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A regioselective palladium-free protocol for accessing unsymmetrical biaryls through ring transformation of 6-aryl-~-pyrones ~

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Abstract-A regioselective synthesis of unsymmetrical biaryls with electron withdrawing or donating substituents is described and illustrated by carbanion-induced ring transfonnation of 6-aryl-a-pyrones with methoxyacetone in excellent yield. Our methodology is an alternative to classical organometal-catalyzed aryl-aryl coupling reactions and can be applied to the synthesis of functionally demanding naphthyl biaryls for the development of new ligands for asymmetric synthesis.

Aryl-aryl bOfd formation for the preparation of symmetrical and unsymmetrical biaryl compounds is a very useful and important tool in organic chemistry. Biaryl ring systems functionalized with electron donor or acceptor moieties are constituents of a large number of natural products I and synthetic pharmaceuticals and are useful as versatile auxiliaries for asymmetric syntheses,2 as chiral phases for chromatography3 and as important substrates for chiralliquid crystalline materials.4 Several biaryl derivatives have been designed as potent glucagon receptor antagonists for the treatment of diabetes.5

Biaryls can be prepared by transition metal-catalyzed intermolecular or intramolecular aryl-aryl cross-coupling reactions. Reductive dimerization of aryl halides is one of thl oldest methods6 for the construction of biaryls using copper bronze as a reducing agent. Oxidative coupling of electron-rich aromatic phenols has also led to the formation of biaryls in moderate yields.7 Palladium-catalyzed cross coupling between electrophilic aromatic halides or triflates and the organometallic species Ar-M (M being Mg, Zn, Sn, and B) has become a general approach for the construction of symmetrical and unsymmetrical biaryls.8 For example, the palladium-catalyzed aryl-boronic acid coupling (Suzuki reaction) has become a general and versatile route to access functionalized biaryls.8f Despite the wide synthetic potential of these metal-assisted cross-coupling reactions, they are associated with expensive organometallic reagents/catalysts, in some cases harsh reaction conditions and undesired byproducts. Thus, there exists a need to develop an expedient route for the synthesis of biaryls that does not require specialized reagents or expensive catalysts, which could offer flexibility with respect to variation in the substitution pattern. Although numerous regio- and stereoselective Diels-Alder reactions9 of a-pyrones with electron-deficient and electron-rich dienophiles provide benzene derivatives, they require forcing thermal reaction conditions to eliminate carbon dioxide from the adduct and/or are associated with the formation of a mixture of positional isomers.

Herein, we report a new palladium-free protocol for the synthesis of functionalized biaryls through a ring transformation reaction of 6-aryl-a-pyrones with methoxyacetone in high yields. The procedure utilizes a simple transformation strategy without using an expensive organometallic reagent or a catalyst.

During our studies on the chemistry of a-pyrones, we observed 10 that a-pyrones prepared from a-oxo-ketene-S,S-acetal" were useful substrates for ring transformation reactions, possessing flexible substitution patterns and a good alkylsulfanylleaving group for generating molecular divt:rsity. Our rt:cent effortsl2 have indicated that the a-pyranone ring can be converted to

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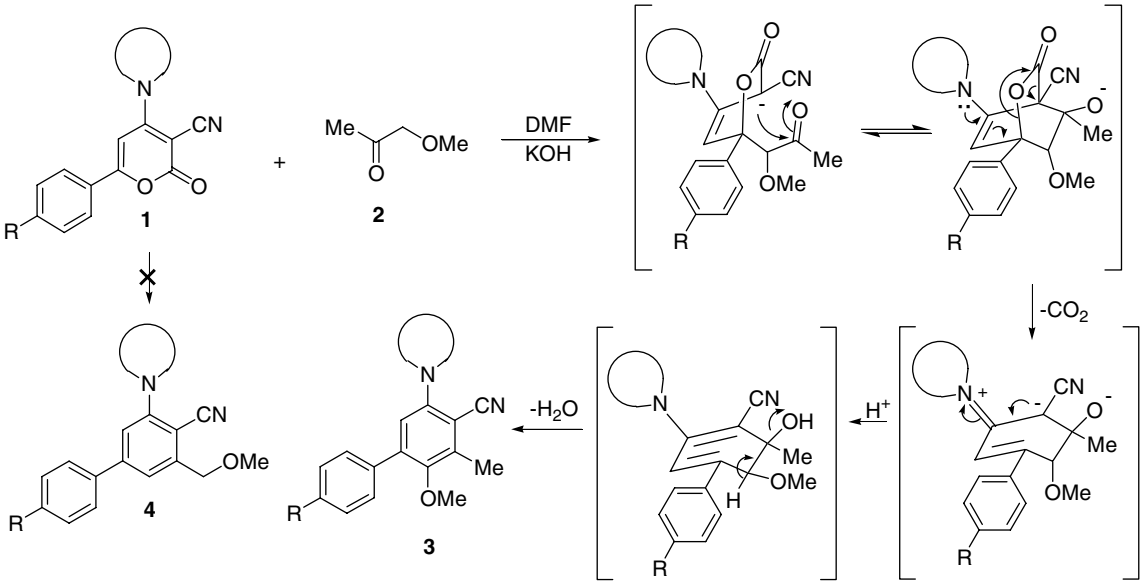
a benzene or pyridine ring depending upon the nucleophile used in the reaction. We have also demonstrated a general methodology for the synthesis of arylated benzenes at room temperature in a controlled manner.[12d]

The introduction of a functional group in biaryl scaffolds, particularly around the biaryl axis, is an important transformation in organic chemistry. Recently, Ram and co-workers[13] reported the regioselective synthesis of biaryl acetates and 1,2-teraryls through a ring transformation strategy. Substrate α-pyrones **1a**–**f** used in this study were prepared by the reaction of methyl 2-cyano-3,3-dimethylsulfanyl-acrylate with substituted acetophenones under alkaline conditions in high yields, followed by reaction with secondary amines.[11] Lactones, **1a**–**f** have three electrophilic centres; C2, C4 and C6 in which the latter position is highly susceptible to nucleophilic attack due to extended conjugation and the presence of electron withdrawing substitutents at positions 2 and 3 of the pyran ring. In a typical process, the synthesis of biaryl compounds **3a**–**f** was achieved by stirring an equimolar mixture of α-pyrones **1a**–**f**, methoxyacetone and powdered KOH in DMF for 10–12 h at room temperature (Scheme 1). The reaction was monitored by TLC and upon completion was poured into ice water and neutralized with dilute HCl. The crude product was filtered and purified on a silica gel column using 25% chloroform in hexane as eluent. All the synthesized compounds were characterized by spectroscopic and analytical analysis.[14]

Formation of compound **4** could occur via reaction with a methyl carbanion instead of a methylene carbanion. However, the presence of methyl group protons at δ 2.50 ppm (s, 3H) in the ^{1}H NMR of **3a** confirmed the structure as 2-methoxy-3-methyl-5-piperidin-1-yl-biphenyl-4-carbonitrile and not 5-methoxymethyl-3-piperidin-1-yl-biphenyl-4-carbonitrile **4a**.

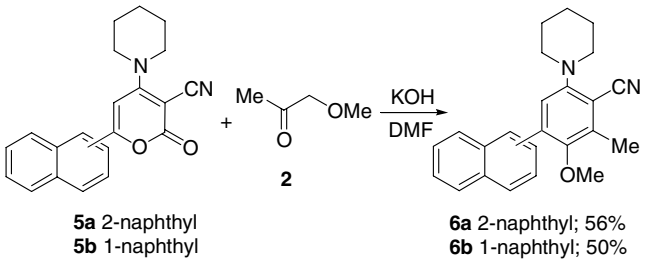
The transformation of 6-aryl-4-amino-α-pyrones **1a**–**f** into biaryls **3a**–**f** is possibly initiated by attack of the methylene carbanion of methoxyacetone at C6 of lactone **1**. Subsequent intramolecular cyclization involving the carbonyl functionality of **2** and C3 of the pyranone ring and elimination of carbon dioxide, followed by protonation and dehydration gave biaryl compounds **3a**–**f** in good yields.

A benzene ring substituted with bulky naphthyl moieties exists as conformational or configurational stereoisomers depending on the extent of steric hindrance around the biaryl axis.[15] The rigid binaphthyl skeleton has a rather high-energy barrier to atropisomerization and thus can be isolated as enantiopure species.[16] Several 2,2′-substituted-1,1′-binaphthyls are widely used as chiral ligands or as auxiliaries for various asymmetric syntheses. In order to demonstrate the utility of this approach in preparing sterically hindered biaryls, we prepared 6-naphthyl-α-pyrones (**5a**, **b**) by stirring a mixture of methyl 2-cyano-3,3-dimethylsulfanyl-acrylate



Product	R	N	Reaction time (h)	Yield (%)
3a	H	piperidine	10	71
3b	Br	pyrrolidine	12	60
3c	Br	piperidine	12	80
3d	Cl	piperidine	11	72
3e	Me	piperidine	12	60
3f	OMe	piperidine	11	75

Scheme 1.



Scheme 2.

with 1- or 2-acetonaphthone in the presence of a base in DMSO as described earlier.[11] The reaction of **5a**, **b** with methoxyacetone **2** in the presence of powdered KOH in dry DMF furnished 3-methoxy-2-methyl-4-naphthalen-1/2-yl-6-piperidin-1-yl-benzonitriles **6a**, **b** in good yields (Scheme 2). This transformation suggests that our methodology can be applied to the synthesis of congested naphthyl systems depending upon the degree of freedom required around the biaryl axis.

In order to demonstrate the synthetic utility and tolerance of other functional groups, we synthesized 2-methoxy-3-methyl-5-methylsulfanyl-biphenyl-4-carboxylic acid methyl esters **8a**–**c**, Our approach to biaryls **8a**–**c** is based on the ring transformation of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl-α-pyrones **7a**–**c** using methoxyacetone **2** as a carbanion source. α-Pyrones **7a**–**c** were prepared in high yields by reaction of methyl 2-carbomethoxy-3,3-di(methylsulfanyl)acrylate[11] with substituted acetophenones under alkaline conditions. Thus, stirring an equimolar mixture of **7a**–**c**, methoxyacetone and powdered KOH in DMF for 9–12 h at room temperature yielded 2-methoxy-3-methyl-5-methylsulfanyl-biphenyl-4-carboxylic acid methyl esters **8a**–**c** (Scheme 3). The reaction was monitored by TLC and thereafter poured onto ice water and neutralized with dilute HCl. The crude product thus obtained was filtered and purified by silica gel column chromatography using 25% chloroform in hexane as eluent. The appearance of a methyl group 3H singlet at δ 2.30 ppm in the ^{1}H NMR of compound **8a** confirmed the structure as the 4′-chloro-2-methoxy-3-methyl-5-methylsulfanyl-biphenyl-4-carboxylic acid methyl ester and not the 4′-chloro-5-methoxymethyl-3-methylsulfanyl-biphenyl-4-carboxylic acid methyl ester **9a**. All the synthesized compounds were characterized by spectroscopic analysis.[14]

In summary, we have prepared functionalized unsymmetrical biaryls through carbanion-induced ring transformation of 6-aryl-α-pyrones in excellent yields. Due to the mild reaction conditions under which the ring transformation occurs, our synthetic protocol can be applied in the presence of various electron-donor or acceptor groups. This methodology provides an easy access to diverse biaryl systems at room temperature under a transition-metal free environment.

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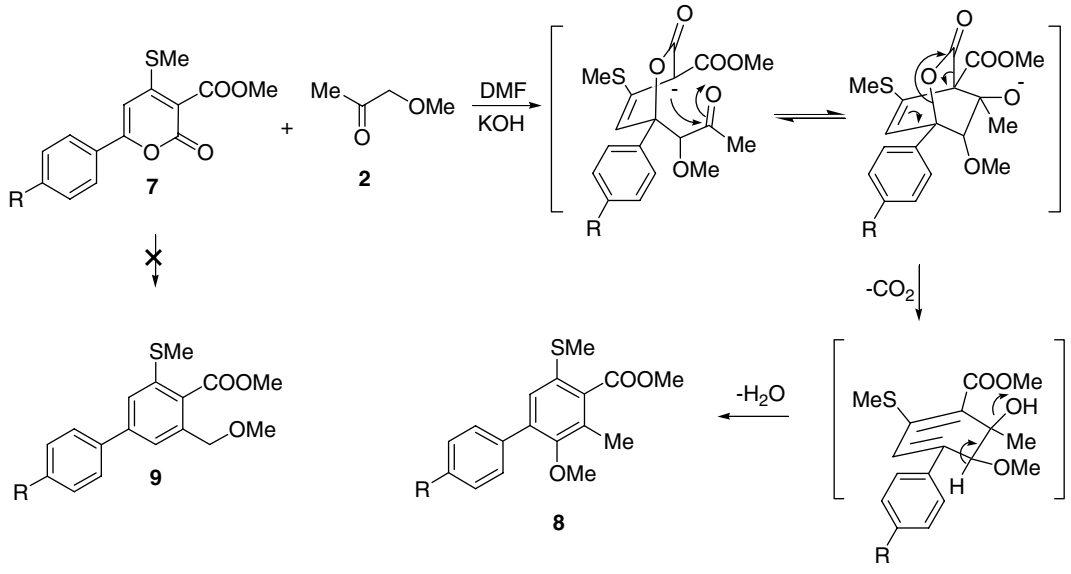

Product	R	Reaction time (h)	Yield (%)
8a	Cl	12	85
8b	Br	12	81
8c	OMe	11	76

Scheme 3.

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14. *General procedure for the synthesis of* **3**, **6** *and* **8**: A mixture of 6-aryl-α-pyrone **1**, **5** or **7** (1 mmol), methoxyacetone (1.2 mmol) and powdered KOH (1.5 mmol) in dry DMF (5 mL) was stirred at room temperature for 9–14 h. On completion (TLC), the reaction mixture was poured onto ice water with vigorous stirring and then neutralized with dilute HCl. The solid thus obtained was filtered and purified on a silica gel column using chloroform–hexane (1:3) as eluent; **3a**: white solid; mp 104–106 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60–1.67 (m, 2H, CH_2), 1.70–1.81 (m, 4H, $2CH_2$), 2.50 (s, 3H, Me), 3.04–3.13 (m, 4H, $2CH_2$), 3.31 (s, 3H, OMe), 6.81 (s, 1H, ArH), 7.35–7.49 (m, 3H, ArH), 7.50–7.59 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.36, 24.48, 26.65, 54.18, 60.64, 108.13, 117.64, 119.35, 128.35, 128.81, 129.25, 137.40, 138.18, 140.18, 150.71, 154.18; IR (KBr) 2212 cm^{-1} (CN); MS (ESI) 307 (M^++1); HRMS Calcd for $C_{20}H_{22}N_2O$ 306.1732; found, 306.1728. Compound **6a**: white solid; mp 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58–1.68 (m, 2H, CH_2), 1.77–1.88 (m, 4H, $2CH_2$), 2.56 (s, 3H, Me), 3.08–3.18 (m, 4H, $2CH_2$), 3.36 (s, 3H, OMe), 6.95 (s, 1H, ArH), 7.52–7.60 (m, 2H, ArH), 7.69–7.76 (m, 1H, ArH), 7.88–7.94 (m, 3H, ArH), 8.03 (s, 1H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.39, 24.50, 26.67, 54.22, 60.75, 108.23, 117.67, 119.57, 126.76, 126.86, 127.31, 128.11, 128.24, 128.34, 128.64, 133.27, 133.73, 135.78, 137.52, 140.10, 150.92, 154.27; IR (KBr) 2212 cm^{-1} (CN); MS (ESI) 357 (M^++1); HRMS Calcd for $C_{24}H_{24}N_2O$ 356.1889; found, 356.1882. Compound **8a**: white solid; mp 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, Me), 2.46 (s, 3H, SMe), 3.36 (s, 3H, OMe), 3.98 (s, 3H, OMe), 7.22 (s, 1H, ArH), 7.42 (d, $J = 8.6$ Hz, 2H, ArH), 7.51 (d, $J = 8.6$ Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.07, 17.45, 51.01, 58.90, 127.34, 128.53, 128.71, 128.75, 129.00, 132.48, 134.12, 134.80, 135.71, 153.38, 167.30; IR (KBr) 1722 cm^{-1}(CO); MS (FAB) 336 (M^+); HRMS Calcd for $C_{17}H_{17}ClN_3O$ 336.0587; found, 336.0577.
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