Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 363

www.rsc.org/greenchem

PAPER

Bio-based synthesis of secondary arylamines from (–)-shikimic acid†

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Received 19th September 2011, Accepted 27th October 2011
DOI: 10.1039/c1gc16162h

A specific family of secondary arylamines, including diarylamines and arylalkylamines have been synthesized in good yields starting from the renewable and biomass-based feedstock (–)-shikimic acid (**1**). The tandem cross-coupling and aromatization reactions between primary amines and the intermediate (–)-methyl-3-dehydroshikimate (**3**) are crucial for realizing this strategy. The application of arylamines and alkylamines provided 3-arylamino-4-hydroxybenzoates (**5**) and 3,4-dihydroxy-5-alkylaminobenzoates (**7**) respectively *via* a selective dehydration or dehydrogenation process.

Introduction

Owing to the limited supply and non-renewability of fossil oil, the conversion of biomass feedstocks to useful chemicals, especially complex molecules with diverse properties or intermediates with a desired scaffold is becoming an increasingly important research area in organic chemistry.[1] From a modern green chemistry perspective, plant biomass, especially those with non-grain or non-corn origin are of great advantage for application as alternatives to fossil oil.[2]

(–)-Shikimic acid (**1**) is a renewable biomass feedstock that is widely distributed in plants, microbes and parasites.[3] It is used as the key precursor for the synthesis of Tamiflu® and can also be converted to a series of fine chemicals such as phenol, benzoic acid, protocatechuic acid, and gallic acid through aromatization.[4] Presently, **1** can be obtained in large amounts through extraction from fruits, branches, and leaves of Chinese star anise (*Illicium verum* Hook. f.). In the fruit of some superior strains of the plant, the content of **1** could be as high as 12% or more.[5] It is worth mentioning that the plant of *Illicium verum* belongs to the category of non-grain biomass and that **1** is not obtained from barks, stems, and roots of the plant. Therefore, the acquisition of **1** from this plant brings no ethical problems caused by competition with food and results in no damage to the plant itself. More encouragingly, recent advances in metabolic engineering have enabled high-yielding and cost-effective fermentative production of **1** from glucose using *E. coli* as a microbial catalyst.[6] Considering the increased availability of **1**, it is obvious that this biofeedstock deserves further research and application as a renewable and reliable resource in place of fossil oil for modern chemical and pharmaceutical industries.

Secondary arylamines, either diarylamines or arylalkylamines, have constantly drawn much attention from synthetic chemists because of their ubiquity in pharmaceuticals and fine chemicals. Typically, the secondary arylamines are mainly obtained by cross-coupling reactions between aryl halides and amines in the presence of transition metal catalysts such as palladium, copper, nickel, and iridium complexes.[7,8] Although great efforts have been made, many limitations still exist concerning the efficiency, applicability and expense of the catalytic systems.[9,10] Moreover, the general strategy for the preparation of secondary arylamines from renewable biomass-based starting materials has never been established. Accordingly, a green and novel procedure for the preparation of these compounds based on renewable biomass resources under mild reaction conditions would be genuinely attractive.

As a part of our ongoing endeavour to develop biomass-based processes for access to natural products and fine chemicals,[11] we herein describe a novel procedure for the synthesis of various secondary arylamines under mild conditions *via* aromatic or aliphatic amine-involved aromatization of (–)-methyl-3-dehydroshikimiate (**3**), a key intermediate readily obtained from **1**.

Results and discussion

Starting from the commercially available (–)-shikimic acid (**1**), the methyl (–)-shikimate (**2**) was readily obtained through esterification with methanol in presence of $SOCl_2$. Compound **3** could then be achieved in 72% yield by highly selective oxidation of 3*R*-hydroxyl group in THF with 2-iodoxybenzoic acid (IBX). It is noteworthy that, although **2** has three unprotected hydroxyl groups in its cyclohexene framework, the oxidizing reaction

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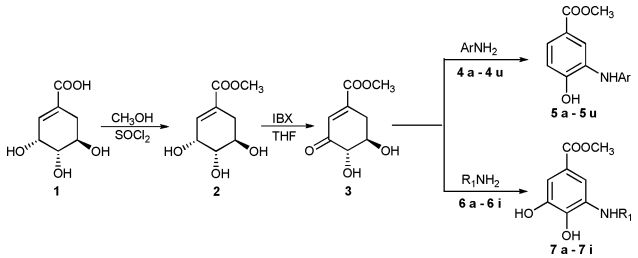
† Electronic supplementary information (ESI) available: See DOI: 10.1039/c1gc16162h

caused by IBX selectively took place at 3*R*-hydroxyl position, whereas the 4*S* and 5*R* hydroxyl groups remained intact even in large excess of IBX (3 equiv), thus affording **3** as the sole product (Scheme 1).[12]

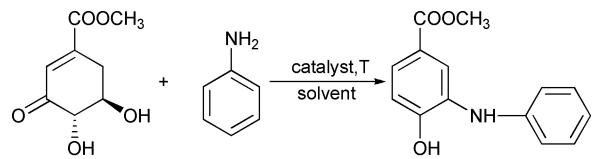


Scheme 1 Aromatization of (−)-shikimic acid promoted by primary amines.

In 1993, M. Baltas *et al.* reported very few examples of primary alkylamine-involved aromatization of **3**, affording methyl 3-alkylamino-4-hydroxybenzoates in low to moderate yields. However, they failed to give any examples of primary arylamine-involved aromatization regarding **3**.[13] We reasoned that, under proper conditions, the aromatization of **3** would theoretically be accomplished both by reaction with primary arylamines and alkylamines, thus implying a great potential for application in the alternative synthesis of diarylamines and arylalkylamines. Unfortunately, to the best of our knowledge, no further study along this road has been conducted.

We proceeded with our investigation using aniline (**4a**) as the model substrate on reaction with **3**. The results are summarized in Table 1. To our delight, the tandem cross-coupling and aromatization reaction proceeded smoothly in refluxing CH_3OH and CH_2Cl_2 in the presence of *p*-toluenesulfonic acid (*p*-TsOH)

Table 1 Screening of conditions for reaction of (−)-methyl-3-dehydroshikimate with aniline[a]



Entry	Solvent	*t*(h)	*T*/°C	Cat. (5 mol%)	Yield (%)[b]
1	CH_3OH	8.0	65 °C	*p*-TsOH	98
2	CH_3OH	8.0	65 °C	—	0
3	*t*-BuOH	8.0	80 °C	*p*-TsOH	85
4	DMSO	8.0	80 °C	*p*-TsOH	87
5	DMF	8.0	80 °C	*p*-TsOH	86
6	CH_3CN	8.0	80 °C	*p*-TsOH	90
7	THF	8.0	65 °C	*p*-TsOH	76
8	CH_2Cl_2	8.0	35 °C	*p*-TsOH	95
9	CH_3OH	8.0	65 °C	HCOOH	70
10	CH_3OH	8.0	65 °C	AcOH	69
11	CH_3OH	8.0	65 °C	H_2SO_4	71
12	CH_3OH	8.0	65 °C	$ZnCl_2$	65
13	CH_3OH	8.0	65 °C	$AlCl_3$	62
14	CH_3OH	12.0	rt	*p*-TsOH	88
15[c]	CH_3OH	12.0	65 °C	*p*-TsOH	81

[a] Reaction conditions: **3** (5.0 mmol), aniline (5.0 mmol), acidic catalyst (0.25 mmol), and solvent (20.0 mL) at indicated temperature. [b] Isolated yield. [c] 1 mol% *p*-TsOH was used.

to afford **5a** in excellent yields (Table 1, entries 1 and 8). Other acidic catalysts such as HCOOH, AcOH, H_2SO_4, $ZnCl_2$, and $AlCl_3$ gave relatively lower yields, indicating that the *p*-TsOH was optimal for this transformation (Table 1, entries 9–13). No desired product was detected in the absence of acidic catalyst (Table 1, entry 2), which gave an explanation for the failure of similar reactions conducted by M. Baltas *et al.* Investigation on the reaction medium revealed that CH_3OH seemed to be the optimal solvent for this reaction. When other solvents (*t*-BuOH, DMF, DMSO, CH_3CN, THF) were utilized, relatively lower yields were obtained (Table 1, entries 3–7). Running the reaction at ambient temperature can also furnish the product with relatively lower yield (88%, Table 1, entry 14). Additionally, the catalyst loading could be successfully reduced to 1 mol% in a gram-scale reaction to give **5a**, albeit in lower yield and prolonged time (Table 1, entry 15).

To illustrate the scope of the present method, the reactions of a range of primary arylamines bearing different functional groups were examined and the results are listed in Table 2. Generally, electron-rich primary arylamines were more reactive and afforded better yields than electron-deficient arylamines (entries 2–4 *vs.* 8–10). The electron-donating groups are expected to increase the nucleophilic activity of arylamines and to accelerate the reactions. Moreover, steric hindrance of arylamines exerts a significant influence on the reactions. The less sterically hindered *o*-aminotoluene (**4m**) reacted with **3** to give **5m** in a good isolated yield of 84% (Table 2, entry 13), while the more sterically hindered 2,4,6-trimethylaniline (**4s**) and 2,6-diethylaniline (**4t**) resulted in a moderate yields of 65% and 62%, respectively (Table 2, entries 19–20). Besides, **4t** required a longer time to complete the reaction. In addition, we have also studied the reaction of **3** with *p*-phenylenediamine and *o*-phenylenediamine. The results indicated that the cross-coupling and aromatization reaction of *p*-phenylenediamine (**4l**) with **3** was accomplished in excellent yield to give the disubstituted product **5l** (87%, Table 2, entry 12), while the same reaction between *o*-phenylenediamine and **3** afforded 4-hydroxyphenazine-2-carboxylic acid methyl ester (**5v**) in 72% yield (Table 2, entry 22). This cyclic product was obviously formed through a successive dehydration-cyclization and dehydrogenation-aromatization process. It is worth noting that the natural phenazine-containing compounds, such as phenazine-1-carboxylic derivatives (PCAs) represent the secondary metabolic pathway of (−)-shikimic acid and possess broad-spectrum antimicrobial effects.[14] To the best of our knowledge, the above-mentioned reaction is the first example documented for access to phenazine derivative *via* a (−)-shikimic acid-based method. The *o*- or *m*-substitued anilines were also workable in our protocol, furnishing the corresponding products with moderate to high yields (Table 2, entries 13–17). Also worthy of mention is that when secondary and tertiary arylamines, such as *N*-methylaniline, *N*-phenylanthranilic acid and *N*,*N*-dimethylaniline were employed, no desired product was observed in the reaction mixture, with only trace amount of protocatechuic acid obtained (Table 2, entries 23–25). A control experiment in absence of primary arylamines also produced protocatechuic acid, indicating that it is the reactant **3** itself undergoes the dehydration reaction in acidic conditions. Furthermore, we examined the reactivity of benzophenone hydrazone (**4u**) with **3**, moderate yield (70%) was obtained after

Table 2 Reaction of (–)-methyl-3-dehydroshikimate with arylamines[a]

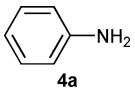
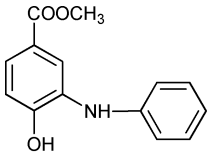
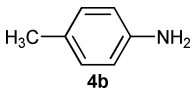
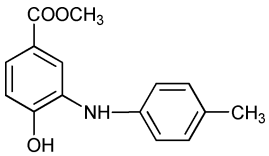
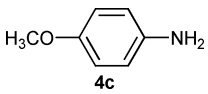
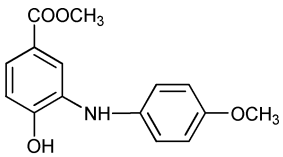
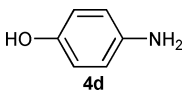
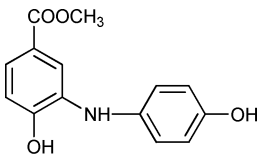
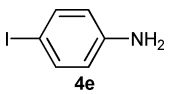
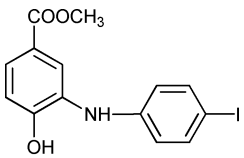
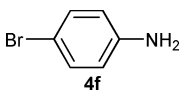
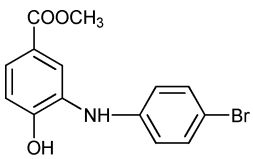
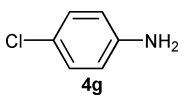
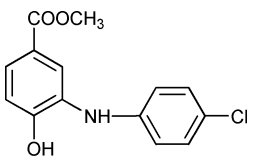
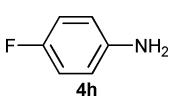
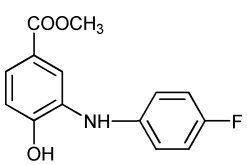
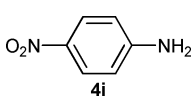
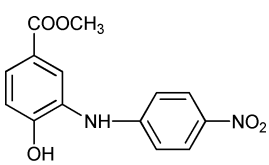
Entry	Amine	*t*(h)	Product	Yield(%)[b]
1	 **4a**	8.0	 **5a**	85
2	 **4b**	5.0	 **5b**	94
3	 **4c**	5.0	 **5c**	98
4	 **4d**	6.0	 **5d**	90
5	 **4e**	6.0	 **5e**	88
6	 **4f**	8.0	 **5f**	66
7	 **4g**	8.0	 **5g**	70
8	 **4h**	8.0	 **5h**	73
9	 **4i**	10.0	 **5i**	67

Table 2 (*Contd.*)

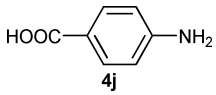
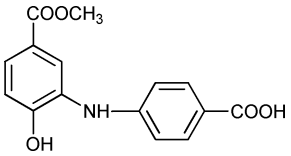
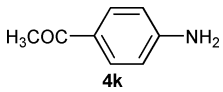
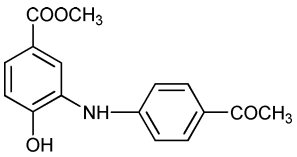
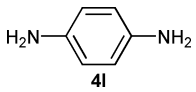
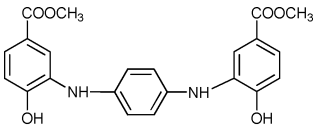
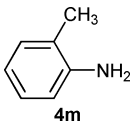
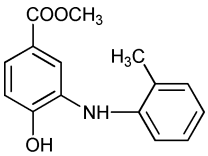
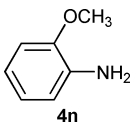
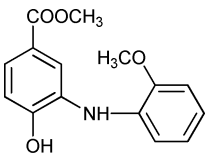
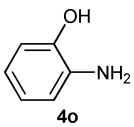
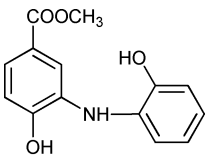
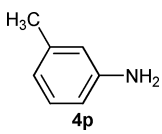
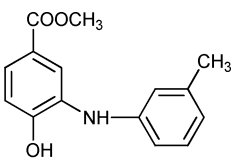
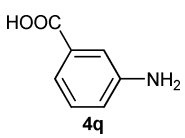
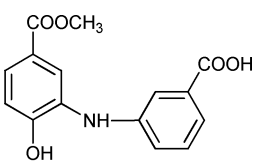
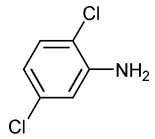
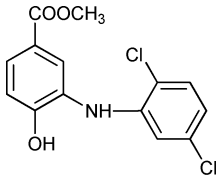
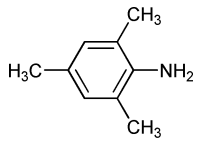
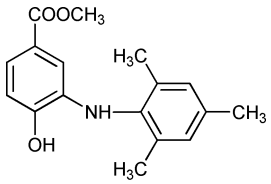
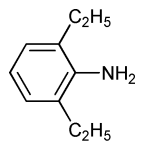
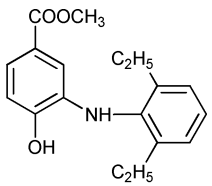
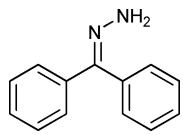
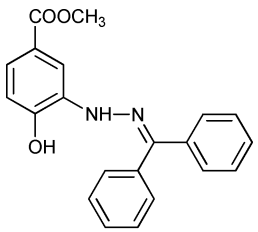
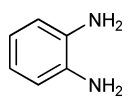
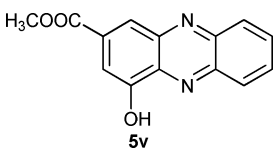
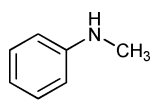
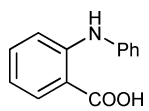
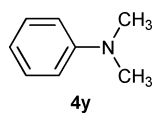
Entry	Amine	*t*(h)	Product	Yield(%)[b]
10	 **4j**	10.0	 **5j**	76
11	 **4k**	10.0	 **5k**	80
12[c]	 **4l**	12.0	 **5l**	87
13	 **4m**	8.0	 **5m**	84
14	 **4n**	8.0	 **5n**	87
15	 **4o**	8.0	 **5o**	87
16	 **4p**	8.0	 **5p**	83
17	 **4q**	10.0	 **5q**	81

Table 2 (*Contd.*)

Entry	Amine	*t*(h)	Product	Yield(%)[b]
18	 **4r**	10.0	 **5r**	68
19	 **4s**	12.0	 **5s**	65
20	 **4t**	24.0	 **5t**	62
21	 **4u**	20.0	 **5u**	70
22[d]	 **4v**	18.0	 **5v**	72
23[e]	 **4w**	36.0	—	—
24[e]	 **4x**	36.0	—	—
25[e]	 **4y**	36.0	—	—

[a] Reaction conditions: **3** (5.0 mmol), arylamines (5.0 mmol), *p*-TsOH (0.25 mmol), and CH_3OH (20.0 mL) at refluxing temperature. [b] Isolated yield. [c] The reaction was carried out with **3** (4.0 mmol) and *p*-phenylenediamine (2.0 mmol). [d] 4-Hydroxyphenazine-2-carboxylic acid (**5v**) was obtained *via* a successive dehydration-cyclization and dehydrogenation-aromatization process. [e] Trace amount of protocatechuic acid was obtained, the control experiment carried out with **3** (5.0 mmol) and *p*-TsOH (0.25 mmol) in refluxing CH_3OH (20.0 ml) also furnished protocatechuic acid.

Table 3 Reaction of (–)-methyl-3-dehydroshikimate with alkylamines[a]

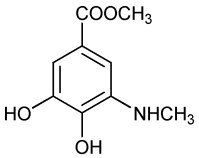
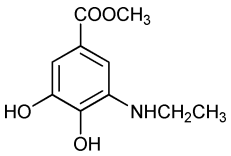
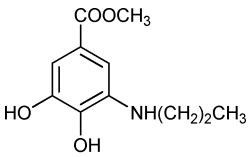
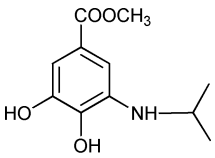
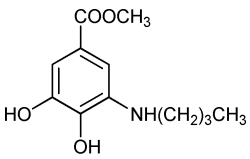
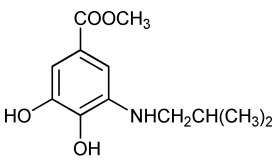
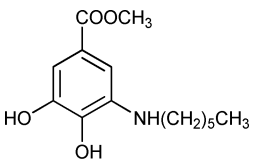
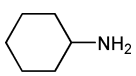
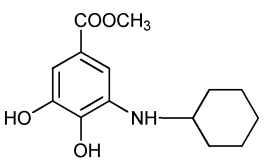
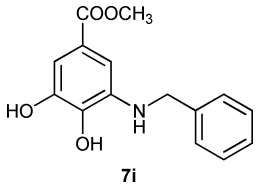
Entry	Amine	*t*(h)	Product	Yield(%)[b]
1	CH_3NH_2 **6a**	2.0	 **7a**	59
2	$CH_3CH_2NH_2$ **6b**	2.0	 **7b**	65
3	$CH_3(CH_2)_2NH_2$ **6c**	2.0	 **7c**	70
4	$(CH_3)_2CHNH_2$ 6d	2.0	 **7d**	75
5	$CH_3(CH_2)_3NH_2$ **6e**	2.0	 **7e**	68
6	$(CH_3)_2CHCH_2NH_2$ **6f**	3.0	 **7f**	61
7	$CH_3(CH_2)_5NH_2$ **6g**	3.0	 **7g**	71
8	 **6h**	3.0	 **7h**	54

Table 3 (*Contd.*)

Entry	Amine	*t*(h)	Product	Yield(%)[b]
9	$PhCH_2NH_2$ **6i**	4.0	 **7i**	65
10	$(CH_3)_2$ NH **6j**	8.0	—	—
11	$(CH_3CH_2)_2NH$ **6k**	8.0	—	—
12	$(CH_3CH_2)_3N$ **6l**	8.0	—	—

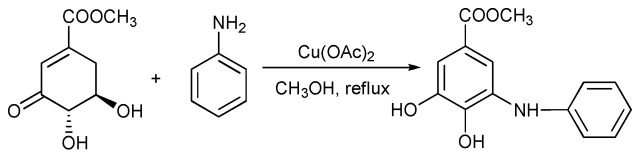
[a] Reaction conditions: **3** (5.0 mmol), aliphatic amines (5.0 mmol), *p*-TsOH (0.25 mmol), and CH_2Cl_2 (20.0 mL) at ambient temperature. [b] Isolated yield.

prolonged reaction time (Table 2, entry 21). Overall, the present protocol proved to be compatible with a wide range of primary arylamines bearing various functional groups.

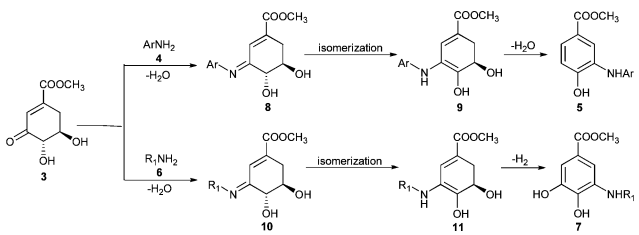
The scope and generality of our protocol were further investigated by coupling of **3** with primary alkylamines in another set of experiments. The results are listed in Table 3. Interestingly, the condensation of primary alkylamines with **3** gave 3,4-dihydroxy-5-alkylamine analogues in moderate to good yields, probably due to a dehydrogenation (or oxidation) reaction took place in this process (Table 3, entries 1–9). It is noteworthy that primary alkylamines showed higher efficiency in accelerating the aromatization of **3** than arylamines did, for these reactions were performed at ambient temperature and completed in much shorter times. In addition, the yields of the products obtained in CH_2Cl_2 were higher than those of obtained in CH_3OH. Similarly to the results mentioned above, when the reactions were tried with secondary or tertiary alkylamines such as dimethylamine, diethylamine and triethylamine, no desired products were obtained (Table 3, entries 10–12), indicating that the primary amine moieties are essential for the aromatization process.

In order to get a better understanding of the different behavior displayed by arylamines and alkylamines which lead to the formation of 3-arylamino-4-hydroxybenzoates (5) and 3,4-dihydroxy-5-alkylaminobenzoates (7) respectively. A control experiment has been conducted and an interesting result has been obtained, the reaction between aniline (**4a**) and (–)-methyl-3-dehydroshikimate (**3**) in CH_3OH in the presence of $Cu(OAc)_2$ which act as an oxidant afforded 3, 4-dihydroxy-5-anilinebenzoates (**12**), indicating that the presence of an oxidant (including oxygen distributed in reaction mixture) is probably responsible for the different behaviour of arylamines and alkylamines (Scheme 2). Further investigation to expand the substrate scope for reaction conditions including or excluding an oxidant is ongoing in our laboratory.

According to the above results, a plausible mechanism for this reaction is illustrated in Scheme 3. Primary amines, either arylamines or alkylamines, coupled with **3** in acidic conditions forming a Schiff base **8** or **10**, which rapidly enolized to form a enamine **9** or **11**, subsequent dehydration of **9** or dehydrogenation (oxidation) of **11** would then occur, affording the aromatization product **5** or **7** respectively. The pre-existing conjugated α,β-unsaturated carboxylic ester scaffold was expected to facilitate the aromatization process.



Scheme 2 Reaction of aniline (**4a**) and **3** in the presence of $Cu(OAc)_2$ as an external oxidant.



Scheme 3 A plausible mechanism for the reaction between (–)-methyl-3-dehydroshikimiate (**3**) and primary amines.

Conclusions

In conclusion, we have developed a novel and efficient method for the synthesis of substituted secondary arylamines starting from the biofeedstock (–)-shikimic acid (**1**). The tandem cross-coupling and aromatization reaction between primary amines and (–)-methyl-3-dehydroshikimiate (**3**) are considered to be involved in the transformation. Arylamines on reaction with **3** gave 3-arylamino-4-hydroxybenzoates (**5**) *via* a dehydration-aromatization process, while alkylamines on reaction with **3** afforded 3,4-dihydroxy-5-alkylaminobenzoates (**7**) *via* an oxidation-aromatization process, both under mild reaction conditions. Our findings provided a conceptually green, simple, and practical methodology for C_{Ar}–N formation based on renewable resources, representing an interesting complement to the existing strategy using aryl halides and transition metal catalysts. Further applications of the protocol using chiral amines as reactants are currently under investigation in our laboratory and will be reported in due course.

Acknowledgements

This work was financially supported by Guangxi Wanshan Spice Co. Ltd., the Science and Technology Program of Guangdong Province, Strategic Cooperation Program between Guangdong Province and Chinese Academy of Sciences and National Key Technology R&D Program, PR China (2003B31603, 2006B35604002, 2009B091300125 and 2007BAD82B02).

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