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A metal-free one-pot cascade synthesis of highly functionalized biaryl-2-carbaldehydes†

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A metal-free one-pot cascade annulation of acyclic substrates dienaminodioate, cinnamaldehydes and allyl amine was achieved for the synthesis of polyfunctional biaryl-2-carbaldehydes. The reaction proceeds at room temperature by a trifluoroacetic acid mediated Diels–Alder pathway. Synthetic applications of the resulting biaryl-2-carbaldehyde have been demonstrated by conversion into an array of diverse molecules with biological and materials chemistry relevance. The present work offers a complementary route to the existing metal mediated cross-coupling methods for the preparation of biaryls.

Biaryl synthesis in the presence of copper was described more than a century ago by Ullman.[1] Majority of synthetic strategies for biaryls rely on transition metal catalyzed cross-couplings with attention particularly focused on palladium-catalyzed methods such as Kharasch, Suzuki–Miyaura, Hiyama, Kumada, Negishi, and Stille coupling reactions.[2] Among the other cross-coupling methods for biaryls include direct arylation,[3] decarboxylative coupling,[4] using hypervalent iodine reagents,[5] and other transition metal free conditions.[6] Alternatively, annulation of acyclic substrates offers the provision to synthesize biaryls with diverse functionalities for molecular complexity.[7] Biaryl motifs have been found as key structural components in a myriad of exotic carbon frameworks which includes a variety of natural products,[8] pharmaceuticals,[9] materials,[10] chiral ligands[11] and agrochemicals[12] (Fig. 1).

Given the importance of biaryls in a multitude of applications there has been a continued interest to complement the existing methods for biaryl synthesis. We report herein a trifluoroacetic acid (TFA) mediated one-pot synthesis of polyfunctional biaryls using dienaminodioate, cinnamaldehyde, and allyl amine. An array of biaryls with diverse functionalities on both the phenyl units were synthesized (Table 2). The other notable facet of the present method is the generation of biaryl-2-carbaldehyde which serves as a key starting material for the synthesis of diverse molecules which are of significance in biology and materials chemistry.[13] The dominant method of choice for biaryl-2-carbaldehyde synthesis has been the Suzuki–Miyaura reaction,[14] and other reports under metal-free conditions generally lack the substrate scope and are limited to simple phenyls.[7k,15] To the best of our knowledge, this is the first report towards the synthesis of highly functionalized biaryl-2-carbaldehydes under metal-free conditions. Thus, the present study offers a one-pot metal-free alternative for biaryl-2-carbaldehyde synthesis which was further transformed into dibenzopyranone, fluorene, 1,4-dihydropyridine (1,4-DHP), 1,2-DHP and bis(indolyl) methane (BIM) (Scheme 3).

We have recently reported 1,2-DHP synthesis by a one-pot cascade annulation of dienaminodioate **1** and imines generated from aromatic aldehydes and amines.[16] During this attempt we have also reported utilization of *p*-nitrocinnamaldehyde **2** as the aldehyde component with *p*-toluidine **3** which was presumed to produce the 1,2-DHP product containing a styryl side-chain. Surprisingly, the 1,2-DHP product in $CDCl_3$

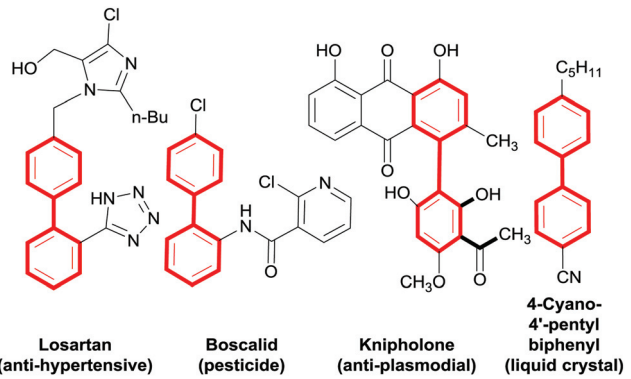

Fig. 1 Representatives of biaryl structural motifs.

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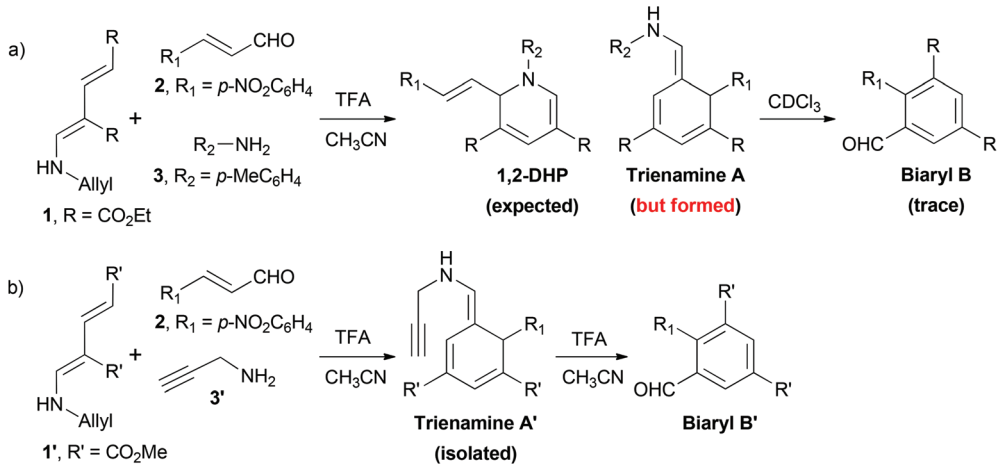
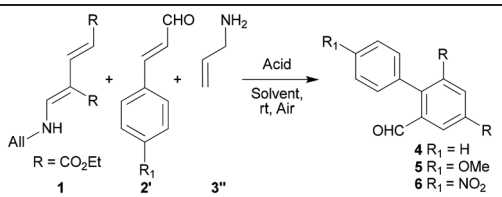


Scheme 1 (a) Unexpected formation of biaryl under three-component annulation conditions. (b) Biaryl formation *via* isolation of trienamine intermediate.

underwent slow rearrangement to a new non-polar product which was characterized by NMR as a biaryl **B** (Scheme 1a). This result led us to doubt the integrity of the 1,2-DHP produced from cinnamaldehyde. A detailed characterization by 2D-NMR studies (see ESI†) revealed the identity of the presumed 1,2-DHP from cinnamaldehyde as a trienamine **A**. To further confirm the formation of trienamine with a simplified NMR spectrum (see ESI†), an annulation reaction was performed with dienaminodioate **1′**, *p*-nitrocinnamaldehyde **2** and propargylamine **3′** which afforded trienamine **A′** (Scheme 1b). The isolated trienamine **A′** was further treated with trifluoroacetic acid under open air which provided the expected biaryl **B′**. Therefore, the reported four 1,2-DHPs derived from cinnamaldehydes and crotonaldehyde, from our previous work, stands corrected to trienamines.

This serendipitous result motivated us to pursue a synthetic method for biaryls under metal-free and mild conditions. Accordingly, a direct biaryl formation was envisaged using TFA–CH_3CN with dienaminodioate **1**, cinnamaldehyde **2′**, and allylamine **3″** in one-pot. Trienamine formation was immediate and predominant but the desired biaryl **4** was formed in a trace amount despite the increase in concentration of TFA (entry 1, Table 1). The structure of biaryl **4** was further supported by a single crystal XRD analysis (Fig. 2).[17] Interestingly, a change of solvent to DCM afforded biaryl **4** in 25% yield (entry 2). However, when MeCN was used along with DCM as a co-solvent and by increasing the concentration of TFA/**2′**/**3″** to three equivalents with respect to one equivalent of dienaminodioate **1** the reaction afforded biaryl **4** with a 60% yield (entry 3). Further attempts using solvent systems MeCN–$CHCl_3$ (1 : 1) and MeCN–DCE (1 : 1) resulted in biaryl **4** in 60% and 43% yields, respectively (entries 4 and 5). There was no biaryl formation when the reaction was attempted either in the absence of TFA or allylamine (entries 6 and 7). Attempts with other acids such as $FeCl_3$, trichloroacetic acid, and acetic acid had no significant improvement in the yield of biaryl **4** (entries 8–10); and there was no biaryl formation in the presence of

Table 1 Optimization of reaction conditions



Entry	Acid (eq.)	Ratio **2′** : **3″**[a]	Solvent[b]	Time (h)	R_1	Yield[c] (%)
1	TFA (5)	1.2 : 1.2	MeCN	2	H	Trace
2	TFA (1)	1.2 : 1.2	DCM	on	H	25
3[d]	TFA (3)	3 : 3	MeCN–DCM	4.30	H	60
4[e]	**TFA (3)**	**3 : 3**	**MeCN–$CHCl_3$**	on	**H**	**60**
5[e]	TFA (3)	3 : 3	MeCN–DCE	on	H	43
6[d]	—	3 : 3	MeCN–DCM	60	H	n.d.
7[d]	TFA (3)	3 : 0	MeCN–DCM	1	H	n.d.
8	$FeCl_3$ (3)	3 : 3	MeCN	7.25	H	44
9[d]	TCA (3)	3 : 3	MeCN–DCM	>96	H	21
10[f]	AcOH	1.2 : 1.2	MeCN	on	H	47
11	$BF_3{\cdot}OEt_2$ (3)	3 : 3	MeCN	on	H	n.d.
12	*p*-TsOH (3)	3 : 3	MeCN	on	H	n.d.
13[d]	TFA (3)	3 : 3	MeCN–DCM	24	OMe	40
14[d]	TFA (3)	3 : 3	MeCN–DCM	on	NO_2	45
15	TFA (3)	3 : 3	MeCN–$CHCl_3$	on	OMe	55
16	TFA (3)	3 : 3	MeCN–$CHCl_3$	on	NO_2	50

[a] Equivalents of **2′** and **3″**, respectively. [b] Undistilled solvents. [c] Isolated yields. [d] MeCN–DCM (1 : 2). [e] MeCN–$CHCl_3$ (DCE) (1 : 1). [f] AcOH–MeCN (0.25 : 2.5 mL). on = overnight, n.d. = not detected.

$BF_3{\cdot}Et_2O$ or *p*-TsOH (entries 11 and 12). Cinnamaldehydes with *para*-substituted methoxy and nitro groups led to the formation of desired biaryls **5** and **6** in 40% and 45% yields, respectively in the MeCN–DCM (1 : 2) solvent system (entries 13 and 14), while with MeCN–$CHCl_3$ (1 : 1) the yields were 55% and 50%, respectively (entries 15 and 16). The results from the latter entries indicate that the electronic influence of *para*-substitution in cinnamaldehydes had no direct consequence on the outcome of the biaryl formation. Further optimization

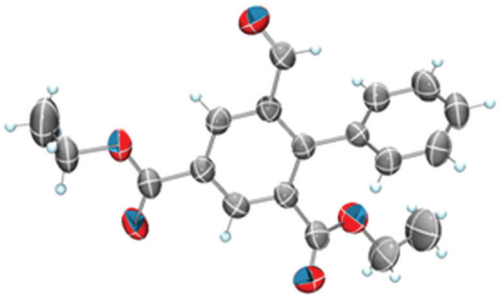
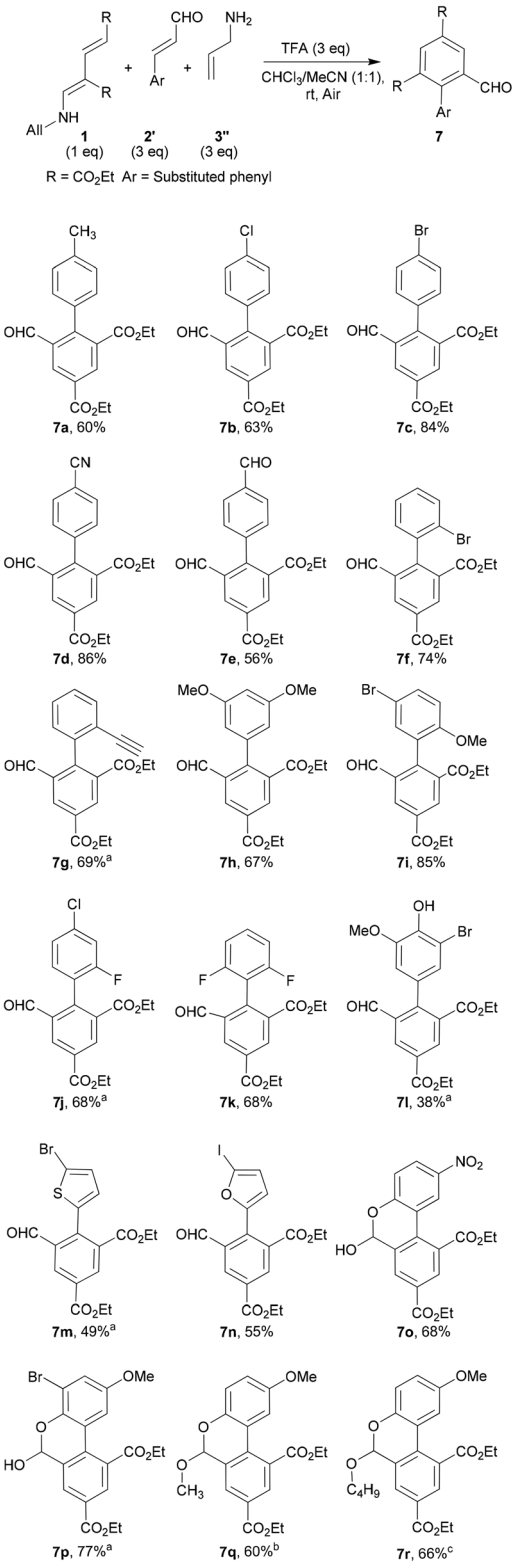


Fig. 2 ORTEP diagram of biaryl **4**.

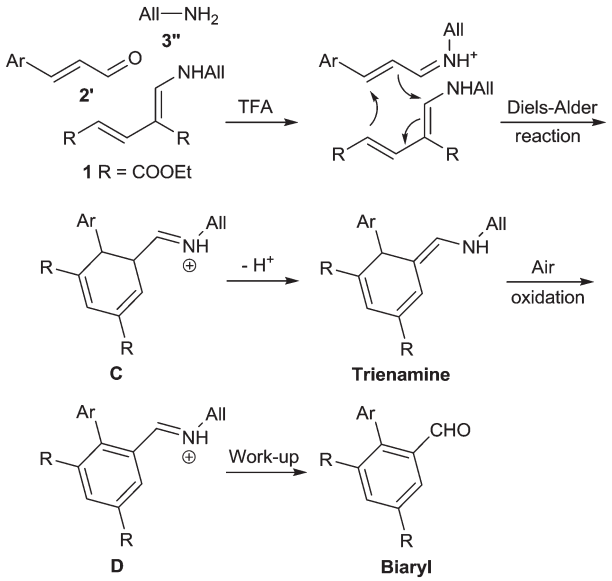
studies by variation of the substrate molar ratio and solvents could not improve the yield of biaryl significantly (see the ESI†), which led us to consider a substrate molar ratio of 1 : 3 : 3 : 3 for **1**/**2′**/**3″**/**TFA** in MeCN–$CHCl_3$ (1 : 1) (0.1 M of compound **1**, 3 mL) as the optimized condition to test the generality of the reaction.

Cinnamaldehydes with diverse mono-, di-, and tri-substitutions that confer varied electronic properties to the phenyl ring were tested for the substrate scope of the reaction (Table 2). Simple cinnamaldehydes with *para*- and *ortho*-substitutions reacted smoothly to afford biaryls **7a–g** in good to excellent yields. Surprisingly, biaryl product **7e** was produced without any competing involvement of the *para*-formyl group. Biaryls **7h–k** were produced in reasonably good yields from disubstituted cinnamaldehydes. Biaryls **7j–k** demonstrate the present method as a viable alternative to the existing traditional Pd catalyzed cross-coupling methodologies to surmount the chemoselectivity obstacle in multi halogen substituted substrates. Furthermore, **7f–g** and **7i–k** mark entry into the tri and tetra *ortho*-substituted class of biaryls. Polyfunctional biaryl **7l** with tri-substitution in each phenyl unit, obtained in 38% yield, demonstrates the operational simplicity and functional group tolerance of the present method. The generality of this method was further extended towards substituted heteroaromatic unsaturated aldehydes which afforded hetero biaryls **7m–n** in moderate yields. Cinnamaldehydes derived from substituted salicylaldehydes resulted in biaryls which spontaneously underwent cyclization to produce benzopyrones **7o–p** in good yields, offering a milder alternative to such products produced by utilizing expensive metal catalysts and pre-functionalized starting materials.[18] A one-pot, four-component reaction towards the existing method was envisaged to add more dimensions to the methodology. As a result, with substituted salicylaldehydes in MeOH–MeCN (1 : 1) the reaction afforded the tricyclic product **7q** in 60% yield by successful incorporation of methanol in the product. Similarly, the reaction with *n*-butanol afforded the expected tricyclic product **7r** in 66% yield. Previous methods for biaryls hitherto achieved multiple substitutions in one of the phenyl rings limiting the other as a simple phenyl unit or with utmost mono-substitution. Notably, the present methodology offers biaryls with diverse mono-, di-, and tri-substitution patterns on both the phenyl units in a one-pot reaction.

Table 2 Generality of the reaction



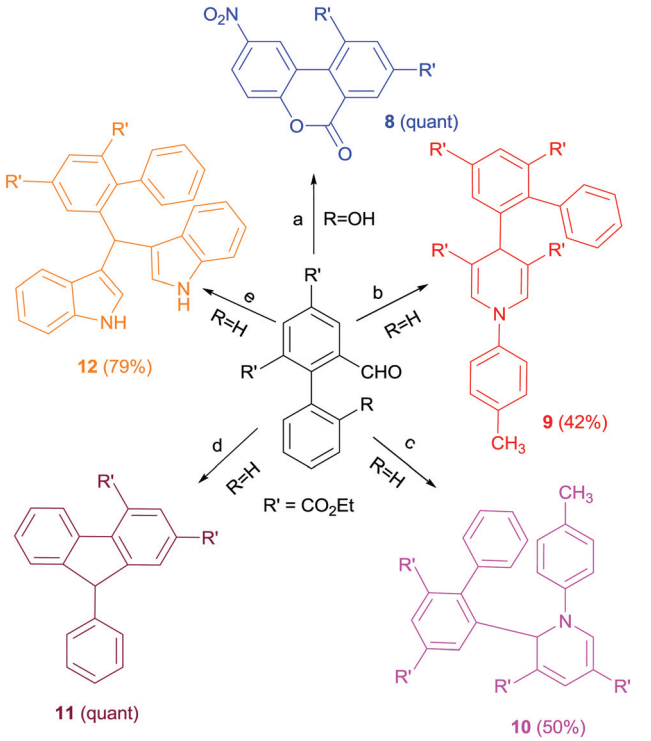
Solvent conditions: [a] DCM–MeCN (2 : 1). [b] MeOH–MeCN (1 : 1). [c] *n*-BuOH–MeCN (1 : 1).



Scheme 2 Mechanistic pathway.

The mechanistic pathway for the formation of biaryl is shown in Scheme 2. The reaction proceeds *via* the Diels–Alder reaction through MacMillan's iminium activation[19] of aldehyde. The resulting adduct **C** undergoes rearrangement to a more stable trienamine intermediate by a loss of proton. Aromatization to intermediate **D** can be facilitated by air oxidation and subsequent work-up affords biaryl. The oxidation step was further confirmed by treating the isolated trienamine intermediate with DDQ/DCM which produced a facile conversion to biaryl.

To justify the importance of 2-carbaldehyde in biaryls, a series of transformations were carried out on biaryls **7o** and **4** to afford dibenzopyranone **8**, 1,4-DHP **9**, 1,2-DHP **10**, fluorene **11**, and bis(indolyl)methane (BIM) **12** (Scheme 3). A number of natural products contain benzopyranone as a core feature and a recent report for its synthesis from biaryl-2-ol involves palladium-catalyzed CO insertion *via* C–H activation.[20] Dibenzopyranone **8** was synthesized from biaryl **7o** in a quantitative yield by the Dess–Martin periodinane oxidation. 1,4-DHP **9** and 1,2-DHP **10** which were synthesized in one step from biaryl **4**, unequivocally, demonstrates a new entry into the repertoire of aryl scaffolds. Fluorenes which gained prominence in the form of conjugated polymers in display applications with exceptional electro optical properties are synthesized by metal-catalyzed annulations.[21] Fluorene **11** was synthesized in two steps in a quantitative yield from biaryl **4** by the Grignard addition followed by the Friedel–Crafts alkylation. BIMs are known to exhibit a broad range of important biological activities against various diseases especially in cancer inhibition.[22] BIM **12** was synthesized in one step from biaryl **4** and indole in the presence of a catalytic amount of *p*-TsOH. The present work for the synthesis of biaryls under mild conditions, in consequence, presents an efficient alternative to synthesize such a diverse array of molecules from biaryl-2-carbaldehydes.



Scheme 3 Transformations of biaryls to various other structural motifs. Reaction conditions: (a) **7o** (1 eq.), Dess–Martin periodinane (3 eq.), DCM, rt; (b) **4** (1 eq.), ethyl 3-(allylamino)acrylate (2 eq.), *p*-toluidine (1 eq.), TFA (1 eq.), MeCN, rt; (c) **1** (1 eq.), **4** (1.2 eq.), *p*-toluidine (1.2 eq.), TFA (1 eq.), MeCN, rt; (d) (i) **4** (1 eq.), PhMgBr (5 eq.), THF, 0 °C (ii) *p*-TsOH (cat.), toluene, reflux; (e) **4** (1 eq.), indole (2 eq.), *p*-TsOH (cat.), ethanol, reflux.

Conclusions

In summary, we have shown a one-pot method for currently inaccessible polyfunctional biaryls bearing an *ortho* carbaldehyde group under metal-free conditions. We have also demonstrated the utility of biaryl-2-carbaldehyde by transformation into molecules which are of significance in biology and materials chemistry.

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