave exclusively the *dl*-coupling product in 83% yield (entry 1). The reaction rate of the present coupling was effectively enhanced by a halogen substituent at the position β to the carbonyl. 3-Chlorocinnamaldehyde participated in the coupling reaction to give the diol in good yield in a short reaction time (entry 2). The use of the 3-bromo and iodo counterparts also provides a clean reaction, giving the products in essentially the same range of yields (entries 3 and 4). The α-bromo-substituted analogue, however, gave the coupling product in decreased yield (entry 5). This particular effect of a halogen substituent was especially prominent in the case of 2-hexenal. Whereas the coupling reaction of 2-hexenal in the presence of titanium tetraiodide gave the desired product in only 16% yield, β-halo-substituted 2-hexenals afforded the *dl*-coupling products in good yields with excellent selectivity (entries 6−8). In strong contrast to their hydrogen analogues, the introduction of chlorine enabled the coupling reaction of the *tert*-butyl and cyclic enals, although the product yields were moderate (entries 9−12).

Scheme 1



An interesting addition of iodide anion was observed in the reaction of propynal derivatives. The pinacol coupling of 3-phenylpropynal in the presence of dry 4 Å molecular sieves (4 Å MS) gave diol **6** in 63% yield with complete *dl*-selectivity, whereas the diiodo derivative **2m** was obtained when the reaction was conducted in the presence of 4 Å MS containing water.[11] The same coupling product was obtained from the reaction of (*E*)-3-iodocinnamaldehyde **1m**, where no isomerization of the double bond was observed. These results indicate that the initial formation of (*E*)-3-iodocinnamaldehyde may be involved in the case of 3-phenylpropynal in the presence of a limited amount of water. Scheme 2 may explain the formation of the diiodo diol **4**.

Scheme 2



An initial 1,4-addition of iodide anion occurred to give the allenoate **7**, which was protonated with water to give (*E*)-β-iodoaldehyde **1m**. This (*E*)-iodocinnamaldehyde **1m** in turn

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(10) Titanium tetraiodide was purified by sublimation (180 °C/0.8 mmHg). A typical procedure is as follows. Propionitrile (1.0 mL) was added to TiI_4 (1.0 mmol) at ambient temperature under an argon atmosphere. The solution was stirred for 10 min, and a propionitrile (1.0 mL) solution of 3-iodocinnamaldehyde (0.5 mmol) was added at −78 °C. After being stirred at from −78 °C to −20 °C, the reaction was quenched with saturated aqueous $NaHCO_3$, 10% aqueous $NaHSO_3$, and triethylamine. The whole mixture was filtered through a Celite pad and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification on preparative silica gel TLC (2:1 *n*-hexane/ethyl acetate as an eluent) gave 1,6-diiodo-1,6-diphenyl-3,4-dihydroxyhexa-1,5-diene (88%).

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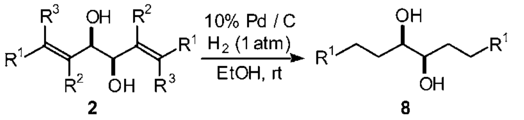
underwent the pinacol coupling reaction under the influence of titanium tetraiodide.

The subsequent functional group transformations of the coupling product demonstrate the utility of the present reaction. Hydrogenation of the coupling products **2** gave the saturated 1,2-diols **8** in good yields where no epimerization of the diol moiety was detected. Table 2 summarizes the results of the hydrogenation. Previously, it was reported that the pinacol coupling of aliphatic aldehydes with complete *dl*-selectivity was not trivial.[12] Although an additional step is needed, the present approach offers a solution to this problem. Diol **6** arising from phenylpropynal also underwent a similar hydrogenation reaction to give the saturated diol **8** in good yield without affecting the diol stereochemistry (Scheme 3). Furthermore, carbon−carbon bond formation was possible using the Heck coupling reaction. After acetonide formation, the reaction of the coupling product **2d** with *tert*-butyl acrylate in the presence of palladium(0) gave the dialkenylated product **9** in good yield without isomerization of the (*Z*)-geometries of the double bonds.[13]

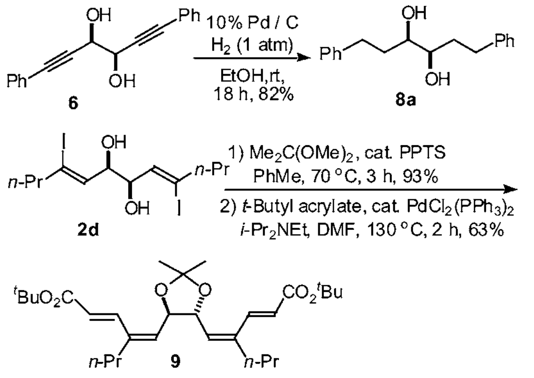
Table 2. Hydrogenation of Coupling Products



entry	R^1	R^2	R^3	time (h)	yield (%)[a]	*dl*:*meso*[b]
1	Ph	H	Cl	20	80	>99:1
2	Ph	H	Br	18	83	>99:1
3	Ph	H	I	20	75	>99:1
4	I	H	Ph	20	80[c]	>99:1
5	Ph	Br	H	18	76	>99:1
6	*n*-Pr	H	Br	12	72	>99:1

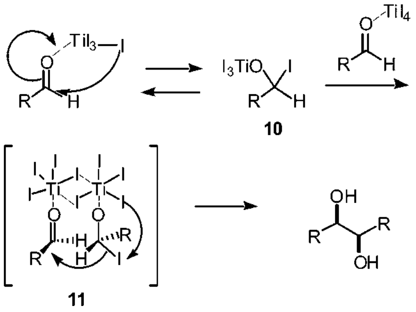
[a] Isolated yield. [b] Determined by ^{1}H NMR. See, refs 4f and 12. [c] 1,6-Diphenylhexane-3,4-diol was obtained.

Scheme 3



Scheme 4 shows a possible reaction pathway of the present pinacol coupling. An initial iodination of the carbonyl group of the aldehyde gives the iodinated intermediate **10**, which is attacked by the iodide anion from titanium tetraiodide to form an anionic species. It has been reported that a similar halogenated intermediate was formed in the reaction of BCl_3 with aromatic aldehydes.[14] The species generated from reductive dehalogenation in turn undergoes addition to another aldehyde to form a pinacol product. The formation of iodinated intermediate **10** appears to be easy in the case of aldehydes with an electron-withdrawing substituent; therefore, the present pinacol coupling proceeds readily with *β*-halo-substituted α,*β*-unsaturated aldehydes.

Scheme 4



In conclusion, we have shown that a complete *dl*-selective pinacol coupling reaction of *β*-halogenated α,*β*-unsaturated aldehyde has been achieved under the influence of titanium tetraiodide, a readily available and stable solid. The halogenovinyl moiety was in turn efficiently utilized for further functional group transformations, making the present procedure a good alternative to the stereoselective pinacol coupling of aliphatic aldehydes previously reported to be difficult.

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

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