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Transition metal-free domino sequential synthesis of (*E*)-stilbenes, biaryl methanes and biaryl ethers using Et_2AlCl as a Lewis acid†

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A transition metal-free domino process has been developed, for the first time, to synthesize (*E*)-stilbenes, biaryl methanes and biaryl ethers from substituted α,β-unsaturated ketones, benzyl acetones and phenacyl ethers, respectively, in moderate to good yields at room temperature using diethyl aluminium chloride (Et_2AlCl) as a Lewis acid.

Stilbenes are a well known class of naturally occurring phytochemicals demonstrating a wide range of biological activities.[1] For example *cis* and *trans* isomers of combretastain A4 (Fig. 1) have antitumor activity.[2] Resveratrol (Fig. 1) has shown cancer chemopreventive, antiplatelet aggregation, antioxidative, antibacterial, anti-inflammatory, and antidyslipidemic activities.[3] Pterostilbene acts as an effective PPARα agonist and hypolipidemic agent and possesses lipid- and glucose-lowering effects.[4] Synthetic stilbenes are used as optical brighteners,[5] phosphors[6] and scintillators.[7] The classical reactions for the synthesis of stilbenes such as Meerwein arylation,[8] the Heck reaction[9] or Mizoroki–Heck reaction,[10] Suzuki–Heck reaction[11] and condensation reactions[12] *e.g.* Knoevenagel-type, Wittig and Wittig–Horner reaction are well reported in the literature. Transition metal-free C–C bond forming reactions in the synthesis of (*E*)-stilbenes are also of crucial importance.[13]

Biaryl methanes frequently appear as subunits in macrocycles and calixarenes.[14] Macrobicyclic receptors are an important class of host molecules for the selective binding of amino acids.[15] Calixarenes are developed for the recognition of ion-neutral organic molecules[16] and are also used as chiral recognition devices for solid phase extraction as a stationary phase and modifiers.[17] Biaryl methanes have been synthesized by the Friedel–Crafts alkylation of aromatic compounds and benzylic halides or the S_N2-type reaction of aryl metals and benzylic halides.[18] Alternatively, metal catalyzed cross-coupling reactions between aryl metals and benzylic halides,[19] or aryl halides and benzylic metals (prepared from benzylic halides), have been also used for the synthesis of biaryl methanes.[20]

Biaryl ethers are common structural features in numerous natural products and in biologically active compounds.[21] Vancomycin and other glycopeptide antibiotics, as well as anti-HIV agents like chloropeptin contain this core.[22] Ulmann reactions between phenol and aryl iodide under stoichiometric ratios of copper at elevated temperatures are the most useful tool for the synthesis of biaryl ethers.[23] Copper-catalyzed coupling at room temperature between aryl boronic acids and phenol in the presence of ligands,[24] and Pd-catalyzed coupling at high temperatures between phenols and aryl iodides in the presence of expensive ligands, are the other protocols for the synthesis of biaryl ethers.[25]

The discovery of an efficient, transition metal-free process for the synthesis of these classes of compounds is always in high demand. As a part of our ongoing programme on domino reactions[26,27] for the synthesis of carbocyclic molecules, we intended to synthesize (*E*)-stilbenes, biaryl methanes, and biaryl ethers using Lewis acid. Therefore, we initiated our work with the synthesis of (*E*)-7-methyl-1-phenylocta-1,6-dien-3-one (**2a**) from commercially available (*E*)-4-phenylbut-3-en-2-one (**1a**) through a

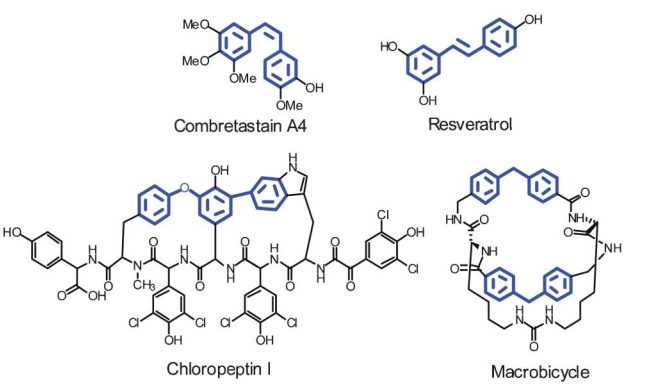

Fig. 1 Stilbene, biaryl ether and biaryl methane scaffold in bioactive compounds.

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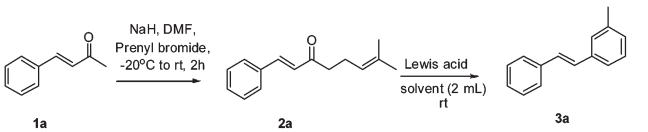
Table 1 Optimization of the reaction conditions[a] for the synthesis of stilbene, **3a**



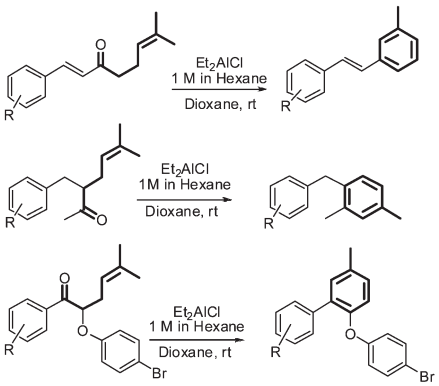
Entry	Lewis acid (eq.)	Solvent	Time (h)	Yield[b] (%)
1	$AlCl_3$ (0.5)	Dioxane	4	Trace
2	$AlCl_3$ (0.5)	Dioxane	12	Trace
3	$AlCl_3$ (1.5)	Dioxane	12	35
4	$AlCl_3$ (1.5)	THF	12	25
5	$AlCl_3$ (1.5)	CH_3CN	12	Trace
6	BF_3–OEt_2 (1.5)	Dioxane	15	—
7	$TiCl_4$ (1.5)	Dioxane	15	—
8	$ZnCl_2$ (1.5)	Dioxane	20	—
9	$SnCl_4$ (1.5)	Dioxane	10	25
10	$SnCl_2$ (1.5)	Dioxane	12	—
11	Et_2AlCl 1 M in hexane (0.5)	Dioxane	4	20
12	Et_2AlCl 1 M in hexane (0.5)	Dioxane	12	22
13	Et_2AlCl 1 M in hexane (0.5)	THF	12	Trace
14	Et_2AlCl 1 M in hexane (0.5)	CH_3CN	12	Trace
15	Et_2AlCl 1 M in hexane (1.5)	Dioxane	4	61

[a] All the reactions were conducted with 0.46 mmol or 1 equivalent of **2a**, Lewis acids were used at an equivalent ratio with respect to **2a**, unless otherwise noted. [b] Isolated yield of **3a** with respect to **2a**.

prenylation reaction (see ESI†) using NaH and by choosing **2a** as a model substrate for the optimization of the reaction conditions for the synthesis of stilbene, **3a** (Table 1).

It was observed that using $AlCl_3$ at different equivalents resulted in a small amount of **3a** at room temperature irrespective of the solvent used (dioxane, THF and CH_3CN) and reaction time (entries 1–5, Table 1). No reaction occurred with Lewis acids such as BF_3–OEt_2, $TiCl_4$, $ZnCl_2$ and $SnCl_2$ in dioxane at room temperature (entries 6–8 and 10). Employment of 1.5 eq. of $SnCl_4$ resulted in a poor yield (entry 9). The reaction with 0.5 eq. diethyl aluminium chloride (1 M in hexane) in dioxane at room temperature gave **3a** in a 20% yield (entry 11) and no improvement in yield was observed with other solvents and reaction conditions (entries 12–14). However, 1.5 eq. diethyl aluminium chloride (1 M in hexane) in dioxane provided the desired stilbene **3a** (3-methylstilbene) in 61% yield after 4 h (entry 15, Table 1) at room temperature.

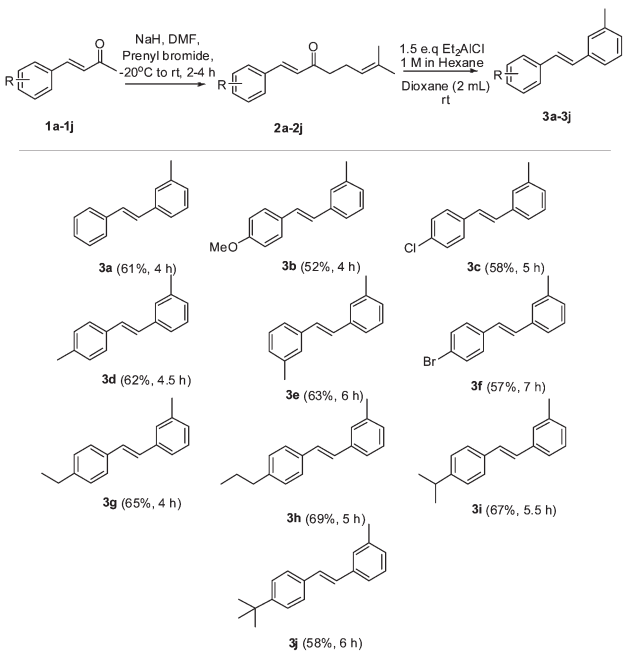
The optimization of the reaction conditions revealed that diethyl aluminium chloride is efficient for carrying out the domino reaction for the synthesis of (*E*)-stilbenes. We wish to further explore diethyl aluminium chloride for the synthesis of various (*E*)-stilbenes, biaryl methanes and biaryl ethers. Diethyl aluminium chloride is an excellent Lewis acid used in ene-reactions,[28] various organic transformations[29] and named reactions such as Ziegler–Natta polymerization,[30] Diels–Alder reactions,[31] and Friedel–Crafts reactions.[32] Herein we report a transition metal-free domino sequential synthesis of (*E*)-stilbenes, biaryl methanes, and biaryl ethers from substituted α,β-unsaturated ketones, benzyl acetones and phenacyl ethers respectively using diethyl aluminium chloride as a Lewis acid (Scheme 1). To



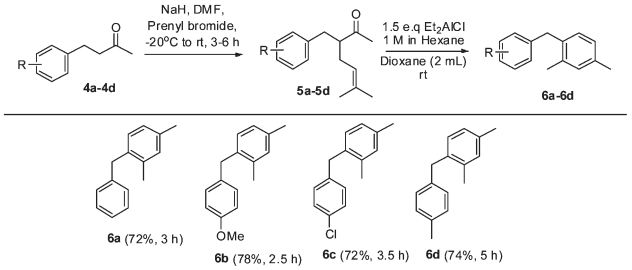
Scheme 1 Synthesis of (*E*)-stilbenes, biaryl methanes and biaryl ethers using Et_2AlCl as a Lewis Acid.

the best of our knowledge such a transition metal-free domino protocol has not been reported in the literature.

With the above optimized reaction conditions, we have performed the domino reaction with various substituted α,β-unsaturated ketones **1b–j** and obtained respective stilbenes **3b–j** with moderate to good yields (Scheme 2). Specifically, α,β-unsaturated ketones with *m*- or *p*-substituted electron-donating groups are all successfully involved in this reaction (**3a–3j**). α,β-Unsaturated ketones with highly electron-donating *p*-substituted methoxy and chloro groups gave moderate yields (**3b** and **3c**). (*E*)-4-(4-Bromophenyl)but-3-en-2-one also gave moderate yields. Satisfactorily, α,β-unsaturated ketones with electron-donating *m* and *p*-substituted alkyl groups reacted with good yields (**3d–3e** and **3g–3j**).



Scheme 2 Synthesis of stilbenes **3a–3j** through domino reactions of substituted α,β-unsaturated ketones **1b–j**, and their isolated yields and reaction times.

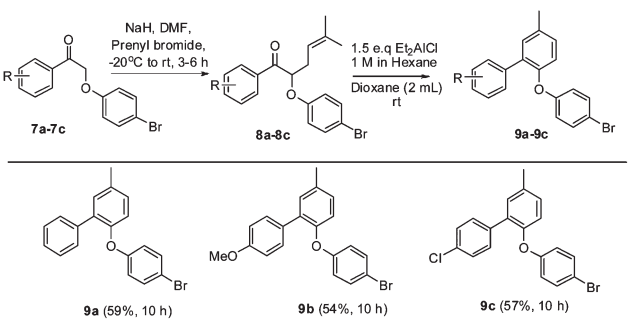


Scheme 3 Synthesis of biaryl methanes **6a–6d** formed through domino reactions of substituted benzyl acetones **4a–4d**, and their isolated yields and reaction times.

We then focused on the synthesis of the biaryl methane class of compounds using the same above optimized reaction conditions. Commercially available substituted benzyl acetones **4a–d** were prenylated using NaH to generate the intermediates **5a–d** (Scheme 3). These prenylated compounds **5a–d** were reacted with diethyl aluminium chloride (1 M in hexane) in dry dioxane providing the anticipated biaryl methanes (**6a–d**) in good yields (Scheme 3). Better yields and shorter reaction times were observed for the formation of biaryl methanes in comparison to stilbenes (Scheme 2). The presence of conjugation in alkenylated ketones (**2a–2j**) might be the reason for the lower yields and longer reaction times in the formation of stilbenes.

The applicability of this reaction was further explored for the synthesis of biaryl ethers. To synthesize biaryl ethers, substituted phenacyl ethers **7a–7c** were prenylated to afford the intermediates **8a–8c** respectively, and further domino reactions were performed under the above optimized conditions, to obtain the respective biaryl ethers (**9a–9c**) in moderate yields (Scheme 4).

The reaction mechanism for the formation of (*E*)-stilbenes, biaryl methanes and biaryl ethers is depicted in Fig. 2. The reaction might be initiated through the diethyl aluminium chloride-mediated intramolecular carbonyl-ene reaction to provide an ene-adduct-Et_2AlCl complex[33] (cyclobutanol intermediate **I**) which might be reacted to afford ethane and ene-adduct-aluminum alkoxide **II**. Next, ring expansion of **II** gives a six membered carbocyclic ring as in **III** and the cleavage of the carbon–oxygen bond[34] of **III** produced **IV** or **V**. The simultaneous dehydrogenation[35] of **IV** or **V** (aerial oxidative aromatization)



Scheme 4 Synthesis of biaryl ethers **9a–9c** accessed through domino reactions of substituted phenacyl ethers **7a–7c**, and their isolated yields and reaction times.

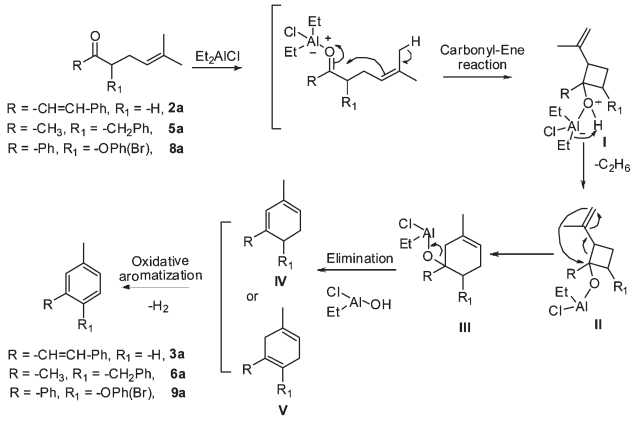


Fig. 2 Plausible reaction mechanism for the synthesis of (*E*)-stilbenes, biaryl methanes, and biaryl ethers using Et_2AlCl.

convincingly furnishes the desired (*E*)-stilbene, biaryl methane and biaryl ether (Fig. 2). Further studies, however, are required to confirm the exact reaction mechanism. The reaction mechanism for formation of **3a**, **6a** and **9a** is presented in Fig. 2 as representative examples from each class of compounds.

In conclusion, we have developed a novel domino protocol for the synthesis of (*E*)-stilbenes, biaryl methanes and biaryl ethers for the first time from prenylated α,β-unsaturated ketones, benzyl acetones and phenacyl ethers respectively with diethyl aluminium chloride in moderate to good yields at room temperature. This efficient process specifically synthesized three different classes of systems (**3a–3j**, **6a–6d** and **9a–9c**) with 3-methyl substitution and avoids the use of transition metals or metal-catalyzed cross-coupling reactions (Meerwein arylation, Mizoroki–Heck reactions, Ullmann reactions).

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