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Expanding the scope of the indium-promoted allylation reaction: 4-(bromomethyl)-1,3-dioxol-2-one as a synthetic equivalent of a 3-arylhydroxyacetone enolate

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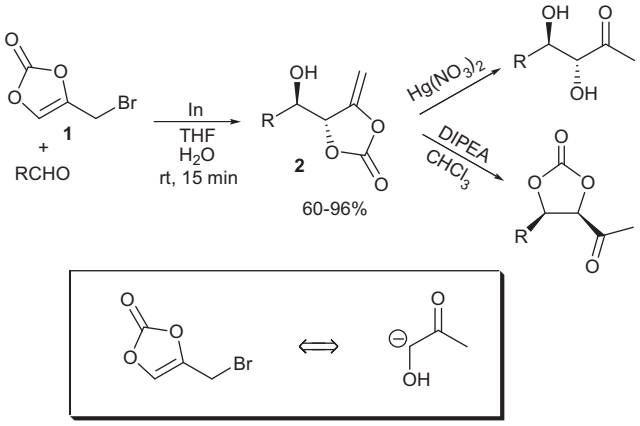
ABSTRACT

Cyclic enol carbonates of type **2**, obtained via the indium-promoted allylation of aldehydes with 4-(bromomethyl)-1,3-dioxol-2-one, undergo Heck reaction with aryl iodides in the presence of silver trifluoroacetate, to give the corresponding arylated products. Thus, 4-(bromomethyl)-1,3-dioxol-2-one can be considered as a synthetic equivalent of 3-arylhydroxyacetone enolate.

Metal-promoted allylation of a carbonyl group is a very important method for carbon–carbon bond formation.[1–4] Of the range of metals which can be used for this purpose, indium (and, to a lesser extent, zinc) is by far the most popular promoter, due to mild reaction conditions, high yields, tolerance of a range of functional groups, and the possibility to effect the reaction in aqueous medium.[2,5–8] An allyl group can be transformed into a variety of functional groups, which contributes to the versatility of the reaction. However, the allylation is a reductive process, and one functional group is lost during the formation of a carbon–carbon bond. Higher levels of functionalization are achieved by using 2oxygenated allylic reagents. Thus 3-acyloxy,[9–12] 3-oxy carbonate[13] and 3-alkoxy[14] allylic reagents have been used for the synthesis of monoprotected diols, while 2-acyloxy[15] and 2-alkoxy[16,17] reagents were employed as synthetic equivalents of acetone enolates.

We have previously reported the use of 4-(bromomethyl)-1,3-dioxol-2-one (**1**) as a highly functionalized allylic synthon, which affords stereoselectively anti-adducts **2** in the indium-promoted reaction with a range of carbonyl compounds (Scheme 1).[18] The initial enol carbonate-type products **2** could be hydrolyzed into dihydroxyketones, or isomerized into saturated cyclic carbonates. Thus, 4-(bromomethyl)-1,3-dioxol-2-one (**1**) represents a synthetic equivalent of a hydroxyacetone enolate.

We set out to further expand the synthetic utility of 4-(bromomethyl)-1,3-dioxol-2-one. Obviously, in addition to being an equivalent of a hydroxyacetone enolate, it would be useful if the title reagent could function as a synthetic equivalent of other hydroxyketone derivatives. Instead of preparing the corresponding 4-(bromomethyl)-1,3-dioxol-2-one derivative for every hydroxyketone unit to be introduced, it would be more efficient to develop a method for derivatization of the allylation products, allowing for the transformation of the initial product into a range of derivatives. As a means of making a carbon–carbon bond with enol carbonates



Scheme 1.

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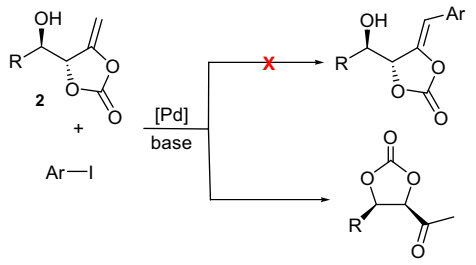
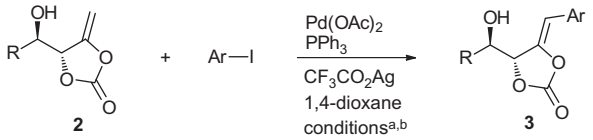


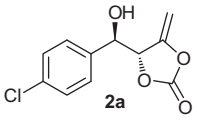
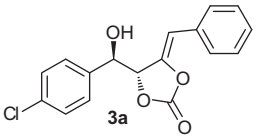
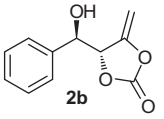
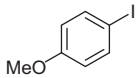
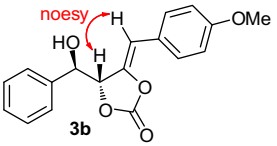
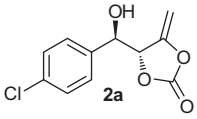
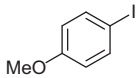
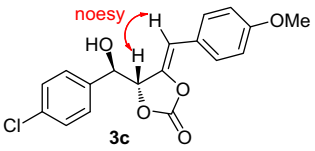
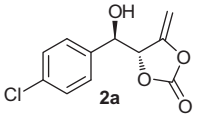
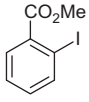
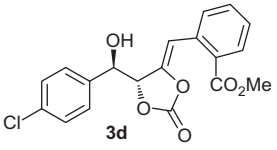
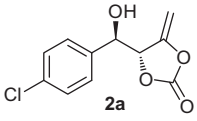
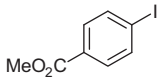
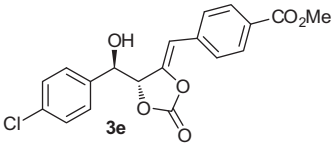
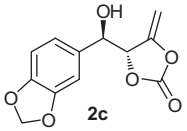
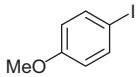
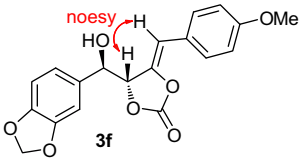
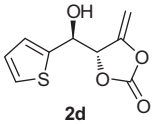
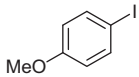
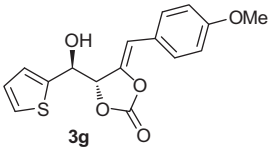
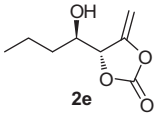
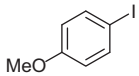
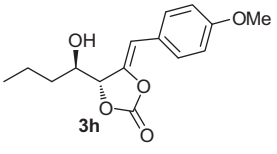
Scheme 2.

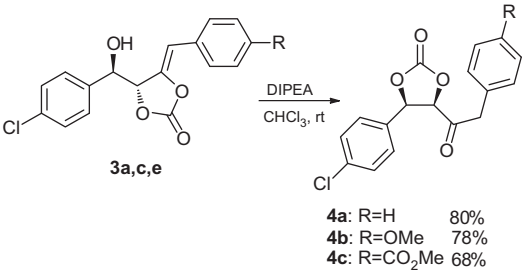
we considered the Heck reaction.[19–22] However, an inherent problem was that the Heck reaction is usually performed in the presence of a base (usually an aliphatic amine),[23,24] unfortunately, under these conditions, isomerization of the starting enol carbonate into a saturated cyclic carbonate is faster than the carbon–carbon bond forming reaction (Scheme 2).[18]

A literature search revealed an alternative way to perform the Heck reaction which seemed promising in our case: in 2000, Dixneuf and co-workers reported that aryl halides react with alkenes in the presence of $Pd(PPh_3)_4$ and CF_3CO_2Ag, to give arylated products in good yields.[25] The absence of a base appeared to be well

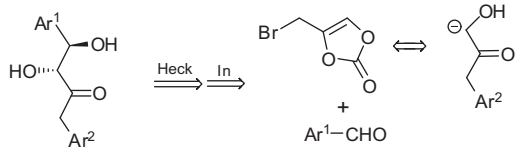
Table 1
Reagents and conditions: enol carbonate (1 equiv), Ar–I (1.5 equiv), CF_3CO_2Ag (1.5 equiv), $Pd(OAc)_2$ (0.2 equiv), Ph_3P (0.2 equiv), 1,4-dioxane, stirred under an argon atmosphere, using the following conditions: (a) heating at 95 °C, 1–3.5 h or (b) irradiated in a microwave reactor, (160 W, 50 min)



Entry	Substrate	Electrophile	Product	Yield (%)
1				58[a] 61[b]
2				51[a] 49[b]
3				55[a] 50[b]
4				50[a] 40[b]
5				61[a] 46[b]
6				53[a] 40[b]
7				53[a] 47[b]
8				38[a] 40[b]



Scheme 3.



Scheme 4.

suited for base-sensitive substrates of type **2**, and we decided to apply these reaction conditions for the arylation.

In the first experiment, enol carbonate **2a** was reacted with iodobenzene under the conditions described in the literature.[25] To our pleasure, the expected adduct **3a** was obtained in 58% yield.[26] The reaction was also performed under microwave irradiation, which brought about a small increase in the yield and shortened the reaction time to 50 min.[27] Several other enol carbonates **2b–e** were then submitted to similar experimental conditions, using either electron-rich (MeO-substituted) or electron-deficient (*o*-CO_2Me, *p*-CO_2Me substituted) aryl iodides as the coupling partners. In all cases the expected products were obtained in moderate yields (Table 1). However, the yields were not always improved under the microwave conditions. The reaction is stereoselective, providing exclusively the *Z*-isomer, as confirmed by NOESY experiments on several Heck products. The products of the Heck reaction are stable in the presence of 2 M hydrochloric acid, and can be purified by chromatography on silica without problems. However, on treatment with DIPEA, they rearrange into cyclic carbonates of the corresponding α,β-dihydroxyketones, with retention of configuration at the stereogenic centers (Scheme 3).[28]

Thus, 4-(bromomethyl)-1,3-dioxol-2-one (**1**) can be considered as a synthetic equivalent of 3-arylhydroxyacetone enolates (Scheme 4).

In conclusion, we believe that the results disclosed in this Letter expand the scope of the indium-promoted allylation with 4-(bromomethyl)-1,3-dioxol-2-one (**1**), and offer an efficient approach to the synthesis of *anti*-α,β-dihydroxyketone derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.115.

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26. *Experimental procedure for the Heck reaction under thermal conditions. 4-Benzylidene-5-[(4-chlorophenyl)-hydroxymethyl]-1,3-dioxolan-2-one (**3a**):* to a solution of enol carbonate **2a** (23.5 mg, 0.098 mmol) in 1,4-dioxane (1 mL) were added iodobenzene (30.0 mg, 17 μL, 0.15 mmol), silver trifluoroacetate (33.2 mg, 0.15 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) and PPh_3 (5.1 mg, 0.02 mmol) under an argon atmosphere. The mixture was stirred vigorously and heated to 95 °C, while the progress of the reaction was monitored by TLC (SiO_2 plates, eluent: 30% EtOAc in benzene). Upon completion, the reaction mixture was partitioned between H_2O and EtOAc, the aqueous layer was extracted with EtOAc and the combined organic extract dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. Purification by dry-flash chromatography (SiO_2; eluent: 20% EtOAc in petroleum ether) afforded 18 mg (58%) of the title compound **3a**, as white crystals. *Physical data for **3a**:* mp 115–7 °C; FT-IR (film, cm^{-1}): 3475, 3029, 1832, 1705, 1494, 1370, 1232, 1129, 1086, 1054, 762, 697. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.40–7.24 (m, 9H), 5.32 (dd, J_1 = 3.7 Hz, J_2 = 1.8 Hz, 1H), 5.13 (d, J = 3.7 Hz, 1H), 5.09 (d, J = 1.5 Hz, 1H), 2.86 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 152.1 (C), 140.6 (C), 134.9 (C), 134.8 (C), 131.9 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 106.0 (CH), 82.6 (CH), 73.7 (CH). HRMS (ESI): calcd for $[C_{17}H_{13}ClO_4 + NH_4^+]$: 334.0841, found for $[M+NH_4]^+$: 334.0839.
27. *Experimental procedure for the Heck reaction under microwave conditions. 4-(Hydroxyphenylmethyl)-5-(4-methoxybenzylidene)-1,3-dioxolan-2-one (**3b**):* a solution of enol carbonate **2b** (1.0 mmol) in 1,4-dioxane (1.5 mL) was placed in a microwave tube, equipped with a magnetic stir bar and a septum. To this solution were added (in the following order): 4-iodoanisole (24.0 mg, 0.12 mmol), silver trifluoroacetate (24.2 mg, 0.12 mmol), $Pd(OAc)_2$ (1.7 mg, 7.5 μmol) and PPh_3 (2.0 mg, 7.5 μmol), under an argon atmosphere. The tube was transferred into a microwave reactor (Biotage Initiator 2.5) and irradiated at 160 W, over 30 min. An additional amount of $Pd(OAc)_2$ (1.7 mg, 7.5 μmol) and PPh_3 (2.0 mg, 7.5 μmol) each were added and irradiation was continued for a further 20 min, until the reaction was complete. Work-up as for the thermally-induced reaction afforded 11.2 mg (49%) of the title compound **3b**, as a yellow oil. *Physical data for **3b**:* FT-IR (film, cm^{-1}): 3447, 2932, 1823, 1512, 1251, 1183, 1051, 762, 703, 623. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.40 (s, 5H), 7.34 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.35 (dd, J_1 = 3.5 Hz, J_2 = 1.5 Hz, 1H), 5.15 (br s, 1H), 5.01 (d, J = 1.5 Hz, 1H), 3.80 (s, 3H), 2.62 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 159.1 (C), 152.3 (C), 139.1 (C), 136.5 (C), 130.0 (CH), 128.9 (CH), 128.7 (CH), 126.6 (CH), 124.8 (C), 114.0 (CH), 105.5 (CH), 82.8 (CH), 74.3 (CH), 55.3 (CH_3). HRMS (ESI): calcd for $[C_{18}H_{16}O_5 + NH_4^+]$: 330.1336, found for $[M+NH_4]^+$: 330.1341.
28. *Experimental procedure for the isomerization. cis-4-(4-Chlorophenyl)-5-(2-phenylacetyl)-1,3-dioxolane-2-one:* a solution of carbonate **3a** (24.0 mg, 0.08 mmol) and DIPEA (2.2 mg, 3.0 μL, 0.04 mmol) in $CHCl_3$ (1.0 mL) was stirred at rt for 1 h. The solvent was removed under reduced pressure and the crude product was purified by dry-flash chromatography (SiO_2; eluent: 20% EtOAc in petroleum ether), to give 21.6 mg (80%) of the title compound, as white crystals. *Physical data for **4a**:* mp 142–3 °C. FT-IR (KBr, cm^{-1}): 3064, 2934, 1808, 1733, 1600, 1494, 1335, 1174, 1154, 1057. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38 (d, J = 8.4 Hz, 2H), 7.26–7.22 (m, 3H), 7.16 (d, J = 8.4 Hz, 2H), 6.74–6.69 (m, 2H), 5.90 (d, J = 8.7 Hz, 1H), 5.34 (d, J = 8.7 Hz, 1H), 3.54 (d, J = 16.9 Hz, 1H), 3.29 (d, J = 16.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 201.0 (C), 153.3 (C), 136.2 (C), 130.5 (C), 130.4 (C), 129.5 (CH), 129.4 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 81.7 (CH), 78.8 (CH), 47.2 (CH_2). HRMS (ESI): calcd for $[C_{17}H_{13}ClO_4 + NH_4^+]$: 334.0502, found for $[M+NH_4]^+$: 334.0831.