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# An unexpected intermolecular chiral biaryl coupling reaction induced by a hypervalent iodine(III) reagent: synthesis of potential precursor for ellagitannin

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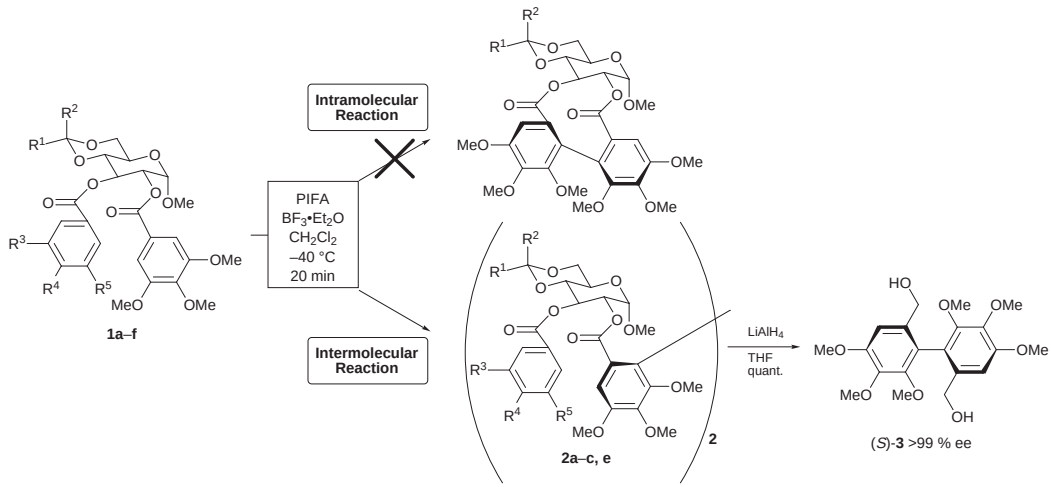
**A novel phenyliodine(III) bis(trifluoroacetate) (PIFA)-induced intermolecular chiral biaryl coupling reaction has been accomplished using α-D-glucose derivatives as chiral templates.**

Chiral biaryl compounds serve as important building blocks in the synthesis of natural products including ellagitannins, which have diverse pharmacological activities, such as inhibition of HIV reverse transcriptase,[1] DNA topoisomerase I mediated relaxation[2] and antioxidant activity.[3] In addition they are also used as chiral catalysts in asymmetric reactions.[4] Although several kinds of asymmetric biaryl coupling reactions leading to ellagitannin have been reported,[5] most of them involve the use of heavy metal reagents, such as $Pb(OAc)_4$, CuCN and Cu–pyridine, affording the products in moderate yields.

In recent years, use of hypervalent iodine(III) reagents has gained importance as a non- or low-toxic alternative to heavy metal reagents, to perform a variety of organic transformations. In continuation of our research on the use of hypervalent iodine(III) reagents in organic synthesis, we reported efficient nucleophilic substitution reactions on electron-rich aromatic compounds using a variety of nucleophiles such as $N_3$,[6] OAc, β-dicarbonyl compounds,[7] SCN and SPh.[8] Very recently, a hypervalent iodine(III)-induced intramolecular biaryl coupling reaction of phenol ether derivatives leading to dibenzo heterocyclic compounds has been reported by us.[9] The facile nature of this reaction prompted us to explore the possibility of using chiral templates in the above coupling reaction with a view to obtaining optically active biaryl compounds. Here we report the first example of an asymmetric intermolecular biaryl coupling reaction induced by phenyliodine(III) bis(trifluoroacetate) (PIFA) with α-D-glucose derivatives as the chiral auxiliary.

Our strategy to obtain the chiral biaryl compounds involves the following three step sequence: (a) synthesis of substituted aroyl derivatives of chiral diols, (b) biaryl coupling reaction using hypervalent iodine(III) reagent and (c) removal of the chiral auxiliary. Accordingly, aroyl derivatives of diols derived from glucose, menthane-3,8-diol, pinane-2,3-diol and hydrobenzoin have been synthesized and their biaryl coupling reaction examined using PIFA. Interestingly, except for the glucose-derived diol derivatives, none of the others were found to participate in the coupling reaction. Thus, the 1,2-diaroyl derivatives (**1a**, **b**)† of protected α-D-glucose underwent a smooth coupling reaction in the presence of PIFA–$BF_3$•$Et_2O$, unexpectedly in an intermolecular fashion, to afford the dimers (**2a**, **b**)† in good yields and with high diastereoselectivity

**Table 1** Novel chiral biaryl coupling reaction using PIFA




| Run | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%)[a] | De (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | Ph | OMe | OMe | OMe | 79 (90) | > 99 |
| 2 | **1b** | Ph | H | OMe | OMe | OMe | 44 (68) | > 99 |
| 3 | **1c** | Me | Ph | OEt | OEt | OEt | 37 (59) | > 99 |
| 4 | **1d** | Me | Ph | OMe | H | OMe | 0[b] | — |
| 5 | **1e** | Me | Ph | H | OMe | OMe | 30 (38) | > 99 |
| 6 | **1f** | Me | Ph | H | H | H | 0[b] | — |

[a] Yields in parenthesis indicate the conversion yields based upon the consumed starting material. [b] Complex mixture.

(Table 1). It is quite surprising that the reaction proceeds in an intermolecular fashion and not in the expected intramolecular way. Even more surprising is that only the aromatic ring attached to the C-2 carbon of the sugar moiety underwent the coupling reaction, while the aromatic ring on the C-3 carbon of the sugar remained intact. However, it has been observed that the substituent on the C-3 aromatic ring exerts a great influence on this biaryl coupling reaction. High yields of the products were obtained in the case where the aromatic ring on the C-3 carbon of the sugar was substituted with three methoxy groups at the 3', 4' and 5' positions. Bulkier substituents on the C-3 aromatic ring reduce the yield of the desired product, while no reaction was observed at all with the unsubstituted one. Noteworthy is that only the α-D-glucopyranoside derivative is effective in bringing about this coupling reaction. No coupling reaction took place with the diaroyl derivatives of methyl-β-D-glucopyranoside. Substituted diaroyl derivatives derived from other carbohydrate molecules such as galactose or mannose proved unsuccessful for this reaction. Furthermore, the choice of the Lewis acid used to activate PIFA seems to be critical. Among tested Lewis acids such as $BF_3$•$Et_2O$, $BF_3$•$Bu_2O$, $BCl_3$, $ZnBr_2$, $TiCl_4$, $SnCl_4$, $Et_2AlCl$, $FeCl_3$, $MgCl_2$, $Sn(OTf)_3$ and TMSOTf, only $BF_3$•$Et_2O$ was found to be an efficient activator in the present case.

In order to obtain the chiral biaryl compound, the coupled adducts (**2a**–**c**, **e**) were treated with $LiAlH_4$. In all cases, the optically active biphenyl compound (**3**) was obtained in quantitative yield, with the regeneration of the chiral sugar auxiliary, which can be used for successive reactions. The optical purity of **3** was determined by HPLC to be >99%, according to the procedure of Meyers.[5d,10]

A plausible explanation for this unexpected intermolecular coupling reaction could be that the sugar moiety and the trimethoxybenzoyl group present at the C-3 carbon of the sugar have a spacial interaction, thereby favorably positioning the aromatic ring on the C-2 carbon to couple with another like molecule.

In summary, we have encountered an unexpected intermolecular biaryl coupling reaction induced by PIFA. The reaction proceeds in high yields and with remarkable diastereoselectivity. The importance of chiral biaryl compounds in organic synthesis as well as in biological sciences, coupled with the use of a hypervalent iodine(III) reagent as a low-toxic reagent, render this method attractive for the synthesis of optically active biphenyl compounds. Detailed investigation of this interesting reaction is in progress.

## Notes and references

† *Preparation of* **1a**: A solution of methyl-4,6-*O*-(1′-methylbenzylidene)-α-D-glucopyranoside (ref. 11) (2.22 g, 7.5 mmol), DMAP (183 mg, 1.5 mmol), DCC (3.25 g, 15.75 mmol) and 3,4,5-trimethoxybenzoic acid (3.18 g, 15.0 mmol) in $CH_2Cl_2$ (125 ml) was stirred at room temperature for 12 h. The precipitate was filtered and the mother liquor was subjected to column chromatography (*n*-hexane–AcOEt = 3 : 2), giving **1a** (4.68 g, 6.83 mmol, 91.0 %) as colorless needles. Mixed benzoates **1c**–**f** were synthesized from methyl-4,6-*O*-(1′-methylbenzylidene)-2-(3′,4′,5′-trimethoxybenzoyl)-α-D-glucopyranoside, which in turn was regioselectively prepared from methyl-4,6-*O*-(1′-methylbenzylidene)-α-D-glucopyranoside using 1-(benzoyloxy)-benzotriazole (ref. 12).

*Preparation of* **2a**: To a stirred solution of **1a** (34.2 mg, 0.050 mmol) in $CH_2Cl_2$ (0.50 ml) was added a solution of PIFA (21.5 mg, 0.050 mmol) and $BF_3$•$Et_2O$ (0.013 ml, 0.100 mmol) in $CH_2Cl_2$ (0.50 ml) at −40 °C under nitrogen atmosphere, and the reaction was stirred at the same temperature for 20 min. The reaction was quenched by the addition of saturated $NaHCO_3$, extracted with $CH_2Cl_2$, washed with brine, dried over $Na_2SO_4$ and evaporated. After column chromatography (*n*-hexane–AcOEt = 1 : 1), **2a** (27.0 mg, 0.0197 mmol, 79%) and **1a** (4.0 mg, 12%) were obtained as colorless needles. *Selected data* for **2a**: mp 168.0–170.0 °C (from $Et_2O$); $\delta_H$(500 MHz, $CDCl_3$) 1.47 (6H, s), 3.32 (6H, s), 3.45 (6H, s), 3.57–3.63 (4H, m), 3.80 (6H, s), 3.82 (6H, s), 3.91 (6H, s), 3.92 (12H, s), 3.96–4.06 (4H, m), 4.64 (2H, dd, *J* 9.77, 3.66), 4.75 (2H, d, *J* 3.66), 5.86 (2H, dd, *J* 9.77, 9.77), 7.20 (2H, s), 7.33 (4H, s), 7.33–7.37 (10H, m); $\delta_C$(75.0 MHz, $CDCl_3$) 31.78, 55.13, 55.65, 56.25, 60.39, 60.82, 60.95, 62.99, 63.73, 70.10, 72.32, 73.01, 97.50, 102.15, 107.06, 109.31, 124.56, 124.54, 125.14, 126.59, 128.13, 128.83, 140.29, 142.65, 145.51, 150.87, 152.03, 153.09, 165.22, 165.41; IR $\nu_{max}$(KBr)/$cm^{-1}$ 1728, 1338, 1223 $cm^{-1}$; *m/z* (FAB) 1366 ($M^+$); HRMS (FAB): calc. for $C_{70}H_{78}O_{28}Na$ 1389.4578, found 1389.4561. Anal. calc. for $C_{70}H_{78}O_{28}$: C, 61.49; H, 5.75. Found: C, 61.09; H, 5.73.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