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Transition-Metal-Free Valorization of Biomass-derived Levulinic Acid Derivatives: Synthesis of Curcumene and Xanthorrhizol

Wen-Yan Xu,[+] Kai-Feng Zhuo,[+] Tian-Jun Gong,* and Yao Fu*

Abstract: Levulinic acid (LA) is acknowledged one of the most promising biomass-derived platform molecules, and can be transformed into various value-added chemicals. Here, we report a new reaction process for the valorization of levulinic acid derivatives under transition-metal-free condition. The protocol combined with the conversion of the levulinate to tosylhydrazone and base promoted arylation, acylation, and etherification cross-coupling. Moreover, our method was applied to synthesize three biologically active molecules, *rac*-curcumene, *rac*-xanthorrhizol and *rac*-4,7-dimethyl-l-tetralone. This reaction discloses a new avenue for the high-value utilization of platform molecules.

Introduction

The development of methods to conversion of renewable biomass-derived platform compounds into high-value chemicals have drawn much attention in the past decades.[1] Levulinic acid, which is produced from hemicellulose or cellulose with multiple catalytic reactions, are promising renewable platform chemicals as it is a vital “C5” resource with enormous synthetic potential.[2-3] Numerous of efforts have been devoted to the conversion of levulinic acid and its esters into highly valuable chemicals under homogeneous or heterogeneous catalytic system (Scheme 1a).[4-11] For examples, hydrogenation to produce γ-valerolactone,[4] 1,4-pentanediol,[5] valerate esters,[6] 2-methyltetrahydrofuran (2-MeTHF), [7] *n*-alkanes [8] depending on the hydrogenation conditions, and reductive amination/cyclization converted into pyrrolidinone or pyrrolidines[9]. Selectivity oxidation for synthesis of maleic anhydride, succinic acid, and 3-hydroxypropanoic acid.[10] Condensation with furfural, α-angelica lactone or dimerization to generate precursors for renewable fuels and polymer monomers.[11] Moreover, Levulinic acid and its esters can also be used to react with phenylhydrazine for the synthesis of drug molecule, Indomethacin.[12] Although a lot of research has been conducted on the conversions of LA, it is still a high desirable to seek more innovative routes to leverage levulinic acid and its esters to synthesize new types of LA-derived compounds. Based on the structure of levulinic esters, we envisaged that one of the route to valorization of levulinic esters is the difunctionalization of carbonyl and carboxyl for synthesis of 1,4-disubstituted frameworks, which possesses delicate structure for applications as key intermediates for the synthesis of biologically active molecules (Scheme 1b).[13] Herein, we report a new method of arylation, acylation and etherification based on levulinate derived tosylhydrazones under transition-metal-free condition. This strategy can realize the diversified utilization of biomass platform compounds levulinic acid, furfural and phenols. Moreover, the obtained products can be transformed into natural aromatic sesquiterpene *rac*-curcumene, *rac*-xanthorrhizol and *rac*-4,7-dimethyl-l-tetralone via simple manipulations (Scheme 1c).

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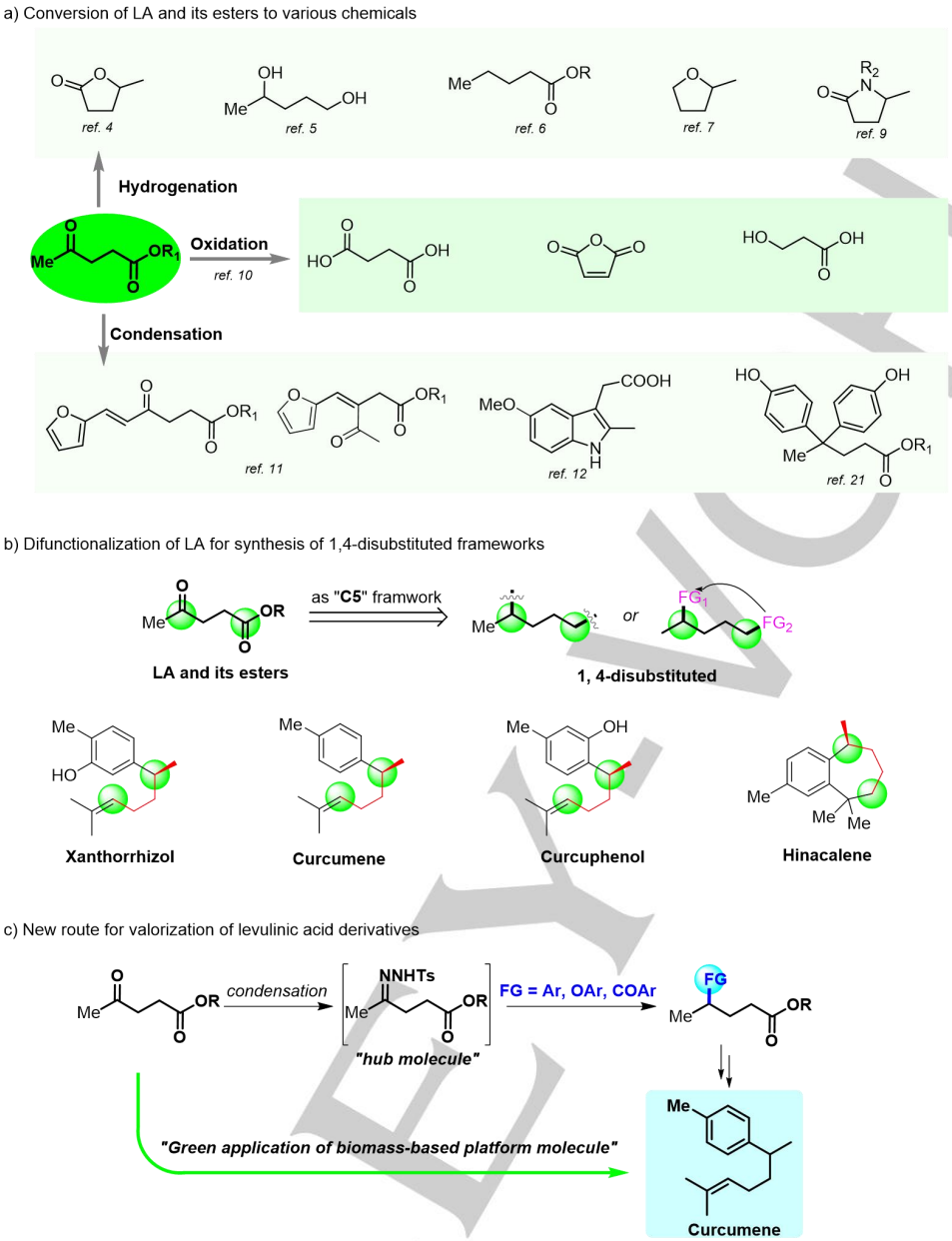
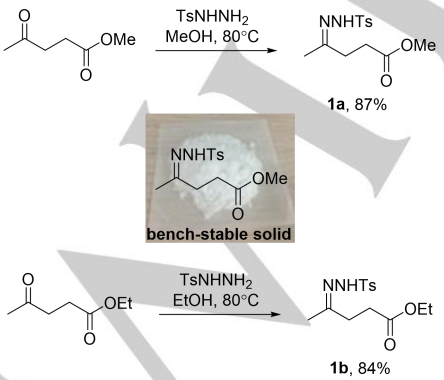


Scheme 1. a) Typical appilication of levulinic acid derivatives as “C5” building block, b) Some bioactive molecules containing 1,4-disubstituted frameworks, c) Our design for conversion of levulinic acid derivatives.



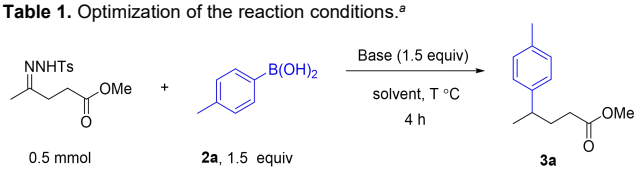
Scheme 2. Gram-scale preparation of levulinate derived tosylhydrazones.

Results and Discussion

Tosylhydrazone compounds, which can easily obtained from carbonyl group (*ketones or aldehydes*) and $TsNHNH_2$ (4-methylbenzenesulfonhydrazide), are very excellent reaction intermediates in organic transformation to forge various C-C and C-hetero bond under metal or non-metal catalytic condition[14-17]. In 2009, Barluenga and Valdés pioneered the reductive cross-coupling of tosylhydrazone and boronic acid to form $C(sp^3)$-C bonds under matal-free condition[15a]. Subsequently, diverse of C-C[15-16], C-O[17a-b], C-N[17c] and C-B[17f] bonds were successfully constructed using tosylhydrazone as

"hub molecule". These series of studies have proved that using tosylhydrazone as the "hub molecule" is an effective way to build C-C or C-X bonds based on carbonyl group. Coincidentally, biomass-derived levulinic acid and its esters contain a carbonyl structure, the use of tosylhydrazone as a "hub molecule" is expected to be a new route to accomplish high-value utilization. We started our studies by condensation of methyl levulinate with $TsNHNH_2$ in methanol solvent at 80℃ for 30 mins to obtain a white solid **1a** (87%). The bench-stable white solid **1a** was identified to be a 10:1 *E/Z* mixture by ^1H NMR spectroscopy (Scheme 2, see SI for details). Ethyl levulinate can also afford the corresponding tosylhydrazone compound by a similar method (EtOH as solvent). Then, we chose **1a** and 4-tolylboronic acid (**2a**) as model substrates for C-C cross-coupling reaction, various parameters on the outcome of the reaction were conducted (table 1). Types of bases was tested,

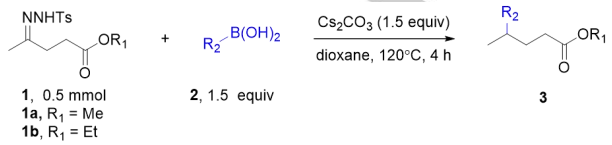
Table 1. Optimization of the reaction conditions.[a]

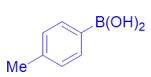
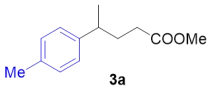
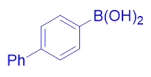
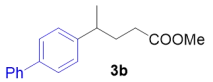
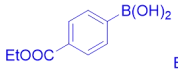
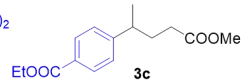
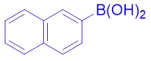
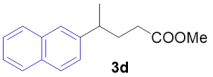
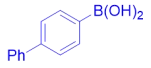
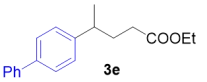
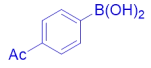
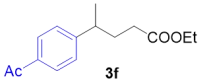
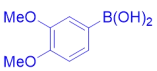
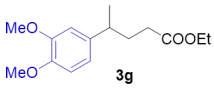
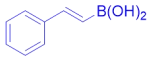
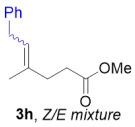
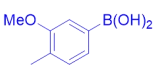
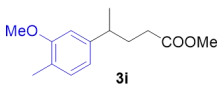


Entry	base (1.5 eq)	solvent	T °C	Yield%[b]
1	Na_2CO_3	Dioxane	110	8
2	K_2CO_3	Dioxane	110	25
3	Cs_2CO_3	Dioxane	110	72
4	CsF	Dioxane	110	14
5	K_3PO_4	Dioxane	110	5
6	NBu_4F	Dioxane	110	3
7	Cs_2CO_3	Dioxane	90	20
8	Cs_2CO_3	Dioxane	100	30
9	**Cs_2CO_3**	**Dioxane**	**120**	**75**
10	Cs_2CO_3	Dioxane	130	66
11	Cs_2CO_3	Toluene	110	42
12	Cs_2CO_3	THF	110	63
13	Cs_2CO_3	2-MeTHF	110	62
14	Cs_2CO_3	2-MeTHF	120	69

[a] All the reactions were carried out with 0.5 mmol of **1a** and 0.75 mmol of **2a** in 2 mL solvent for 4h. [b] Isolated yield. Ts=4-Toluolsulfonyl; Dioxane=1,4-Dioxacyclohexane; THF=Tetrahydrofuran; 2-MeTHF=2-methyltetrahydrofuran.

we were delighted to found that Cs_2CO_3 can achieve 72% yield of **3a**, and the reaction efficiency of Na_2CO_3, K_2CO_3, CsF, K_3PO_4 and NBu_4F were poor. Then, different reaction temperatures were examined, it was found that higher yields can be obtained under 120℃. Lowering the temperature to 90℃ or 100℃ (entry 7-8), the conversion of starting materials were not complete. Increasing the temperature to 130℃ leads to condensation of the product under alkaline condition. Moreover, the influence of different solvents was examined in the transformation, it was found that ether solvents can promote the reaction afford the target product in moderate yields. It should be noticed that, bio-based solvent 2-MeTHF (which can be prepared by hydrogenation of levulinic acid [7]) can promote the reaction afford acceptable yield (entry 13, 14). This result indicates that 2-MeTHF can be used as an alternative green solvent for the valorization of biomass.[18]



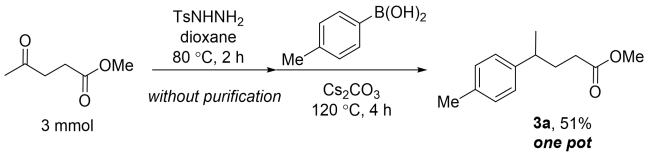
Entry	Substrate **2**	Product **3**	Yield [%]
1		 **3a**	75%
2		 **3b**	81%
3		 **3c**	69%
4		 **3d**	76%
5		 **3e**	78%
6		 **3f**	72%
7		 **3g**	66%
8		 **3h**, *Z/E mixture*	79%
9		 **3i**	72%

Scheme 3. Substrate scope. **1** (0.5 mmol), arylboronic acids **2** (0.75 mmol), Cs_2CO_3 (0.75 mmol), dioxane (2 mL), 120 ℃, 4 h under Ar atmosphere. Isolated yield.

With the optimized reaction conditions in hand, we examined the substituent effect of the arylboronic acids (Scheme 3). Types of arylboronic acids were tested, both electron-donating and withdrawing arylboronic acids exhibited

good reactivities. Naphthyl-substituted boronic acid and 4-biphenylboronic acid could be well compatible in this reaction. For electron-withdrawing arylboronic acids, 4-Ac and 4-COOEt substituted boronic acids could be employed in this reaction to afford corresponding products in moderate yields (**3c**, **3f**). It was noteworthy that, alkenylboronic acid was also compatible in this reaction and afford the mixed products, which was in consist with previous result.[15b]

Considering the simplicity and efficiency of the sequential process of condensation and arylation, we tried to prepare **3a** through a "one-pot, two-step" procedure (Scheme 4, see SI for details). First, 3 mmol of methyl levulinate and sulfonyl hydrazide were reacted in dioxane at 80℃ for 2 hours, then 4.5 mmol of 4-tolylboronic acid and 4.5 mmol of Cs_2CO_3 were added, the mixture were heated at 120℃ for 4 hours. After separation and purification, the product **3a** can be obtained in a total yield of 51%. This operation can shorten the reaction time and save more solvent.



Scheme 4. "One-pot two steps" procedure for synthesis of **3a**.

The above results motivated us to further explore the application of this transformation (Figure 1). First, scaled-up experiment was conducted afford **3a** in 74% (10 mmol scale). The product **3a** can be converted to aldehyde (**4**) through the hydrogenation using diisobutylaluminum hydride. *Rac*-curcumene (**5**), an natural aromatic sesquiterpene, [13a-d] was obtained by the subsequent Wittig reaction. Moreover, the product **3a** can also be readily converted to trinorsesquiterpene **7** [19] by means of hydrolysis and Friedel-Crafts acylation. It was noticed that *rac*-4,7-dimethyl-l-tetralone **7** was aslo very important intermediate for biologically active compounds.[20] Similarly, The *rac*-xanthorrizol precursor **8** was synthesized via arylation, hydrogenation and alkenylation sequences.

Encouraged by the successful conversion of the arylation reaction, we tried to tested other types of conversion to further expand the application of biomass-derived levulinic esters. As we all know, lignocellulose were consist by cellulose, hemicellulose and lignin, where cellulose or hemicellulose can be transformed into furan compounds by hydrolysis, and lignin can be converted into phenolic compounds. The development of the upgrading reaction using two biomass-derived components is appealing for the utilization of biomass resources. We first tried the reaction of **1a** with furfural, by using cesium carbonate as the base, and react at 110℃ for 6 hours. It was delighted to found that product **10a** can be obtained in 57% yield. Furfural can also react with **1b** afford product **10b** in 54%. Moreover, the cellulose-derived 5-methylfurfural and methyl 5-formylfuran-2-carboxylate can also participate in the reaction afford the target products **10c-10f** in moderate yields (Figure 2). Compared with the previous literature, this reaction provides a new strategy for C-C coupling of biomass-derived levulinic esters and furfural.[11a, b] Both the arylation and acylation reactions mentioned above have achieved the construction of C-C bonds, the development of other types of C-hetero bond cross-coupling was also valuable in promoting the high-value utilization of biomass. Then, we tried the reaction of **1a** with phenol under base condition at 120℃ for 24 hours, 49% yield of etherification product **11a** was obtained. This method provides an approach to synthesize different structural compound compounds, which is an important supplementary to previous reaction of levulinic acid with phenol to prepare diphenolic acid.[21] By using vanillin as a starting material, product **11b** and **11c** can be obtained in 53% and 57% yields, respectively.

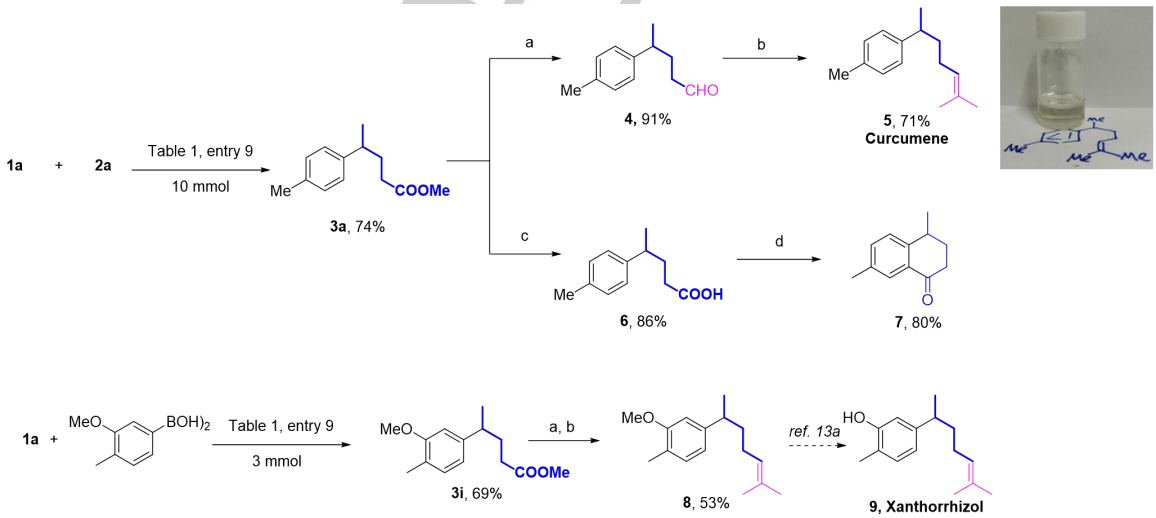


Figure 1. Synthesis of bioactive compounds. a) DIBAL, CH_2Cl_2, -40 ℃; b) *iso*-propyltriphenylphosphonium iodide, *n*-BuLi, THF, -10 ºC to 0 ℃; c) LiOH, THF:MeOH:H_2O, 50 ℃; d) TFAA, TFA, 0 ℃.

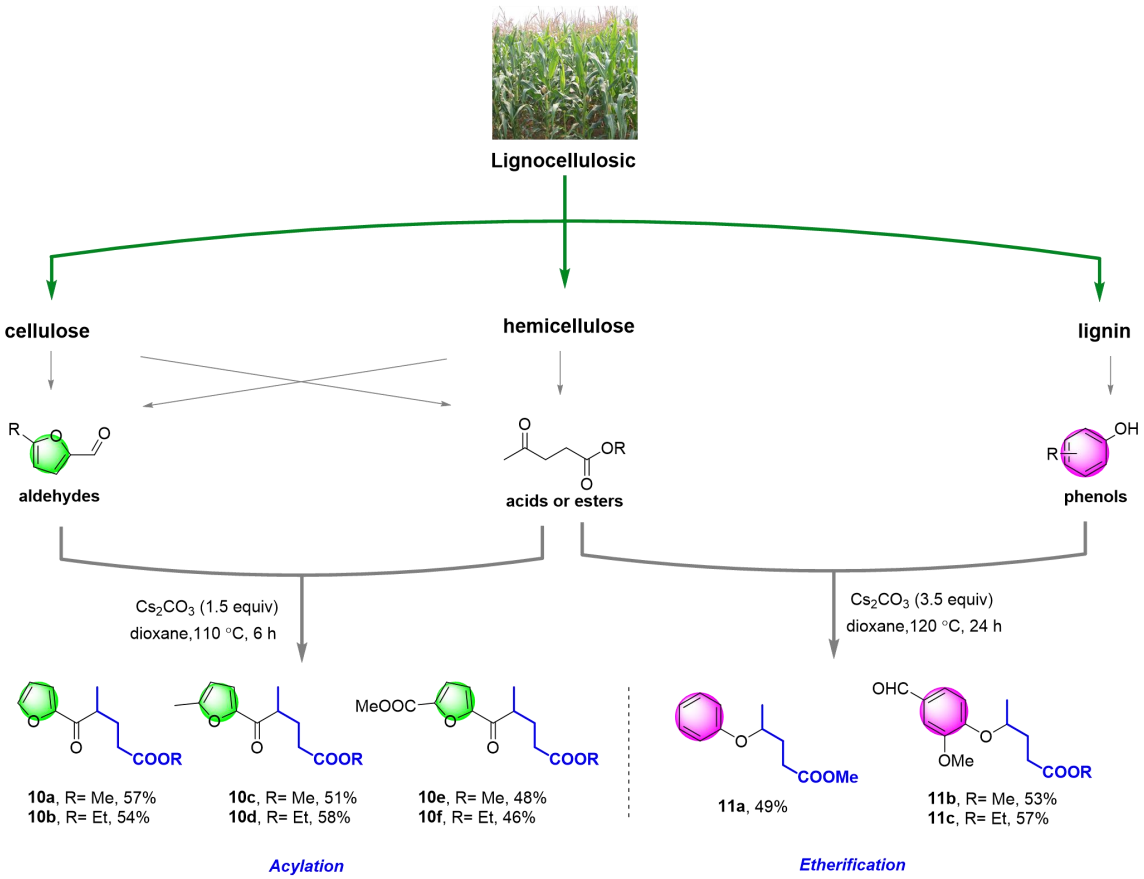


Figure 2. Valorization of methyl levulinate with bio-based aldehydes and phenols.

Conclusion

We reported an unprecedented example of transition-metal-free arylation, acylation, and etherification reactions of levulinic acid derivatives. Types of arylboronic acids can be applied in this transformation to afford γ-aryl valerates. Using methyl levulinate ester as a starting material, the condensation and arylation reaction can be achieved smoothly through a "one-pot, two-step" process without isolation of the tosylhydrazone intermediate. Moreover, the arylated products can be used for further transformation to obtain three biologically active molecules, *rac*-urcumene, *rac*-xanthorrhizol, and *rac*-4,7-dimethyl-l-tetralone. In addition to the cross-coupling reaction with boronic acid, the metal-free reductive cross-coupling can also undergo acylation and etherification with lignocellulose derivatives (*aldehydes and phenols*) to prepare more types of products. Therefore, the strategy reported here is an important supplement to the high-value utilization of levulinic acid and its esters, and it also provides a new idea for the high-value utilization of other biomass platform molecules.

Experimental Section

Preparation of tosylhydrazone derivatives 1: A 500 mL round bottom flask equipped with a magnetic stirrer was charged with $TsNHNH_2$ (50 mmol), then 100 mL of dry methanol or ethanol was added. The reaction mixture was stirred at 80 ℃ until the solid was dissolved. The methyl (or ethyl) levulinate (50 mmol) was added slowly, and the mixture was heated in an oil bath at 80°C for 30 min, the mixture was then cooled to 0 ℃, white solid precipitated and the product was collected on a Büchner funnel, washed with cold methol or ethanol (5 mL) and petroleum ether, and then dried in vacuo to afford the corresponding N-tosylhydrazones.

Reaction of 1 with boronic acid: A 10 mL Schlenk tube equipped with a magnetic stirrer was charged with tosylhydrazone **1a** or **1b** (0.5 mmol), Cs_2CO_3 (1.5 equiv., 0.75 mmol), and arylboronic or alkenylboronic acids (1.5 equiv., 0.75 mmol). The tube was evacuated and backfilled with argon for three times, and then dioxane (2 mL) was added by syringe under argon. The reaction mixture was stirred at 120 ℃ for 4 h. Then EtOAc and water were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 mL x 2) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the corresponding products.

General procedure for synthesis of *rac*-crucumene:

A 250 mL Schlenk tube equipped with a magnetic stirrer was charged with tosylhydrazone **1a** (10 mmol), Cs_2CO_3 (1.5 equiv., 15 mmol), and 4-tolylboronic acid (1.5 equiv., 15 mmol). The tube was evacuated and backfilled with argon for three times, and then dioxane (40 mL) was added by syringe under argon. The reaction mixture was stirred at 120 ℃ for 4 h. Then EtOAc and water were added and the layers were separated. The aqueous phase was extracted with EtOAc (20 mL x 2) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was

purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the products **3a** (74%).

At -40 ℃, under nitrogen atmosphere, DIBAL (1.0 M in PhMe, 8.2 ml, 8.2 mmol) was added dropwise to a solution of **3a** (7.4 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at -40 ℃ for 1h. After quenching the reaction with MeOH (5 mL) at -40 ℃, saturated potassium sodium tartrate (20 mL) was added. The solution was stirred until it turned clear. Then Et_2O (30 mL) and water were added and the layers were separated. The aqueous phase was extracted with Et_2O (20 mL × 3) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to afford the aldehyde **4** (91% yield) as a colorless oil.

Under nitrogen atmosphere, n-BuLi (1.6 M in n-hexane, 10 mL, 16 mmol) was added dropwise to a stirred suspension of *iso*-propyltriphenylphosphonium iodide (6.9 g, 16 mmol) in dry THF (5 mL) at -10 ℃. The solution was stirred for 30 min at that temperature. Then aldehyde **4** (6.7 mmol) in THF (10 mL) was slowly added at 0 ℃. The resulting solution was stirred for 1 h at ambient temperature and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (20 mL × 3) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to afford **5** (71% yield) as a colorless oil.

Reaction of 1a with aldehydes: A 10 mL Schlenk tube equipped with a magnetic stirrer was charged with **1a** (0.5 mmol), Cs_2CO_3 (1.5 equiv., 0.75 mmol). The tube was evacuated and backfilled with argon for three times, then furfural or 5-methylfurfural (1.2 equiv., 0.6 mmol), dioxane (2 mL) was added by syringe under argon. The reaction mixture was stirred at 110 ℃ for 6 h. Then EtOAc and water were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 mL x 2) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the corresponding products.

Reaction of 1a with phenols: A 10 mL Schlenk tube equipped with a magnetic stirrer was charged with **1a** (0.5 mmol), Cs_2CO_3 (3.5 equiv., 1.75 mmol). The tube was evacuated and backfilled with argon for three times, and then phenol or vanillin (2 equiv., 1 mmol) in dioxane (2 mL) was added by syringe under argon. The reaction mixture was stirred at 120 ℃ for 24 h. Then EtOAc and water were added and the layers were separated. The aqueous phase was extracted with EtOAc (3 mL x 2) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the corresponding products.

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Keywords: biomass conversion • levulinic acid derivatives • tosylhydrazone • *rac*-curcumene • *rac*-xanthorrhizol

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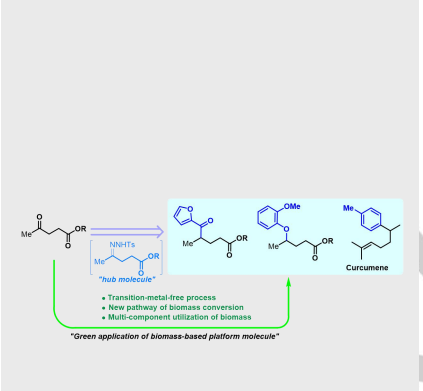
Metal-free reductive cross-coupling arylation, acylation, and etherification reactions of biomass-derived levulinic esters were reported herein. Three biologically active molecules, rac-curcumene, rac-xanthorrhizol, and rac-4,7-dimethyl-l-tetralone *were accomplished by this method. This reaction provides a new route for the high-value utilization of biomass platform molecules.*



Wen-Yan Xu, Kai-Feng Zhuo, Tian-Jun Gong, and Yao Fu**

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Transition-Metal-Free Valorization of Biomass-derived Levulinic Acid Derivatives: Synthesis of Curcumene and Xanthorrhizol

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