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$Et_3B/Et_2AlCl/O_2$-Mediated Radical Coupling Reaction between α-Alkoxyacyl Tellurides and 2-Hydroxybenzaldehyde Derivatives

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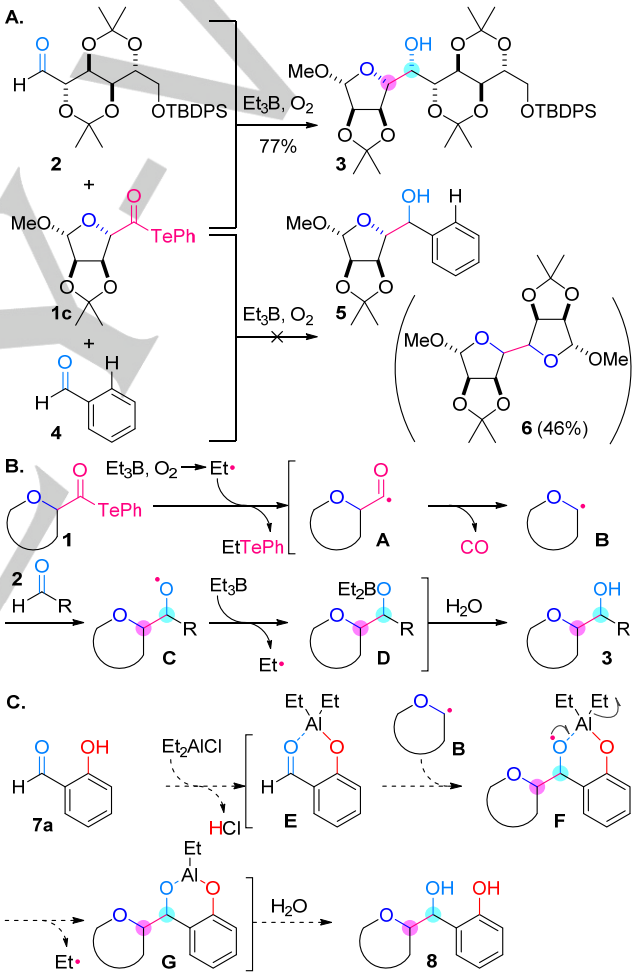
Abstract: A newly devised radical-based strategy enabled coupling between multiply oxygenated α-alkoxyacyl tellurides and 2-hydroxybenzaldehyde derivatives. A reagent combination of Et_3B, Et_2AlCl, and O_2 promoted the formation of the α-alkoxy carbon radical from the α-alkoxyacyl telluride and the addition of the radical to the carbonyl group of 2-hydroxybenzaldehyde. The reaction chemo- and stereoselectively forged the hindered C–C bond between two oxygen-functionalized carbons at ambient temperature. The method was applied to the preparation of 12 coupling adducts with three to six contiguous stereocenters and to the concise synthesis of an antitumor compound, LLY-283.

Radical addition reactions are generally compatible with diverse polar functionalities, and thus highly applicable to multiply oxygen- or nitrogen-substituted compounds.[1] In these transformations, carbon radicals generated from the corresponding radical precursors add to the unsaturated bonds of radical acceptors to form new carbon–carbon (C–C) bonds. In contrast to the frequent use of C=C, C≡C, and C=N bonds as radical accepting functional groups, C=O bonds are rarely utilized. Radical addition to the carbonyl group is disfavored because it produces an oxyl radical intermediate that is more unstable than the starting carbon radical.[2] Therefore, the direct construction of alcohol upon radical coupling remains challenging.[3]

In 2020, we developed a new radical-based convergent strategy for linking monosaccharide-derived α-alkoxyacyl tellurides and aldehydes.[4] As exemplified in Scheme 1A, **1c** and **2** were coupled in the presence of Et_3B under an O_2 atmosphere, giving rise to polyoxygenated carbon chains **3** in high yield. The reaction started with the generation of the ethyl radical from Et_3B and O_2 (Scheme 1B).[5] The ethyl radical reacts with the tellurium atom of the precursor **1** to the corresponding acyl radical **A**,[6] which spontaneously loses carbon monoxide to afford α-alkoxy carbon radical **B**.[7,8] Radical **B** adds to the aliphatic aldehyde acceptor **2** to form **C**. Et_3B captures **C** to convert the unstable oxyl radical **C** to the stable borinate **D** by expulsion of the ethyl radical, thereby preventing the reverse reaction from **C** to **B** and **2**. Protonation of **D** by aqueous workup produces alcohol **3** as the coupling adduct. This simple and powerful strategy was implemented in our recent total syntheses of hikizimycin[4] and diospyrodin,[9] both of which possess contiguously heterofunctionalized 11-carbon chains.



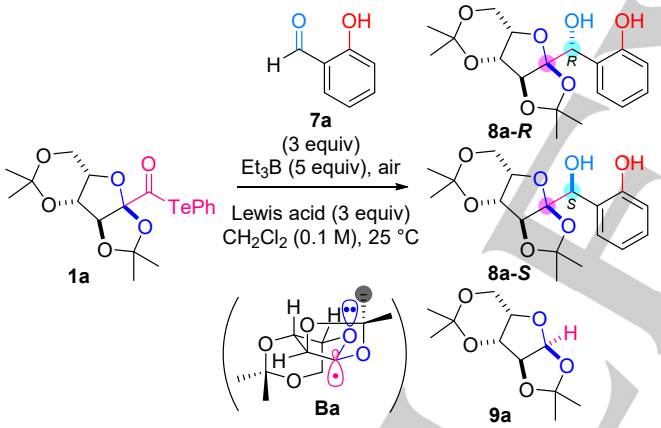
Scheme 1. A) Intermolecular radical addition of α-alkoxy carbon radicals to aldehydes. Reagents and conditions: **1c** (1 equiv), **2** or benzaldehyde (**4**) (3 equiv), Et_3B (5 equiv), air, CH_2Cl_2 (0.1 M), -30 °C, **3**: 77%, **5**: 0%, dimer **6**: 46% (NMR yield). B) Potential mechanism of Et_3B/O_2-mediated addition of an α-alkoxy radical to an aldehyde. C) Presumed mechanism of $Et_3B/Et_2AlCl/O_2$-mediated addition of an α-alkoxy radical to 2-hydroxybenzaldehyde (**7a**). TBDPS = *tert*-butyldiphenylsilyl.

Despite the broad scope of the method for assembling saturated polyol systems, benzaldehyde (**4**) did not function as a radical acceptor, presumably due to the lower electrophilicity of the carbonyl group in the conjugated system (Scheme 1A).

Namely, treatment of **1c** and **4** with Et_3B/O_2 failed to produce coupling adduct **5** and only provided **6** though dimerization of the resultant α-alkoxy radical.[7c] Herein, we report that a new reagent combination comprising Et_3B, Et_2AlCl, and O_2 allowed the coupling of α-alkoxyacyl tellurides with variously substituted 2-hydroxybenzaldehydes. The applicability of the method was demonstrated by the synthesis of an antitumor compound, LLY-283.

We envisioned accelerating the intermolecular radical addition to benzaldehyde derivatives by the action of a Lewis acid. The Lewis acid was expected to not only enhance the electrophilicity of the aldehyde, but also to quench the oxyl radical intermediate. Accordingly, we planned to employ Et_2AlCl as a Lewis acid and 2-hydroxybenzaldehyde (**7a**) as a radical acceptor. The presumed reaction course is illustrated in Scheme 1C. Upon addition of Et_2AlCl to **7a**, a six-membered aluminum chelate **E** would be formed through exchange of the phenolic proton with Et_2Al. As the strong aluminum coordination should reduce the LUMO energy level of the C=O bond, the addition of α-alkoxy radical **B** to aldehyde **E** would be greatly facilitated. The oxyl radical **F** would react with the chelated aluminum to immediately eject an ethyl radical, thereby furnishing the aluminum dialkoxide intermediate **G**, the hydrolysis of which would result in the formation of adduct **8**.

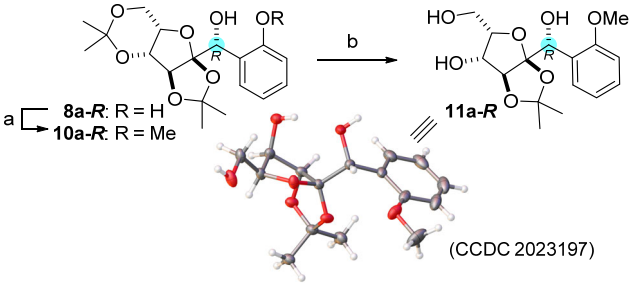
Table 1. Investigation of Lewis acids for coupling between α-alkoxyacyl telluride **1a** and 2-hydroxybenzaldehyde (**7a**).[a]



Entry	Lewis acid	Yield of **8a**	*R* : *S*	Yield of **9a**[b]
1	–	24%	5.8 : 1	17%
2	Et_2BOMe	41%	2.2 : 1	16%
3	Et_3Al	32%	1 : 1.2	16%
4	Et_2AlCl	69%	1 : 1.7	4.4%
5	$EtAlCl_2$	48%	1 : 1.4	0%
6[c]	$AlCl_3$	55%	1 : 6.4	0%
7	Me_2AlCl	60%	1 : 1.4	8.2%
8[d]	Et_2AlCl	27%	1 : 1.8	0%
9[e]	Et_2AlCl	48%	1 : 2.3	0%
10[f]	Et_2AlCl	49%	1 : 1.3	11%
11[g]	Et_2AlCl	0%	–	0%
12[h]	Et_2AlCl	36%	1 : 1.6	0%

[a] Reagents and conditions: **1a** (1 equiv), 2-hydroxybenzaldehyde (**7a**) (3 equiv), Et_3B (5 equiv), Lewis acid (3 equiv), air, CH_2Cl_2 (0.1 M), 25 °C. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as the internal standard. [c] Reaction was conducted in CH_2Cl_2/THF = 15/1 (0.1 M). [d] Reaction was conducted at -30 °C. [e] Reaction was conducted in $(CH_2Cl)_2$ at 50 °C. [f] Et_2AlCl (1 equiv) was used. [g] Et_3B was not used. [h] Et_2B (2.5 equiv) was used.

Lewis acids were screened for coupling between the diprogulic acid-derived acyl telluride **1a** and 2-hydroxybenzaldehyde (**7a**), revealing the superiority of Et_2AlCl (Table 1). When 5 equiv of Et_3B was used in the absence of a Lewis acid with **1a** (1 equiv) and **7a** (3 equiv) in CH_2Cl_2 under air at 25 °C, the coupling product **8a** was obtained in only 24% yield (entry 1).[10] The direct hydrogenation of the radical intermediate **Ba** competed in this reaction to generate **9a**[4] as the major byproduct (17%).[11] The addition of 3 equiv of Et_2BOMe increased the yield of **8a** to 41% (entry 2), suggesting the importance of the formation of the six-membered chelate prior to the radical addition. Among the four aluminum reagents (Et_3Al,[12] Et_2AlCl,[13] $EtAlCl_2$, and $AlCl_3$; entries 3–6), Et_2AlCl exhibited the highest yield of **8a** (entry 4). Thus, the addition of 3 equiv of Et_2AlCl to the original reaction conditions increased the yield of **8a** from 24% to 69% and decreased the yield of **9a** from 17% to 4.4% (entry 1 vs. entry 4). This drastic difference indicated that Et_2AlCl effectively facilitated the radical reaction as both the Lewis acid and the trapping agent of the unstable oxyl radical intermediate **F**. Changing Et_2AlCl to Me_2AlCl[13] (entry 7), applying lower (-30 °C, entry 8) and higher (50 °C, entry 9) temperatures, or decreasing the amount of Et_2AlCl to 1 equiv (entry 10) did not improve the yield. The reaction did not proceed without Et_3B even in the presence of Et_2AlCl (entry 11), while the use of 2.5 equiv of Et_3B resulted in a significant reduction of the yield of **8a** (36%, entry 12). These results indicated that the excess amount of Et_3B (5 equiv) is necessary for the constant production of the chemically unstable ethyl radical during the reaction.[14,15] Therefore, we selected entry 4 as the optimum conditions for the radical addition reaction. Remarkably, the coupling under mild conditions forged the sterically hindered C−C bond between the tetra- (pink circle) and trisubstituted sp^3-carbons (cyan circle).



Scheme 2. Determination of stereochemistry of **8a-*R***. Reagents and conditions: a) MeI, K_2CO_3, DMF, 25 °C, 84%; b) aq. AcOH/THF, 50 °C, 88%.

The pink α-alkoxy stereocenter was completely controlled presumably due to the approach of the reacting aldehyde from the opposite side from the gray-highlighted methyl group within the convex face of α-alkoxy radical **Ba** (Table 1).[4] Alternatively, the selectivity of the cyan benzylic stereocenter turned out to be low (**8a-*R*/8a-*S*** = 1:1.7, entry 4). The stereochemistry of the benzylic position of one of the diastereomers, **8a-*R***, was

established as follows (Scheme 2). Chemoselective methylation of the phenolic hydroxy group of **8a-*R*** in the presence of the secondary alcohol was realized using MeI and K_2CO_3 to provide **10a-*R***. Regioselective removal of the terminal acetonide with aqueous AcOH in turn yielded crystalline triol **11a-*R***. X-ray crystallographic analysis of **11a-*R*** unambiguously established its absolute structure.

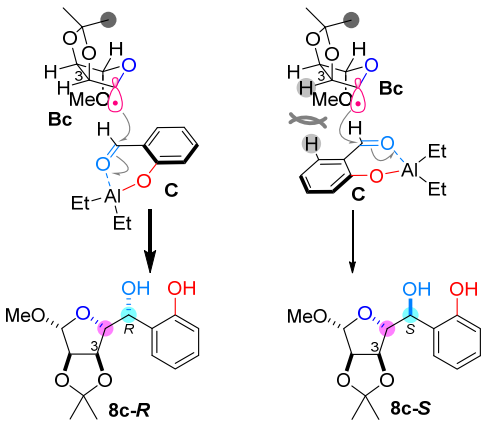
Table 2. Reactions of α-alkoxyacyl tellurides **1b–1e** with 2-hydroxybenzaldehyde (**7a**).[a]

acyl telluride / aldehyde	**1b**	**1c**	**1d**	**1e**
7a	**8b**: 57% (*R* : *S* = 1 : 1.2)	**8c**: 94% (*R* : *S* = 3.5 : 1)	**8d**: 65% (*R* : *S* = 1.7 : 1)	**8e**: 91% (*R* : *S* = 6.0 : 1)
plausible conformation of radical **Bb**–**Be**	**Bb**	**Bc**	**Bd**	**Be**

[a] Reagents and conditions: **1b**–**1e** (1 equiv), 2-hydroxybenzaldehyde (**7a**) (3 equiv), Et_3B (5 equiv), Et_2AlCl (3 equiv), air, CH_2Cl_2 (0.1 M), 25 °C.

Next, to explore the scope of the radical coupling reactions, the optimized conditions were applied to four α-alkoxyacyl tellurides **1b**–**1e** (Table 2). Acyl tellurides **1b**, **1c**/**d**, and **1e** were easily prepared from D-fructose, D-ribose, and D-tartaric acid derivatives, respectively.[4,7a,b] Upon treatment with 2-hydroxybenzaldehyde (**7a**, 3 equiv) in the presence of Et_3B (5 equiv) and Et_2AlCl (3 equiv) in CH_2Cl_2 under air at 25 °C, the radical precursors **1b**–**1e** were transformed into the corresponding α-alkoxy radicals, which reacted with aldehyde **7a** to afford **8b**–**8e** in 57% to 94% yields. Consequently, the structurally complex and diverse adducts **8b**–**8e** with three to six contiguous oxygen functionalities were generated in a single step. It is worth noting that converting **1c** and **7a** to **8c** using $Et_3B/Et_2AlCl/O_2$ gave the highest yield (94%) among the four coupling reactions, whereas the Et_3B/O_2-mediated reaction of **1c** and benzaldehyde (**4**) only led to radical dimerization (Scheme 1A).[16] These two contrasting outcomes clarified that the combined use of Et_2AlCl and 2-hydroxybenzaldehyde remarkably accelerated the radical addition to the C=O bond.

The two new stereocenters were installed in the radical coupling reactions shown in Table 2. Although the stereoselectivities at the benzylic positions of **8b**–**8e** varied, those at the α-alkoxy positions were completely controlled.[17] The stereochemical outcomes at the α-alkoxy positions can be explained by the three-dimensional structures of the radical intermediates **Bb**–**Be**.[7,18] The favorable orbital interaction between the axial-oriented radical and the axial-oriented oxygen lone pair would fix the conformation to **Bb**–**Be**, the gray-circled functional groups of which would sterically block the top face of the molecule, allowing for bond formation only from the bottom face. Selective installation of the (*R*)-stereocenter from **1c**/**d**/**e** would also be attributable to the three-dimensional shape of the corresponding radicals **Bc**/**d**/**e**. The two potential transition states that lead to **8c-*S*** and **8c-*R*** from **Bc** are depicted as an example in Scheme 3. On the bottom-face approach of the aluminum-chelated aldehyde **C** to radical **Bc**, the steric repulsion between the C3-hydrogen of **Bc** and the hydrogen of the phenyl ring of **C** would disfavor the formation of **8c-*S***. Consequently, **8c-*R*** was obtained as the major diastereomer.

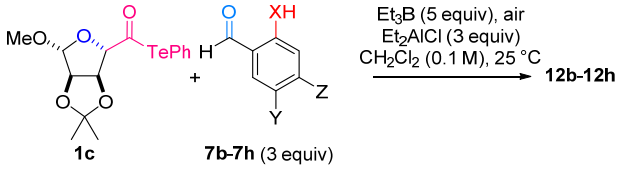


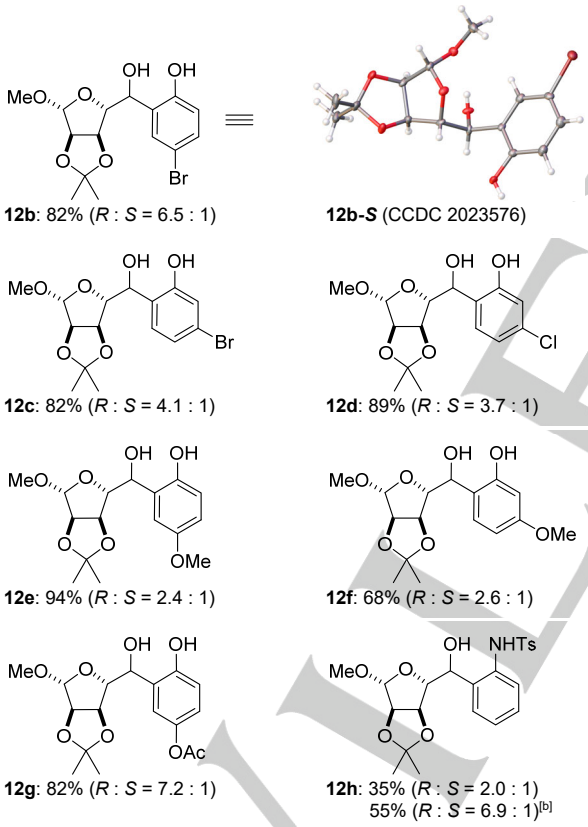
Scheme 3. Rationale for stereoselectivity of the radical addition.

The generality of the $Et_3B/Et_2AlCl/O_2$-mediated addition reactions was further corroborated by applying acyl telluride **1c** as the radical precursor and seven aldehydes **7b**–**7h** as radical acceptors (Table 3). Aldehydes **7b**–**7g** possess bromo, chloro, methoxy, or acetoxy at the C4- or C5-position of 2-hydroxybenzaldehyde. When **7b**–**7g** (3 equiv) were subjected to the mixture of **1c**, Et_3B (5 equiv), and Et_2AlCl (3 equiv), the

adducts **12b**–**12g** were obtained in high yields. Thus, the potentially reactive bromo group of **12b**/**c** and acetoxy group of **12g** were retained under these conditions, confirming the mildness of the present procedure. The (*R*)-stereoselectivity was consistently observed for the benzylic position of **12b**–**12g**, and the absolute structure of the minor (*S*)-diastereomer of **12b** was established by X-ray crystallographic analysis. Interestingly, the optimized conditions realized the coupling between **1c** and 2-(tosylamino)benzaldehyde (**7h**) in 35% yield. The addition of 2,6-di-*tert*-butyl-4-methylpyridine (3.6 equiv) as a proton scavenger increased the yield of adduct **12h** to 55% yield, showing the high potential of aniline derivative **7h** as a radical acceptor.

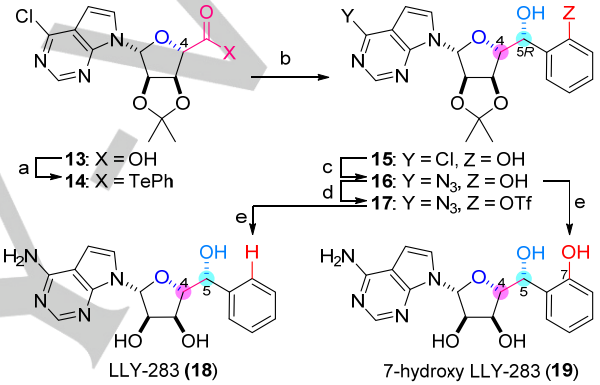
Table 3. Reactions of α-alkoxyacyl telluride **1c** with substituted 2-hydroxybenzaldehydes **7b**–**7h**.[a]





[a] Reagents and conditions: **1c** (1 equiv), 2-hydroxybenzaldehydes **7b**–**7h** (3 equiv), Et_3B (5 equiv), Et_2AlCl (3 equiv), air, CH_2Cl_2 (0.1 M), 25 °C. [b] 2,6-di-*tert*-butyl-4-methylpyridine (3.6 equiv) was used.

The chemo- and stereoselective radical addition was then applied to the preparation of the antitumor nucleoside derivative **18** (Scheme 4).[19] Eli Lilly researchers reported that LLY-283 (**18**) is a selective inhibitor of protein arginine methyltransferase 5 (PRMT5).[20] Radical precursor **14** was first derivatized from the known carboxylic acid **13** through the formation of the activated ester, followed by the attack of an anionic phenyltelluride prepared from $(PhTe)_2$ and iBu_2AlH.[21] The $Et_3B/Et_2Al/O_2$-mediated coupling between acyltelluride **14** and 2-hydroxybenzaldehyde (**7a**) installed the requisite C4- and C5-stereocenters, furnishing **15** in 36% yield without affecting the 6-chloro-7-deazapurine moiety. The chlorine atom of **15** was then replaced with the azide group by employing NaN_3 to afford azide **16**. The phenolic hydroxyl group of **16** was triflated with Tf_2O and iPr_2NEt selectively over the benzylic hydroxy group, giving rise to **17**. Hydrogenolysis of the azide and triflate groups of **17** by the catalysis of $Pd(OH)_2/C$,[22] followed by acidic detachment of the acetonide in the same pot, delivered LLY-283 (**18**). The present radical-based method uniquely permitted the synthesis of the C7-hydroxylated analogue of **18**. Specifically, submission of **16** instead of **17** for the last reaction conditions furnished 7-hydroxy LLY-283 (**19**).



Scheme 4. Synthesis of LLY-283 and its C7-hydroxylated analog. Reagents and conditions: a) isobutyl chloroformate, *N*-methylmorpholine, THF, 0 °C; $(PhTe)_2$, iBu_2AlH, THF, 0 °C, 47%; b) **14** (1 equiv), **7a** (7 equiv), Et_3B (5 equiv), Et_2AlCl (7 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (8.3 equiv), air, CH_2Cl_2 (0.1 M), 25 °C, 36%; c) NaN_3, DMF, 85 °C; d) $(CF_3SO_2)_2O$, iPr_2NEt, CH_2Cl_2, -30 °C; e) H_2, $Pd(OH)_2/C$, MeOH, 50 °C; 1 M aq. CF_3CO_2H, 25 °C, **18**: 39% (over 3 steps from **15**), **19**: 41% (over 2 steps from **15**).

In summary, we devised new $Et_3B/Et_2AlCl/O_2$-mediated radical conditions and realized coupling reactions between various α-alkoxyacyl tellurides and 2-hydroxybenzaldehyde derivatives. Et_3B and O_2 initiated the formation of the α-alkoxy radical from the α-alkoxyacyl telluride, while Et_2AlCl functioned as the Lewis acid for activation of the C=O bond and as the radical terminator of the unstable oxyl radical. The advantageous features of the reactions are the high compatibility with oxygen functional groups and efficiency for intermolecular formation of hindered bonds under mild conditions. Therefore, the present method will serve as a new strategy for the efficient synthesis of multiply oxygenated natural products and pharmaceuticals.

Acknowledgements

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Innovative Areas (JP18H04384) to M.N. from JSPS. A fellowship from JSPS to H.F. (JP17J09814) is gratefully acknowledged. Determination of the X-ray crystallographic structures was financially supported by the Nanotechnology Platform of MEXT (JP12024046).

Keywords: C–C coupling • radical reactions • oxygen heterocycles • tellurium • aldehydes

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[16] Even when the optimized conditions using Et_3B, Et_2AlCl, and O_2 were applied to the coupling of **1c** and **4**, only dimer **6** was obtained in 5.3% NMR yield, confirming the importance of the six-membered aluminum chelate for the aldehyde addition. See Supporting Information for details.

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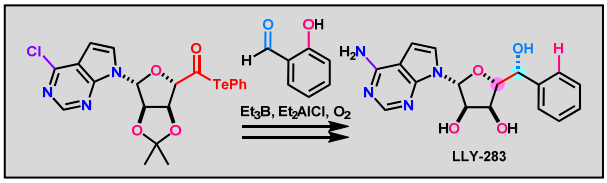

New $Et_3B/Et_2AlCl/O_2$-mediated radical conditions realized coupling reactions between various α-alkoxyacyl tellurides and 2-hydroxybenzaldehyde derivatives. Et_3B and O_2 initiated the formation of the α-alkoxy radical from the α-alkoxyacyl telluride, while Et_2AlCl acted as both a Lewis acid to activate the C=O bond and a radical terminator of the unstable oxyl radical. This mild, powerful method was effectively used to synthesize antitumor compound LLY-283.