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Et_3B-Mediated Radical-Polar Crossover Reaction for Single-Step Coupling of O, Te-Acetal, α,β-Unsaturated Ketones, and Aldehydes/Ketones

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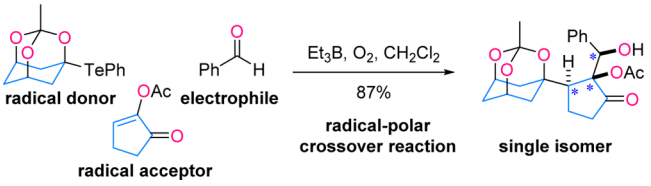
ABSTRACT



Et_3B-mediated three-component coupling reactions between O,Te-acetal, α,β-unsaturated ketones, and aldehydes/ketones were developed. Et_3B promoted the generation of the potently reactive bridgehead radical from the O,Te-acetal of the trioxaadamantane structure and converted the α-carbonyl radical of the resultant two-component adduct to the boron enolate, which then underwent a stereoselective aldol reaction with the aldehyde/ketone. This powerful, yet mild, radical-polar crossover reaction efficiently connected the hindered linkages between the three units and selectively introduced three new stereocenters.

One-pot, three-component coupling is a powerful and rapid means for construction of functionalized molecules[1] because it minimizes the number of synthetic operations and maximizes the build up of structural and functional complexity. While these reactions have historically employed either ionic or radical processes, the in situ combination of radical and ionic reactions, designated as radical-polar crossover reactions, has recently emerged.[2,3] Since the reactivities of the radical and ionic intermediates are orthogonal, sequential application of these two mechanisms offers great advantages in the assembly of complex molecular architectures. Despite these synthetically valuable features, these reactions have been unexplored in the context of target-oriented synthesis.

Multiply fused and highly oxygenated structures of terpenoids generally present a daunting synthetic challenge (Scheme 1).[4] We have been interested in developing new three-component coupling reactions for construction of the substructures of bioactive terpenoids, such as cytotoxic trigohownin A[5] and potassium channel blocker correolide.[6] These compounds share a common motif, in which the

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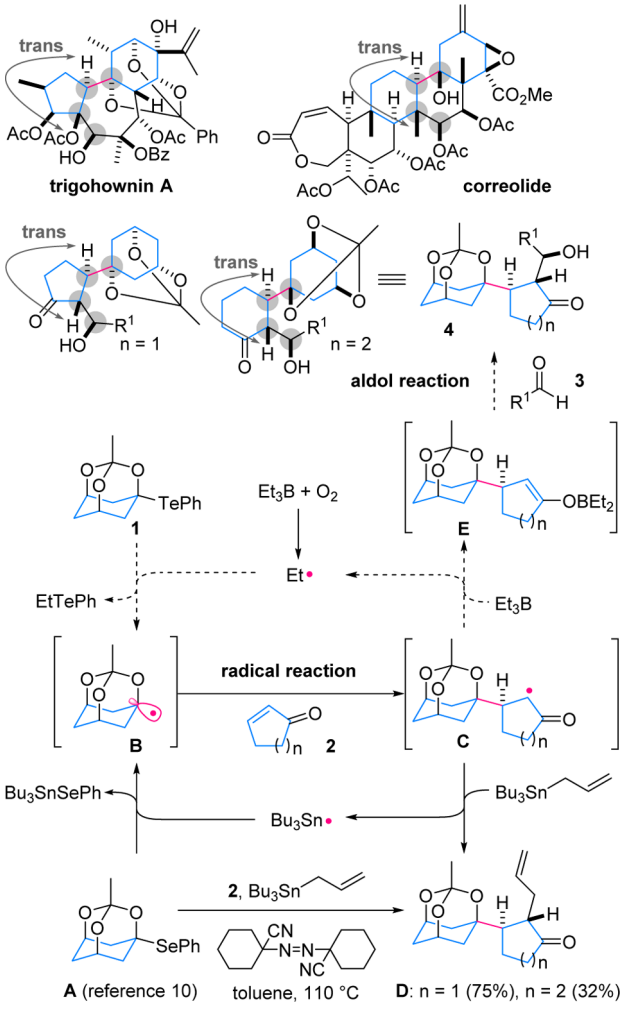
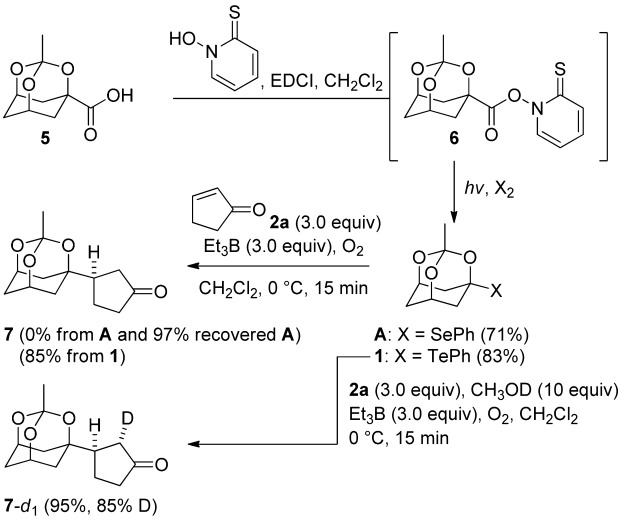
tetrasubstituted carbon of the highly oxygenated cyclohexanol derivatives is linked to the tertiary carbon of the 2,3-*trans*-disubstituted cycloalkane structures (highlighted in blue and red). Here, we report development of a novel three-component coupling reaction using O,Te-acetal **1**, α,β-unsaturated ketone **2**, and aldehyde/ketone **3**. The single-step reaction proceeded through the radical-polar crossover mechanism under mild conditions and generated the complex ring connection motifs (**4**) of trigohownin A or correolide with stereoselective formation of the one C−O and two C−C bonds.

Scheme 1. Plan of Radical-Polar Crossover Reaction



A possible scenario of the radical-polar reaction is illustrated in Scheme 1. We selected O,Te-acetal **1** with the 2,4,10-trioxadamantane orthoester structure as the radical precursor and Et_3B as the radical initiator and terminator. Ethyl radical, which is generated by the reaction of Et_3B and O_2,[7] would induce the homolytic cleavage

Scheme 2. Preparation and Et_3B-Mediated Radical Reaction of O,Se-Acetal **A** and O,Te-Acetal **1**[a]



[a] EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

of the highly activated C−Te bond of **1** to produce α-alkoxy bridgehead radical **B**.[8−12] Since the sterically unshielded radical **B** possesses potent reactivity as a nucleophilic radical, a congested C−C bond would be formed through the intermolecular addition of **B** to cycloalkenone **2**, leading to **C**. Radical intermediate **C** would then be converted to anionic intermediate **E** via the reaction with Et_3B and subsequent ejection of ethyl radical.[2b,13] Finally, aldol reaction of the resultant boron enolate **E** with the carbonyl group of **3** would yield **4**. This attractive sequential reaction can only be realized when the reactivity of each component is completely differentiated and Et_3B enables the radical initiating (**1**→**B**) and trapping processes (**C**→**E**).

We previously reported the radical-based three-component coupling of O,Se-acetal **A**, α,β-unsaturated ketone **2**, and allyl tributyltin (Scheme 1).[10] The C−Se bond of **A** was homolytically cleaved by the action of tributyltin radical at 110 °C, and two subsequent radical reactions led to product **D**. Thus, **A** was first treated with Et_3B, the key ingredient of the radical-polar crossover process (Scheme 2). However, the C−Se bond was found to be inert upon treatment with Et_3B/O_2 at 0 °C, and **A** was almost quantitatively recovered. Therefore, the C−Se bond in **A** was replaced with the weaker C−Te bond in the alternative

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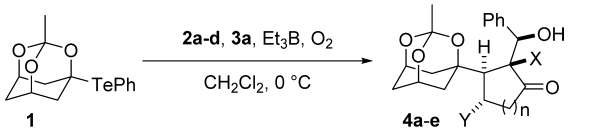
radical donor **1**.[14,15] Condensation of carboxylic acid **5** with 2-mercaptopyridine *N*-oxide using EDCI yielded Barton ester **6**,[16] which was immediately photoirradiated in the presence of $(PhTe)_2$ to afford the requisite O,Te-acetal **1**.[17,18] The reaction of **1** and cyclopentenone **2a** (3 equiv) in the presence of Et_3B (3 equiv) under air in CH_2Cl_2 proceeded at 0 °C within 15 min to produce **7** in 85% yield. This facile adduct formation at low temperature without the toxic tin reagent[19,20] clearly demonstrated the superiority of **1** over **A** as the radical donor. When CH_3OD (10 equiv) was present in the same reaction mixture, deuterated **7**-d_1 (85% D) was exclusively obtained, indicating that the boron enolate was indeed formed and quenched by the acidic deuteron of CH_3OD.

Once the radical initiating and trapping ability of Et_3B was verified by the deuteration experiment, benzaldehyde **3a** was applied as the third component together with O,Te-acetal **1** and various cycloalkenones **2a**–**d** (Table 1). When a mixture of **1**, cyclopentenone **2a** and **3a** was treated with Et_3B/O_2 in CH_2Cl_2 at 0 °C for 15 min, the coupling adduct **4a** was produced through stereoselective installation of the three new stereocenters (89%, 9:1 dr at the benzylic position, entry 1). The radical addition to 4-TBSoxycyclopentenone **2b** proceeded selectively from the opposite face of the C4-substituent, giving rise to **4b** as a single diastereomer (entry 2). Moreover, 2-acetoxycyclopentenone **2c**[21] underwent the three-component coupling with **1** and **3a** to provide **4c** (entry 3). Not only the cyclopentenone structures but also cyclohexenone **2d** (entry 4) was applicable as the radical acceptors. However, the aldol adduct **4d** was prone to undergo retroaldol reactions to produce large amounts of the two-component adduct **8** under the original conditions (entry 4). To increase the yield of the three-component adduct over the two-component counterpart, **4d** was silylated in the same pot (entry 5). As a result, TMS-ether **4e** was isolated in 73% yield (3:2 dr). It is worth noting that the four contiguous stereocenters in **4c** directly matched those of trigohownin A (circled in gray in Scheme 1), and compound **4e** possessed the bicyclic substructure of correolide. These results demonstrated the potential utility of the present one-pot reaction in building up the multiply oxygenated natural products.

The stereostructures of the coupling products **4a** and **4c** were established by X-ray crystallography, and the stereochemistries of **4b**, **4d**, and **4e** were confirmed by NMR experiments on derivatized compounds.[22] Importantly,

Table 1. Three-Component Coupling of **1**, **2a**–**d**, and **3a**[a]



entry	radical acceptor	electrophile	product	yield
1	**2a**: X = Y = H	**3a**	**4a**: X = Y = H	89% (9:1)[b]
2	**2b**: X = H, Y = OTBS	**3a**	**4b**: X = H, Y = OTBS	86%[c]
3[d]	**2c**: X = OAc, Y = H	**3a**	**4c**: X = OAc, Y = H	87%[c]
4[e]	**2d**	**3a**	**4d**: R = H	27%[c,f]
5	**2d**	**3a**	**4e**: R = TMS	73%[g] (3:2)

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[a] Conditions: **1** (1 equiv), **2** (3 equiv), **3a** (3 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 15 min. [b] **4a** was obtained as the major isomer. [c] Product was obtained as a single isomer. [d] Conditions: **1** (1 equiv), **2c** (2 equiv), **3a** (5 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), rt, 60 min. [e] Conditions: **1** (1 equiv), **2d** (2 equiv), **3a** (5 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 15 min. [f] Compound **8** was obtained in 65% yield. [g] Conditions: **1** (1 equiv), **2d** (2 equiv), **3a** (5 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 15 min; TMS-imidazole (10 equiv), DMAP (0.3 equiv), 0 °C, 3 h. Compound **4e** was obtained as the major isomer.

the stereochemical relationship of the newly introduced three centers of **4a**–**c** was consistent. This remarkable selectivity is explained by the six-membered transition state model depicted in Figure 1.[23] After the addition of bridgehead radical **B** to the radical acceptor and subsequent formation of boron enolate **E**, **3a** can only approach from the face opposite to the bulky trioxadamantane structure, thereby establishing the *trans*-relationship between the radical donor and the electrophile. The chairlike six-membered

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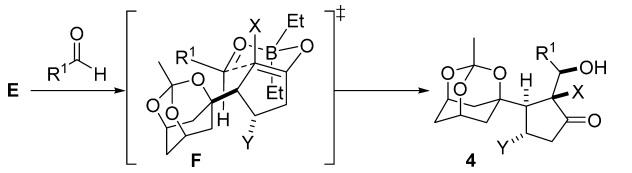
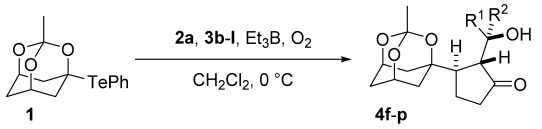


Figure 1. Rationale of the stereochemical outcome.

Table 2. Three-Component Couplings of **1**, **2a**, and **3b**–**l**[a]



entry	radical acceptor	electrophile	product	yield[b]
1[c]	**2a**	**3b**: R^1 = Me	**4f**: R^1 = Me	86%
2	**2a**	**3c**: R^1 = *n*-C_6H_{13}	**4g**: R^1 = C_6H_{13}	77%
3	**2a**	**3d**: R^1 = cyclohexyl	**4h**: R^1 = cyclohexyl	99%
4[d]	**2a**	**3e**: R^1 = *t*-Bu	**4i**: R^1 = *t*-Bu	74%
5[e]	**2a**	**3f**: R^1 = (*E*)-CH=CHMe	**4j**: R^1 = (*E*)-CH=CHMe	41%
6[f]	**2a**	**3g**: R^1 = CH=CMe_2	**4k**: R^3 = CH=CMe_2	76%
7[f]	**2a**	**3h**	**4l**	64%
8[f]	**2a**	**3i**: n = 1	**4m**: n = 1	22%[g]
9[f]	**2a**	**3j**: n = 2	**4n**: n = 2	86%
10	**2a**	**3k**: X = O	**4o**: X = O	90%
11	**2a**	**3l**: X = NBoc	**4p**: X = NBoc	92%

[a] Conditions: **1** (1 equiv), **2a** (3 equiv), **3** (3 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 15 min. [b] Product was obtained as a single isomer. [c] 10 equiv of **3b** was used. [d] Conditions: **1** (1 equiv), **2a** (2 equiv), **3** (5 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), rt, 60 min. [e] 2 equiv of **2a** was used. [f] Conditions: **1** (1 equiv), **2a** (2 equiv), **3** (5 equiv), Et_3B (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 15 min. [g] Compound **7** was obtained in 63% yield.

transition state **F** would then control the stereocenters of the α- and β-positions of the ketone, resulting in formation of the adduct **4** in a stereoselective fashion.

The broad scope of the present coupling was further demonstrated using **3b**–**l** as the third component (Table 2). The reactions of enolizable acetaldehyde **3b** and *n*-heptanal **3c** with O,Te-acetal **1**, cyclopentenone **2a** and Et_3B/O_2 resulted in efficient formation of **4f** and **4g**, respectively, as the sole stereoisomers (entries 1 and 2). The sterically more cumbersome aliphatic aldehydes **3d** and **3e** also served as electrophiles without decreasing the yields to afford **4h** and **4i**, respectively (entries 3 and 4). Even the α,β-unsaturated aldehydes **3f** and **3g** were found to be applicable to the three-component coupling reactions (entries 5 and 6), although these compounds can function as both radical and carbanion acceptors. The bridgehead radical **B** was preferentially added to α,β-unsaturated ketone **2a** in the presence of **3f** and **3g**, and the resultant boron enolate selectively reacted with the aldehyde, leading to **4j** and **4k**, respectively. Significantly, the adducts **4f**–**k** were obtained as single isomers, further supporting the stereochemical rationale in Figure 1.

When acetone **3h** was mixed with **1** and **2a** in the presence of Et_3B/O_2, the in situ aldol reaction constructed a new tetrasubstituted carbon center to afford **4l** (entry 7). Furthermore, the three cyclic structures were connected in a single step upon using the cyclic ketones (entries 8–11). Cyclopentanone **3i** and cyclohexanone **3j** were coupled with **1** and **2a** to deliver the tricarbocyclic structures **4m** and **4n**, respectively (entries 8 and 9). The tetrahydropyran and piperidine structures were effectively incorporated into the coupling adducts **4o** and **4p** by using **3k** and **3l**, respectively, as the third components (entries 10 and 11). The smooth formation of **4l**–**p** under mild conditions reflected the generality of the present method for connecting the sterically hindered bonds between the three components.

In conclusion, we have developed a new three-component coupling reaction to construct **4** from O,Te-acetal **1**, α,β-unsaturated ketone **2** and aldehyde/ketone **3** by the action of Et_3B and O_2. The single-step reaction simultaneously constructed the bridgehead carbon center in a stereospecific fashion, and the contiguous three stereocenters in a stereoselective fashion. The tin-free procedure, the mild conditions, the broad substrate scope, the high stereoselectivity, and the efficient construction of the two hindered linkages are particularly useful features for the target-oriented synthesis. Because of these advantages, this three-component coupling introduces a novel and valuable strategy for streamlined synthesis of multiply functionalized terpenoids with complex architectures.

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

The authors declare no competing financial interest.