# Convenient Synthesis of Electron Deficient Dienes via Pd(0) Catalyzed Coupling

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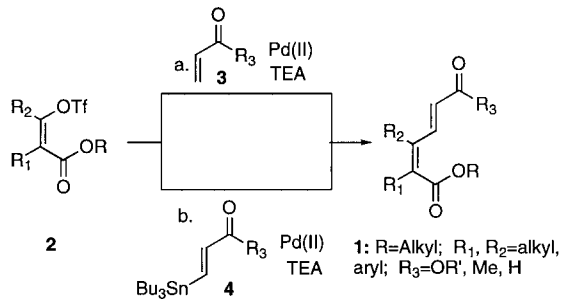
**Abstract:** The convenient preparation of 1,6-dicarbonyl-2,4-butadienes by the coupling of enol triflates with α,β-unsaturated carbonyls in the presence of $Pd(PPh_2)_2Cl_2$ is described.

As a part of our continuing research in the area of peptide secondary structure mimetics,[1] we required a facile method for the preparation of dienes of type **1** (Eq. 1). Electron-deficient dienes can serve as 4π donors in the inverse electron demand Diels-Alder reaction. With differentiable terminal functionality, these dienes and their correponding cycloadducts can be selectively transformed into useful synthetic intermediates.

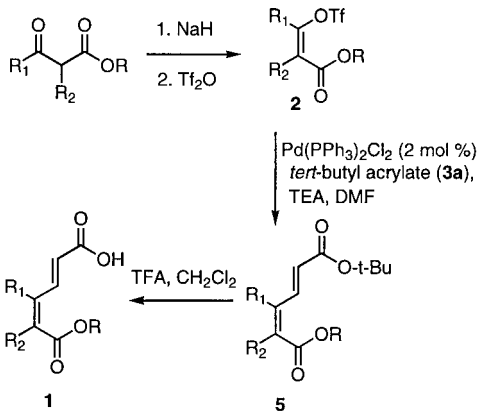
Although there are several preparative methods available in the literature,[2] we sought a more direct and efficient alternative to synthesizing these dienes. Drawing upon Pd(0) catalyzed[3] coupling methodology, which has been extensively investigated for the coupling of enol triflates **2** and β-stannyl-α,β-unsaturated carbonyls **4**, we were able to join **2** with the readily available α,β-unsaturated carbonyl compounds **3** to provide the desired dienes. This particular approach serves to simplify the laborious workup associated with stannyl reagents and led to the desired coupled products.



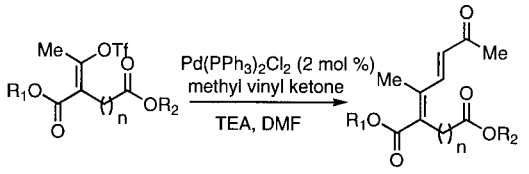

Enol triflates **2** were prepared from methyl acetoacetate or methyl 2-oxocyclopentane carboxylate by the reaction with NaH and triflic anhydride in dichloromethane at 0 °C (Eq.2). The resulting enol triflates **2** were then coupled with *tert*-butyl acrylate (**3a**) under Stille conditions.[3a] These coupling reactions resulted in the formation of the desired dienoic diesters **5a-e** in moderate to excellent yields. Deprotection of the *t*-butyl group of **5** by treatment with TFA in dichloromethane afforded the dienoic acids **1a-e** in quantitative yields.[4]

The coupling of enol triflates with methyl vinyl ketone and acrolein were also examined. These reactions proceeded smoothly to give the corresponding 1,6-dicarbonyl dienes in good yields (Eq. 3, 4). In the case of **1f-h**, the coupled products were the orthogonally protected keto diesters.

While these dienoic esters could be used directly in the Diels-Alder reaction, we desired to transform either the ketone or ester functional groups prior to cycloaddition. For example, when the dienoic methyl ester of **5i** was treated with $NaBH_4/CeCl_3$, the corresponding hydroxy ester **6a** was afforded in 95% yield (Eq.5). The resulting hydroxy ester **6a** was then protected with either THP or TBDMS groups to form dienes **6b** and **6c** in 73% and 93% yield respectively. Furthermore, the

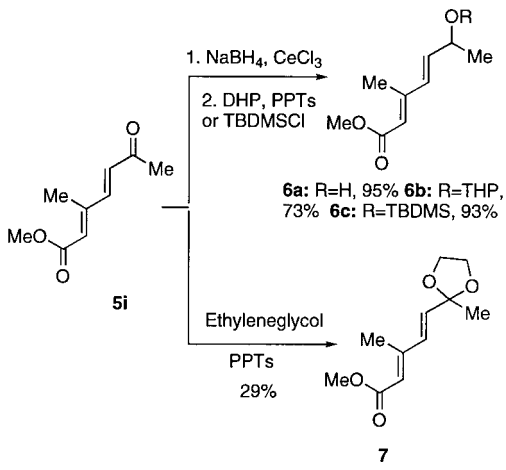



**1a**: $R_1$=Me, $R_2$=H, R=Me, 25% **1b**: $R_1$=Ph, $R_2$=H, R=Et, 41% **1c**: $R_1$=$CH_2CH_2Ph$, $R_2$=H, R=Me, 24% **1d**: $R_1$=Me, $R_2$=$CH_2Ph$, R=Et, 35% **1e**: $R_1$, $R_2$=-$(CH_2)_3$-, R=Me, 92%

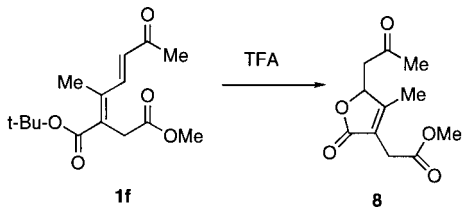



**1f**: n=1, $R_1$=t-Bu, $R_2$=Me, 35%, **1g**: n=1, $R_1$=Me, $R_2$=t-Bu, 33%, **1h**: n=2, $R_1$=t-Bu, $R_2$=Et, 60%

ketone functional group in **5i** can be protected through the formation of the ketal **7** in 29% yield.




Among the dienes examined, **1f** displayed unexpected reactivity when the *t*-butyl group was cleaved. Dienoic ester **1f** upon treatment with TFA underwent an intramolecular cyclization (presumably catalyzed by TFA) to provide lactone **8** (Eq.6).




**1f** **8**

In summary, we have demonstrated facile synthesis of a wide variety of electron deficient dienes through the reaction of enol triflates with α,β-unsaturated carbonyls in the presence of Pd(II).

**Acknowledgment**. The authors thank Dr. Tomas Vaisar for obtaining the mass spectra.

**Reference and Notes**

1. a) Peptide Secondary Structure Mimetics. *Tetrahedron* Symposia-in-print no. 50, Kahn, M. Ed., **1993**, *49*, 3444. b) Kahn, M. *Synlett* **1993**, 821. c) Kim, H. -O.; Lum, C.; Lee, M. S. *Tetrahedron Lett*. **1997**, *38*, 4935.
2. Houpis, I. N.; DiMichele, L.; Molina, A. *Synlett* **1993**, 365 and references cited therein.
3. a) Scott, W. J.; Pena, M. R.; Sward, K.; Stoessel, S.; Stille, J. K. *J. Org. Chem*. **1985**, *50*, 2302. b) Ritter, K. *Synthesis* **1993**, 735.
4. **Typical Procedure for 1: Synthesis of 1a**: To a stirred solution of methyl acetoacetate (1.1 mL, 10 mmol) in dichloromethane (30 mL) was added NaH (400 mg of 60%/oil, 10 mmol) at 0 $^{o}$C. After 10 min, $Tf_2O$ (2 mL, 12 mmol) was added at the same temp. After 30 min, 1N HCl (50 mL) was added and the solution was extracted with dichloromethane (100 mL). The organic extract was then dried ($MgSO_4$), passed through a short pad of $SiO_2$, and concentrated to provide an oil in quantitative yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.77 (s, 3H), 5.77 (s, 1H). Without further purification the oil was used for the next reaction.
To a stirred solution of above triflate in DMF (30 mL) was added *t*-butyl acrylate (**3a**) (3 mL, 20 mmol), followed by $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) and TEA (4.2 mL, 30 mmol) at rt. The solution was heated at 80 $^{o}$C for 22h. After dilution with $Et_2O$ (100 mL) and $H_2O$ (100 mL), the aqueous phase was separated and extracted with $Et_2O$ (100 mL). The combined organic extracts were washed with $H_2O$ (100 mL), dried ($MgSO_4$), and concentrated to give an oil. The crude product was purified by flash chromatography (hexane:EtOAc = 95:5 to 90:10 to 80:20) to provide an oil (560 mg, 25 % for two steps). Less Polar fraction: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.23 (d, 3H, *J*=1.5Hz), 3.69 (s, 3H), 5.97 (d, 1H, *J*=0.5Hz), 6.10 (d, 1H, *J*=16Hz), 7.14 (dd, 1H, *J*=16, 1Hz). More polar fraction: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.01 (d, 3H, *J*=1.5Hz), 3.73 (s, 3H), 5.90 (d, 1H, *J*=0.5Hz), 6.08 (dd, 1H, *J*=16, 1Hz), 8.50 (d, 1H, *J*=16Hz). The ratio was about 3:1.
A solution of above diene diester (550 mg, 2.4 mmol) in dichloromethane (2 mL) was treated with TFA (2 mL) at rt for 1.5h. Concentration gave **1a** as a pale yellow solid (420 mg, 100 %). Minor: $^1$H NMR (500 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.77 (s, 3H), 6.00 (s, 1H), 6.18 (d, 1H, *J*=16Hz), 8.72 (d, 1H, *J*=16Hz). Major : 2.03 (d, 3H, *J*=1 Hz), 3.77 (s, 3H), 6.10 (s, 1H), 6.23 (d, 1H, *J*=16Hz), 7.38 (d, 1H, *J*=16Hz), 9.92 (br). MS $ES^-$ m/z 169.5 ($M-H^+$); $ES^+$ m/z 171.6 ($M+H^+$).