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[3 + 2] Coupling of Quinone Monoacetals by Combined Acid–Hydrogen Bond Donor

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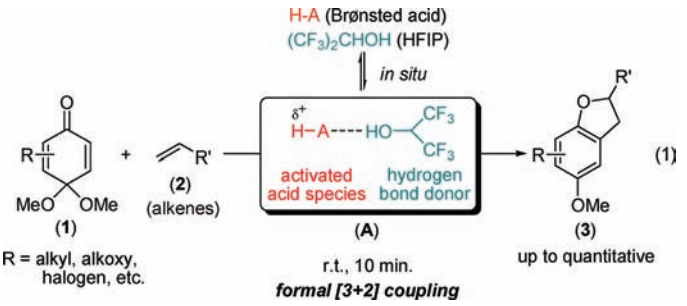
ABSTRACT



The expeditious and efficient [3 + 2] coupling approach of quinone monoacetals 1 with alkene nucleophiles 2 by the action of an activated Brønsted acid in the presence of a hydrogen bond donor perfluorinated alcohol has been achieved. With the optimized combined acid, the reaction could proceed under mild conditions by only mixing the two reactants to afford the cycloadducts 3 in a short time (within 10 min) with good to quantitative yields.

Quinone monoacetals, which possess not only an unsaturated carbonyl, but also allyl acetal moieties in one skeleton, have attracted considerable interest due to their broad utilities in organic synthesis as intermediates for natural products and related compounds.[1] Due to their bifunctional structures, varied reactivities during nucleophilic attack on quinone monoacetals can be produced, for instance, conjugated addition to an enone moiety,[2] addition to a carbonyl carbon,[3] acetal displacement (such as hydrolysis), etc. Among them, only a few strategies have been developed for the construction of substitution reactions to the α-position of the carbonyl group.[4]

Very recently, we reported a new substitution method of quinone monoacetals **1** with aromatic nucleophiles to give oxygenated biaryls catalyzed by montomorillonite clay as a rare example for enabling the substitution under nonbasic conditions.[5,6] Extensive investigation of this attractive strategy was anticipated, and we have now found that the use of the bifunctional molecules **1** for formal [3+2] coupling *via* substitution with the resulting formation of dihydrobenzofurans **3**[7] would be possible by further optimizing the activator conditions. Herein,

(1) For preparation and synthetic utility of quinone monoacetals, see: (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (b) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856.

(2) For selected examples, see: (a) Foster, C. H.; Payne, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 2834. (b) Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1980**, *45*, 1218. (c) Ciufolini, M. A.; Dong, Q.; Yates, M. H.; Schunk, S. *Tetrahedron Lett.* **1996**, *37*, 2881. (d) Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413. (e) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623. (f) Grecian, S.; Wrobleski, A. D.; Aübe, J. *Org. Lett.* **2005**, *7*, 3167. (g) Giroux, M.-A.; Guerard, K. C.; Beaulieu, M.-A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871.

(3) Early examples: (a) Evans, D. A.; Cain, P. A.; Wong, R. Y. *J. Am. Chem. Soc.* **1977**, *99*, 7083. (b) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1988**, *53*, 2465. (c) Imamoto, T.; Takiyama; Nakamura, N.; K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (d) Parker, K. A.; Coburn, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 8516.

(4) (a) Coutts, I. G. C.; Hamblin, M. *J. Chem. Soc., Chem. Commun.* **1976**, 58. (b) Sartori, G.; Maggi, R.; Bigi, F.; Giacomelli, S.; Porta, C.; Arienti, A.; Bocelli, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2177. (c) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422. (d) Mal, D.; Pahari, P.; Bidyut, B. K. *Tetrahedron Lett.* **2005**, *46*, 2097.

(5) Dohi, T.; Washimi, N.; Kamitanaka, T.; Fukushima, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 6142. A similar transformation using Pt(IV) catalysts recently appreared during the course of natural product synthesis. See: Sloman, D. L.; Mitasev, B.; Scully, S. S.; Beutler, J. A.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 2511.

(6) Related reactions of O,S-acetals: (a) Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 2434. (b) Matsugi, M.; Murata, K.; Anilkumar, G.; Nambu, H.; Kita, Y. *Chem. Pharm. Bull.* **2001**, *49*, 1658.

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the strategy for the [3 + 2] coupling of the quinone acetal **1** with a series of alkene nucleophiles **2** utilizing an activated Brønsted acid *in situ* formed in equilibrium by the aid of the hydrogen bond donor solvent, hexafluoroisopropanol (HFIP), is reported (eq 1).

Initially, the [3 + 2] coupling of the quinone acetal **1a** (eq 1, R = H) with allyltrimethylsilane **2a**[8] was tested using our reported system along with aluminum pillared montmorillonite in HFIP.[5] This indeed produced the coupling adduct, dihydrobenzofuran **3aa**, in an expectedly (61%), but the reaction was very slow and required a very long time (1 day) to consume all the starting material. Furthermore, this method was too case-sensitive for the combination of the quinone acetal **1a** and nucleophile **2a** to allow formation of the extended series of cycloadducts **3**. The montmorillonites unfortunately showed a limited generality and performance in the [3 + 2] coupling; hence the screening of several types of Brønsted acid activators was envisioned instead as just alternatives. As illustrated in Scheme 1, we hypothesized the [3 + 2] coupling of the quinone acetal **1a** based on the combined use of a Brønsted acid and highly polar HFIP having a super hydrogen bond donor ability, but not showing the property as a hydrogen bond acceptor.[9] The mechanism of the [3 + 2] coupling concerns the following rational steps involving charged quinone acetal **B** generation promoted by the combined acid species **A**: Preactivation of the Brønsted acid first occurs by coordinating the hydrogen bond donor, HFIP, to the Lewis basic functionality of the acid (Brønsted acid activation by HFIP).[10] The combined acid would work as an indispensable promoter to generate the charged species **B** of the quinone acetal **1a** in equilibrium in the polar solvent, which can then react with the nucleophile **2a** at the less hindered carbon site remote from the acetal rather than the sterically congested acetal carbon. This regioselective trend might also be pronounced by the steric factor of the associating acid in the proposed acetal activation mode. Finally, cyclization of the carbonyl moiety in the keto-type tautomer **C** was accompanied by aromatization as the driving force to afford the formal [3 + 2] coupling product **3aa**. To confirm the hypothesis, we envisioned the use of a Brønsted acid having a good hydrogen bond-accepting functionality, and for such acids, a series of carboxylic acids and related compounds showing varied pH values were evaluated.

As a result, the different product yields were observed during the optimization of the carboxylic acids in the [3 + 2] coupling (Table 1). These results clearly indicated that only carboxylic acids with a suitable acidic proton range[11] showed good performance in order to develop

Scheme 1. [3 + 2] Coupling Strategy Based on the Combined Use of Brønsted Acids and HFIP

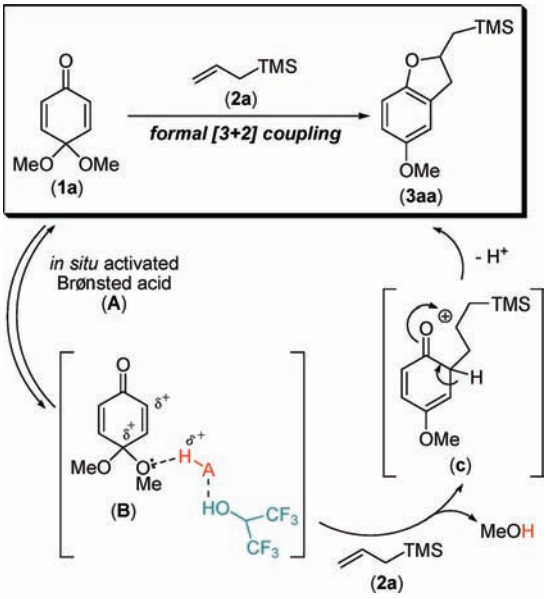


Table 1. Effect of the Acid Activator and Solvent[a]

entry	activator	solvent	time	yield of **3aa**[b,c]
1	acetic acid	HFIP/DCM	7 h	19%
2	4-methyl benzoic acid	//	1 day	n.d.
3	benzoic acid	//	2 h	9%
4	4-nitro-benzoic acid	//	2 h	14%
5[d]	pentafluoro-benzoic acid	//	1 h 10 min	86% (90%)[e]
6	2,4,6-trichloro-benzoic acid	//	10 min	59%
7	phthalic acid	//	10 min	58%
8	pentafluoro-benzoic acid	TFE/DCM	1 h	21%

[a] The screenings were carried out with 2 equiv of acid, 5 equiv of allyltrimethylsilane **2a** at room temperature unless otherwise noted. For more details of other acids see SI. [b] Isolated yield after purification. [c] Formation of noncyclized allylation product **4aa** was observed (see SI). [d] Acid (1 equiv) and **2a** (2 equiv). [e] Performed at 0 °C.

(7) For the synthesis and utility of the dihydrobenzofurans, see a review: Bertolini, F.; Pineschi, M. *Org. Prep. Proced. Int.* **2009**, *41*, 385.

(8) For allylsilane in cyclizations, see the examples: (a) Schmidt, A. W.; Knöelker, H.-J. *Synlett* **2010**, 2207. (b) Knöelker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304. (c) Berard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (d) Bérard, D.; Giroux, M. A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, *64*, 7537.

(9) Reviews and accounts: (a) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (b) Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *Chem. Commun.* **1996**, 2105. (c) Begue, J.; Bonnet-delpon, D.; Crousse, B. *Synlett* **2004**, 18. (d) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(10) (a) Allard, B.; Casadevall, A.; Casadevall, E.; Largeau, C. *Nouv. J. Chim.* **1980**, *4*, 539. (b) Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409. Recent works of H_2O_2 activation by the hydrogen bonding: (c) Neimann, K.; Neumann, R. *Org. Lett.* **2000**, *2*, 2861. (d) Berkessel, A.; Adrio, J. A. *Adv. Synth. Catal.* **2004**, *346*, 275.

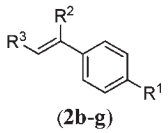
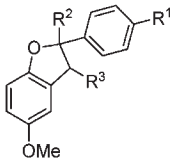
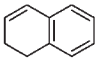
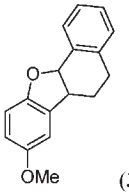
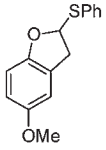
(11) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) In *Encyclopedia of Reagents for Organic Synthesis*, 2nd ed.; Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G. A., Eds.; John Wiley & Sons: Chichester, 2009; Vol. 10, pp 7654–7656. The pK_a order of the tested acids is as follows: AcOH, 4-Me$C_6H_4CO_2H$ > $C_6H_5CO_2H$ > 4-$NO_2C_6H_4CO_2H$ > $C_6F_5CO_2H$ > 2,4,6-Cl-$C_6H_2CO_2H$, phthalic acid > CF_3CO_2H > $MeSO_3H$ > CF_3SO_3H.

the coupling, among which pentafluorobenzoic acid (pK_a: ca. 1.5)[11b] especially gave the most impressive result regarding not only the product yield but also the observed reaction rate (entry 5). Otherwise, incomplete coversions of the quinone acetal **1a** were observed for the less acidic activators (entries 1−4), while the stronger acids, such as trichlorobenzoic and phthalic acids (entries 6 and 7), as well as trifluoroacetic and methanesulfonic acids, caused considerable decomposition of **1a**, affording the cycloadduct **3aa** in poorer yields (see the results in Supporting Information (SI)). One plausible explanation for the ineffectiveness of the latter is that the stronger acids would promote irreversible formation of the phenoxenium ion from the quinone acetal **1a** by accelerating the release of MeOH from the acetal group (*vide infra*).[12] HFIP has played an indispensable role in this new coupling system because the consumption of the quinone acetal **1a** by pentafluorobenzoic acid in other solvents was very slow, and the product **3aa** would not be smoothly formed, even in the parent but less polar and weaker hydrogen bond donor, 2,2,2-trifluoroethanol (TFE, entry 8). Therefore, the combined use of the acid in HFIP is highly important to achieve an effective reaction. The mixed solvent system of HFIP and DCM was employed due to the solubility of the reactants **1a** and **2a** in the fluoroalcohol.

With the established reagent and conditions, the scope of the reactions in the alkene coupling partners **2** was initially investigated using the quinone acetal **1a** as the test substrate (Table 2). To our delight, the use of the activated alkenes like **2a** was not necessary, and the coupling alkenes **2b**−**i** in this strategy would not limit the reaction scope. The couplings could thus proceed very fast and provided the expected products **3ab**−**ai** in good yields at room temperature. It should be noted that the use of these alkenes as nucleophiles only in this strategy could afford the corresponding cycloadducts **3ab**−**ai**, which were somewhat troublesome to obtain by reported methods starting from phenols.[13] Utilization of the *gem*-substituted methylstyrene **2f** was also possible for the construction of the cycloadduct **3af** (entry 5). Due to the mildness of the reaction conditions, the vinyl sulfide **2i** was also the appropriate nucleophile, giving the cyclized O,S-acetal **3ai** in good yield (entry 8).

Regarding the quinone acetals **1**, we investigated the influence of its ring substituent. Employing styrene **2b** as the counterpart, an extensive range of quinone acetal derivatives **1b**−**h** with varied ring moieties did not alter the activation course of the acid, and the

Table 2. [3 + 2] Coupling Using Various Alkenes **2b**−**i**[a]

entry	alkene (**2**)	product (**3**), yield
	 (**2b-g**)	 (**3ab-ag**)
1	$R^1 = R^2 = R^3 = H$ (**2b**)	$R^1 = R^2 = R^3 = H$, (**3ab**), 93%
2	R^1 = Me, $R^2 = R^3 = H$ (**2c**)	R^1 = Me, $R^2 = R^3 = H$ (**3ac**), 83%
3	R^1 = *t*-Bu, $R^2 = R^3 = H$ (**2d**)	R^1 = *t*-Bu, $R^2 = R^3 = H$ (**3ad**), 92%
4	R^1 = Cl, $R^2 = R^3 = H$ (**2e**)	R^1 = Cl, $R^2 = R^3 = H$ (**3ae**), 94%
5	$R^1 = R^3 = H$, R^2 = Me, (**2f**)	$R^1 = R^3 = H$, R^2 = Me, (**3af**), 81%
6	R^1 = OMe, R^2 = H, R^3 = Me (**2g**)	R^1 = OMe, R^2 = H, R^3 = Me (**3ag**), 93%
7	 (**2h**)	 (**3ah**), 83%
8	 (**2i**)	 (**3ai**), 80%

[a] The reactions were conducted for 10 min at room temprature according to the optimized reaction condition described in Table 1.

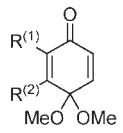
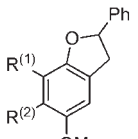
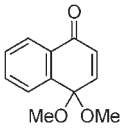
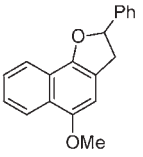
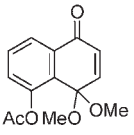
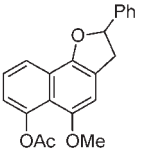
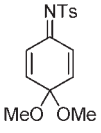
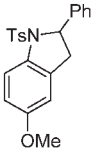
reactions smoothly proceeded in acceptable yields, some of which were almost quantitative (Table 3). The reactions occurred quite regioselectively at the less hindered α-position of the carbonyl in the quinone acetals. Substitution of the *tert*-butyl group at the neighboring position of the acetal in the substrate **1c** somewhat hampered the substrate reactivity due to its steric demand (entry 2). On the other hand, the halogen functionality and *tert*-butyl group at the α-position of the carbonyl in **1e** and **1f** permitted the efficient conversions to the products **3eb** and **3fb** (entries 4 and 5). Quantitative formations of the naphthalene dihydrofurans **3gb** and **3hb** occurred by using the naphthoquinone acetals **1g** and **1h** (entries 6 and 7). Gratefully, the valuable indoline skeleton was accessible from the

(12) (a) Davis, B. R.; Gash, D. M.; Woodgate, P. D.; Woodgate, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1499. (b) Endo, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.* **1982**, *104*, 6393. (c) Kirti, L.; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 379. These alkenes could also partially cause oligomerization under strongly acidic conditions.

(13) (a) Wang, S.; Gates, B. D.; Swenton, J. S. J. *Org. Chem.* **1991**, *56*, 1979. (b) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (c) Berard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (d) Sabot, C.; Berard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629.

(14) In addition to these, aliphatic alkenes could couple with the quinone acetals **1**, and extended [3 + 2] coupling for the construction of spirocycles was possible. See SI.

Table 3. Scope of the Quinone Acetals **1b**–**i**

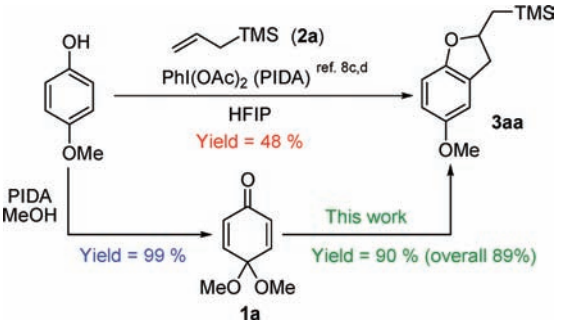
entry	quinone acetal (**1**)	product (**3**), yield
	 (**1b-f**)	 (**3bb-fb**)
1	$R^{(1)}$ = H, $R^{(2)}$ = Me (**1b**)	$R^{(1)}$ = H, $R^{(2)}$ = Me (**3bb**), 83%
2	$R^{(1)}$ = H, $R^{(2)}$ = *t*-Bu (**1c**)	$R^{(1)}$ = H, $R^{(2)}$ = *t*-Bu (**3cb**), 64%
3 [a]	$R^{(1)}$ = H, $R^{(2)}$ = OMe (**1d**)	$R^{(1)}$ = H, $R^{(2)}$ = OMe (**3db**), 78%
4	$R^{(1)}$ = Cl, $R^{(2)}$ = H (**1e**)	$R^{(1)}$ = Cl, $R^{(2)}$ = H (**3eb**), 86%
5	$R^{(1)}$ = *t*-Bu, $R^{(2)}$ = H (**1f**)	$R^{(1)}$ = *t*-Bu, $R^{(2)}$ = H (**3fb**), quant.
6	 (**1g**)	 (**3gb**), quant.
7	 (**1h**)	 (**3hb**), 98%
8	 (**1i**)	 (**3ib**), 82%

[a] 2 equiv of the acid activator and 3 equiv of styrene **2b** were used. Ts = *p*-toluensulfonyl.

iminoquinone acetals as exemplified by the result using **1i** (entry 8).[14]

Finally, we compared the superiority of our coupling method for synthesizing dihydrobenzofurans **3** starting from phenols. Previously, the oxidative couplings of phenols with alkenes to produce dihydrobenzofurans have been rarely reported,[8c,d,13] as such methods typically suffered from the obtained product yield and limited substrate scope. For example, the oxidative annulation of 4-methoxyphenol with allylsilane **2a** involving the generation of the phenoxenium ion could produce **3aa** in only 48% yield at best

Scheme 2. Dihydrobenzofuran **3aa** from the Phenol



(Scheme 2).[8c,d] Instead, the synthesis of the target **3aa** was conducted in an overall 89% yield starting from the phenol by utilizing our new strategy. The one-pot conversion of the phenol to the cycloadduct **3aa** *via* the formation of the quinone acetal **1a**[15] was also developed without purification of the synthetic intermediate, and the product **3aa** could be obtained in 81% yield.

In summary, we have successfully achieved the [3 + 2] coupling of the quinone acetals **1** with various alkenes **2** on the basis of a new substitution strategy promoted by the Brønsted acid that is activated by the hydrogen bond donor, HFIP. The reversible generation of the charged quinone acetal species developed *in situ* by the combined acid, rather than the formation of the unstable phenoxenium ion, during the stated conditions would suppress the substrate decomposition to realize a new efficient coupling strategy under mild conditions at room temperature.

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Supporting Information Available. The experimental details and spectroscopic data containing NMR charts of the all products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For preparation of quinone monoacetals **1** using a hypervalent iodine reagent, see: (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (c) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *5*, 327.