Synthesis of Biaryls via AlCl₃ Catalyzed Domino Reaction Involving Cyclization, Dehydration, and Oxidation
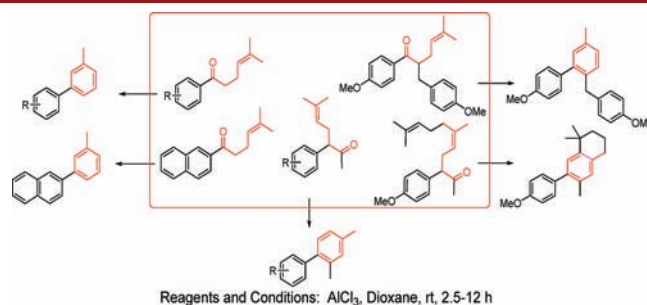
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ABSTRACT

Reagents and Conditions: AlCl₃, Dioxane, rt, 2.5-12 h

A new chemical access has been developed to synthesize biaryls from substituted acetophenones, phenylacetones, dihydrochalcone, and 2-acetylnaphthalene in reasonably good yields at room temperature via a domino reaction sequence of AlCl₃ catalyzed cyclization, dehydration, and then oxidation.

Domino or cascade reactions are sequential transformations where one reaction occurs after the other in the same reaction vessel. These cascading processes can include two or more reactions in the same vessel without addition of other reagents or modification of the reaction conditions. Domino reactions are classified in various ways; examples include cationic, anionic, radical, pericyclic, photochemical, and metal catalyzed.[1] Pericyclic domino reactions such as cycloadditions, sigmatropic rearrangements, electrocyclic reactions, ene reactions, and carbonyl-ene reactions are frequently used for the synthesis of a carbocyclic framework.[2] We intended on developing a new method for the synthesis of biaryls based on Lewis acid catalyzed pericyclic domino reactions.

The biaryl scaffold is a widely occurring component in many biologically active molecules (Figure 1) such as Felbinac[3] (anti-inflammatory), (±)-Glaucine[4] (anti-
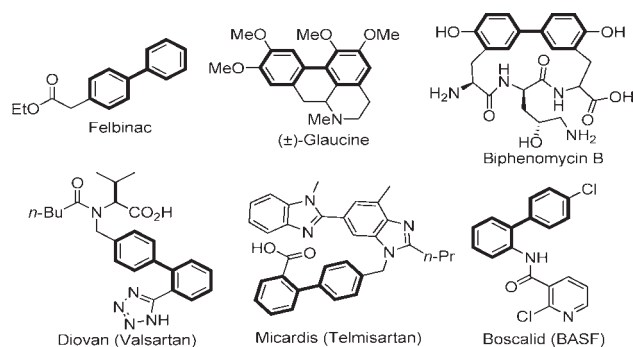

Figure 1. Examples of biaryl containing drugs and fungicide.

inflammatory), Biphenomycin[5] (antibiotic), Diovan[6] (hypertension), Micardis[7] (hypertension), and Boscalid[8]

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(fungicide). Biaryls are also used in several industrial applications such as polymers, advanced materials, and liquid crystals (LCD).[9]

The synthesis of biaryls has a long history from the old Pschorr reaction (1896)[10] to several transition metal catalyzed cross-coupling reactions such as Kumada,[11] Negishi,[12] Stille,[13] Suzuki,[14] Hiyama,[15] Sonogashira,[16] and further improvements in these procedures. Alternative methods such as direct arylation through C−H bond activation[17] and decarboxylative cross-coupling reactions[18] in place of conventional coupling reactions have begun to emerge in the past few years. These methods also however use transition metal catalysts. Synthesis of biaryls without coupling reactions are also welcomed by the chemical community. Recently, Shahzad and co-workers synthesized the phenyl-naphthyl compounds through cyclization of β-ketoester substituted stilbene derivatives using PhSeCl as a electrophile in the presence of Lewis acids.[19] Similarly Qun Liu and co-workers developed a new route for *p*-terphenyls and heteroaryl analogues including bipyridines via [5C 1C(N)] annulation of aryl-alkenoyl ketene-(*S,S*)-acetals (five carbon 1,5-bielectrophilic species) with nitroethane or ammonium acetate.[20] In this letter we also wish to report a new chemical access for the synthesis of biaryls from substituted acetophenones, phenylacetones, dihydrochalcones, and 2-acetylnaphthalene via an AlCl$_3$ catalyzed domino reaction.[21]

In order to synthesize biaryls without coupling reactions, commercially available acetophenone (**1a**) was prenylated using NaH to generate the key intermediate **2a** (Scheme 1).[21] We anticipated that Lewis acids might induce a carbonyl-ene reaction. To explore this idea the prenylated compound **2a** was reacted with a few Lewis acids (BF$_3$·Et$_2$O, ZnCl$_2$, TiCl$_4$, AlCl$_3$) and also inorganic acids at various molar ratios. Among them 20 mol % AlCl$_3$ in dry dioxane provided the desired biaryl **3a** (3-methyl-biphenyl) in moderate yield (Scheme 1 and Table 1).[21]

Encouraged by these results the domino reaction was explored with various substituted aromatic ketones **2b−f** and obtained respective biaryls **3b−f** with moderate to good yields (Table 1) under similar reaction conditions.

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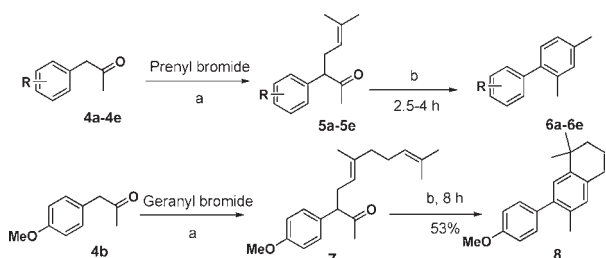(17) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

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(21) Please see the Supporting Information for experimental procedures.

Scheme 1. Synthesis of Biaryl via AlCl$_3$ Catalyzed Domino Reaction from Substituted Acetophenones[a]
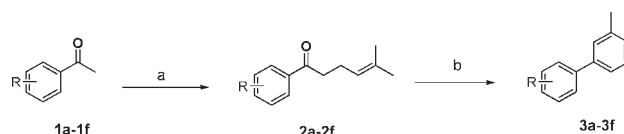
[a] Reagents and conditions: (a) Prenyl bromide, NaH, DMF, −20 °C to rt, 3.5−7 h; (b) 20 mol % AlCl$_3$, Dry Dioxane, rt.

Table 1. Reaction Time and Isolated Yields of Biaryls from Substituted Acetophenones

entry	alkenylated ketone	biaryl compound	time (h)	isolated yields (%)
1	2a	3a	4	59
2	2b	3b	3.5	80
3	2c	3c	6	56
4	2d	3d	4.5	41
5	2e	3e	6.5	45
6	2f	3f	7	54

The versatility of this new method and reaction conditions was further examined with substituted phenylacetones. The compounds **5a−5e** were prepared from respective phenylacetones (**4a−4e**) by a prenylation reaction and subsequent reaction with 20 mol % AlCl$_3$ in dry dioxane provided the desired biaryls **6a−6e** in good yields (Scheme 2, Table 2).[21] To expand the reaction utility, an attempt was made to synthesize biaryls from geranylated derivative **7** instead of prenylated derivatives (Scheme 2). The biaryl **8** formed from **7** has an aryl fused tetrahydronaphthalene skeleton due to aromatization of a geranyl group and subsequent cyclization of a C-5 side chain of the geranyl group with a newly generated aromatic ring.

To synthesize phenyl-naphthalene, 2-acetylnaphthalene (**9**) was prenylated to give an intermediate **10** and further reaction with AlCl$_3$ provided 2-*m*-tolyl-naphthalene (**11**) in good yields (Scheme 3). Prenylated dihydrochalcone **13** which was obtained from **12** was also tested for the formation of biaryls using a similar reaction protocol, which gave benzylated biaryl **14** with 72% yield (Scheme 3).
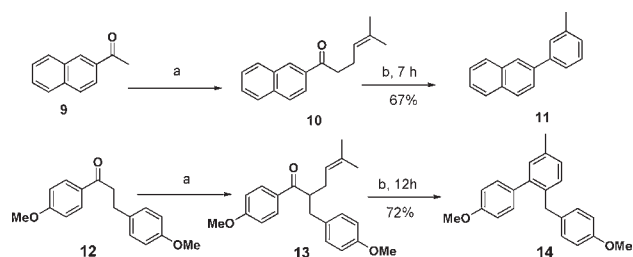
a Reagents and conditions: (a) NaH, DMF, −20 °C to rt, 3−4 h; (b) 20 mol % AlCl₃, Dry Dioxane, rt.

Table 2. Reaction Time and Isolated Yields of Biaryls from Substituted Phenylacetones

entry	alkenylated ketone	biaryl compound	time (h)	isolated yields (%)
1	5a	6a	3	72
2	5b	6b	2.5	79
3	5c	6c	4	72
4	5d	6d	3.5	69
5	5e	6e	3	74

Scheme 3. Synthesis of Biaryls via AlCl₃ Catalyzed Domino Reaction from Substituted 2-Acetylnaphthalene and Dihydrochalcone[a]


a Reagents and conditions: (a) Prenyl bromide, NaH, DMF, −20 °C to rt, 3−4 h; (b) 20 mol % AlCl₃, Dry Dioxane, rt.

Comparatively high yields and shorter reaction times were observed in the biaryls formation from substituted phenylacetones (Table 2) compared to those of substituted

acetophenones (Table 1). It appears that the chairlike transition state requires partial carbonyl oxygen in the equatorial position to provide high yields. Thus, transition state coordinates of **2a** and **2c**−**2f** would push the bulky aryl group in the axial position. On the other hand, the transition state coordinates of **5a**−**5e** could easily arrange to give the partial carbonyl oxygen and the vicinal aryl group a 1,2-diequatorial coordinate. In the cases of **2b** and **13**, the highly electron-donating methoxy group may have changed the transition state toward the starting material. The above argument is also applied for the naphthyl compound **10**, since naphthyl is much better electron-donating than phenyl or tolyl. On the other hand, **7** has gone through two cyclizations to give **8**, the second of which has to be the slower reaction when compared to the related cyclization of **5b** (2.5 h, 79% yield; entry 2, Table 2) and hence is rate-determining.

The reaction mechanism for the formation of biaryls from prenylated acetophenones (**2a**−**2f**), phenylacetones (**5a**−**5e**), geranylated phenylacetone (**7**), 2-acetylnaphthalene (**10**), and dihydrochalcone (**13**) appears to be a Lewis acid catalyzed intramolecular carbonyl-ene reaction[22] to provide cyclobutanol intermediate **I/IV** followed by ring expansion to give a six-membered carbocyclic ring as in **II/V**.

Scheme 4. Possible Reaction Mechanism for the Formation of Biaryls from Acetophenones and Phenylacetones via AlCl₃ Catalyzed Domino Reaction Sequence
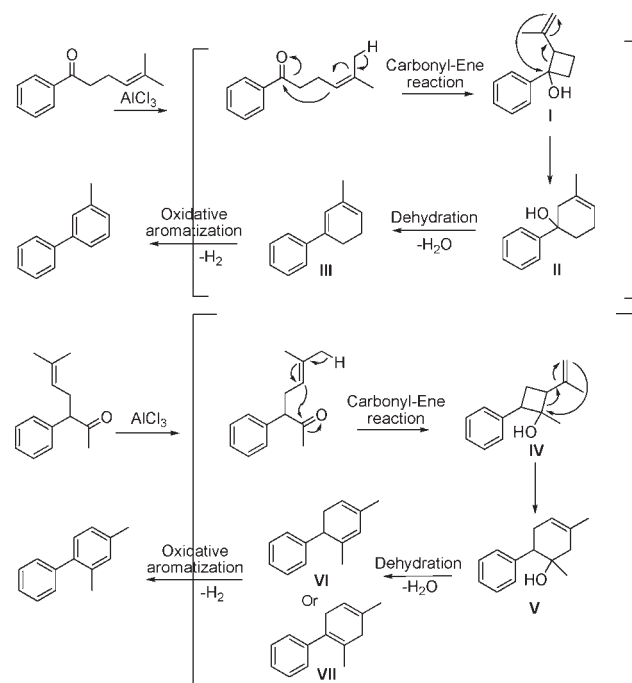
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The dehydration of **II/V** and subsequent dehydrogenation (oxidative aromatization)[23] might be furnishing the desired biaryl skeleton (Scheme 4). To find out the oxidative aromatization process by a redox cycle (disproportionation: formation of dihydro or tetrahydro derivatives of **III**, **VI**, or **VII**), all the minor products were isolated from the reaction mixture and their NMR spectral data examined. Our NMR data, however, indicated that none of them belongs to such a class. We therefore anticipate that the dehydrogenation of diene intermediate **III**, **VI**, or **VII** might be due to air oxidation in the presence of $AlCl_3$.[23] Stabilization of **III**, **VI**, or **VII** could be the driving force in losing the hydrogen by air oxidation to form the aromatic compound. Further studies however are required to confirm the exact reaction mechanism in the formation of biaryls (Scheme 4).

In conclusion we have developed a novel chemical access for the synthesis of substituted biaryls in moderate to good yields for the first time from prenylated acetophenones, phenylacetones, dihydrochalcone, 2-acetylnaphthalene, and geranylated phenylacetone using $AlCl_3$. The biaryl formation appears to be via an $AlCl_3$ catalyzed domino reaction sequence, i.e. ring formation (intramolecular carbonyl-ene reaction and ring expansion), dehydration, and then oxidative aromatization. Some of the biaryls synthesized using our method would not be readily accessible from alternative methods (for example, compounds **6a**−**6e**, **8**, and **14**). This new method avoids transition metal catalyzed cross-coupling reactions, C−H bond activation, and decarboxylative biaryl coupling. Further work is in progress at our laboratory to demonstrate the application of this methodology for the synthesis of stilbenes, biarylethers, biphenylmethanes, and other natural products of biological importance without coupling reactions.

Supporting Information Available. Experimental procedures and spectroscopic characterization of all new compounds along with their ^{1}H and ^{13}C NMR, mass, and 2D-NMR spectral data for **3b**, **6b**, **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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