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Cross-Coupling

Rapid Bis-Coupling Reactivity with Triarylbismuth Reagents: Synthesis of Structurally Diverse Scaffolds and Step-economic Convergent Synthesis of Quebecol

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Abstract: The cross-coupling study of *gem*-dibromoesters with triarylbismuths as threefold arylating reagents was investigated under palladium-catalyzed conditions. This study using triarylbismuth reagents explored the cross-coupling reactivity with various functionalized *gem*-dibromoesters. It furnished a variety of multi-functional trisubstituted acrylates embedded with aryl, alkene and alkyne scaffolds in high yields. The present study in turn, provided easy access to various triarylated acrylates and functionalized 1,3-dienyl and 1,3-enyne esters. Further, the established method applied in the step-economic and convergent synthesis of quebecol natural product in good yield.

Introduction

Triarylethylene containing scaffolds are prominent for their presence in drugs and various optical materials.[1] For instance, triaryl functionalized tamoxifen and their derivatives panomifene and clomifene are studied in breast cancer and other therapeutic applications (Figure 1).[1a,1b] Importantly, quebecol as process-derived phenolic compound isolated from Canadian maple syrup, was known for its structural similarity with tamoxifen. It was associated with antioxidant, antiproliferative and anti-inflammatory properties.[1c–1e] In material applications, triphenylamine containing triarylethylene compounds or functionalized with extended π-conjugation involving alkenes (F1–F3, Figure 1) are studied for several photophysical properties.[1f–1l]

In this context, functionalized acrylates provide ample and flexible opportunities for selective synthetic manipulations. A few approaches are reported in the literature[2,3] to access triarylated acrylates. For example, triarylated acrylates with varied aryl groups could be availed through Pd-catalyzed addition reactions of aryl organometallic reagents either using boron or tin reagents with alkyl 3-arylpropiolates.[2b,3a,3b] Similarly, Pd-catalyzed three-component coupling of ethyl 3-phenylpropiolate, aryl iodide and arylboronic acid reported affording triarylated acrylates.[3c,3d] These two methods are known to give

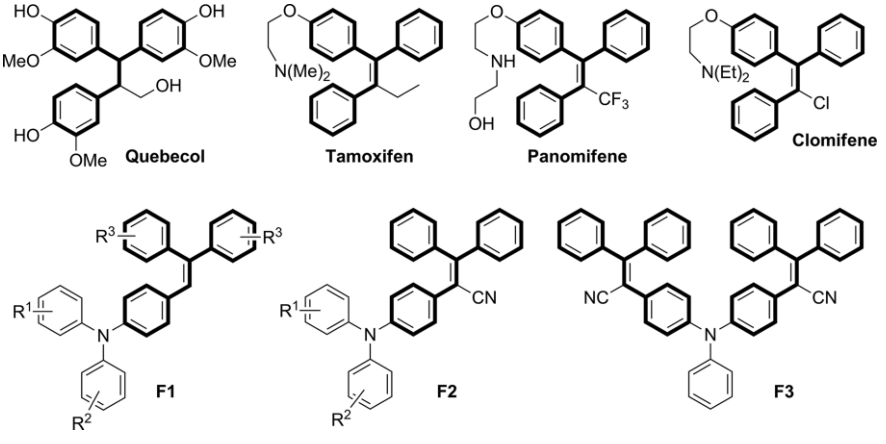

Figure 1. Important triarylethylene derived compounds.

cis-addition to alkyne affording *cis*-α,β-diarylacrylates. The addition reaction of bis(pinacolato)diboron reported with ethyl 3-arylpropiolate provides *trans*-α,β-diboryl acrylates and these are cross-coupled with aryl bromides to obtain triarylated acrylates.[3e] On the other hand, bromination of ethyl 3-phenylpropiolate followed by Suzuki coupling also provides triarylated

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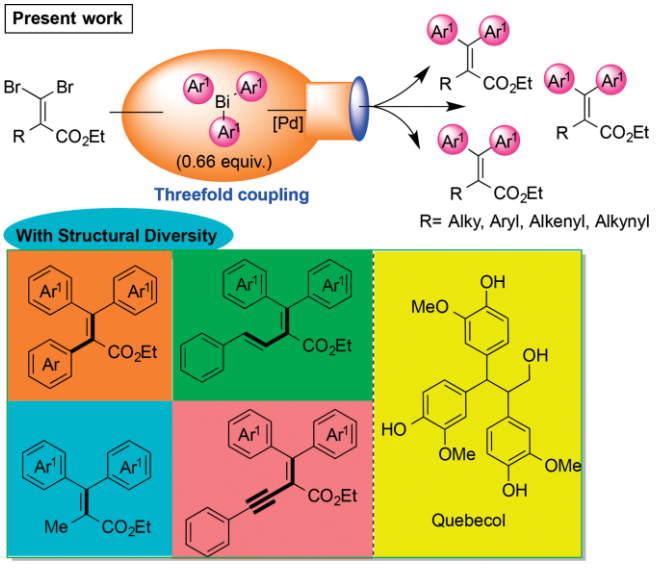
acrylates.[3f] The Suzuki coupling of ethyl 3,3-dibromo-2-arylacrylates under Pd-catalyzed conditions provides bis-coupled products in a facile manner.[3g] Also, metallo-esterification of diphenylacetylene with Cp_2ZrEt_2/ chloroformate and its coupling with iodobenzene reported giving triarylated acrylates under Pd-catalyzed conditions.[3h] Recently, α,β,β-triarylation of methyl acrylate was reported under Pd-catalyzed Matsuda–Heck coupling conditions involving 4-methoxybenzenediazonium tetrafluoroborate.[3i]

As enumerated, most of these reported methods provide variously arylated acrylates with different substrate combinations under metal-catalyzed conditions. However, a few of them not bestowed with a broader substrate scope in terms of synthetic applicability. The bis-coupling reactivity of ethyl 3,3-dibromo-2-arylacrylates under Pd-catalyzed conditions needs a special mention as this method provides extensive substrate scope and flexibility with structural variations. Surprisingly, not many studies are reported to exploit its synthetic utility. It intrigued us to explore this reaction with triarylbismuths as threefold organometallic coupling reagents and this bestowed broad substrate scope towards diversified reactivity (Scheme 1). This interest originated from our earlier coupling studies carried out under palladium catalysis with *gem*-dibromo alkenes.[4] As *gem*-dibromoester substrates are easily accessible from keto esters functionalized with various alkyl, aryl, alkenyl, alkynyl groups,[5] using CBr_4/PPh_3 conditions,[6] the developed process demonstrated high synthetic advantage when applied to structurally diverse functional molecular skeletons. Again, the threefold coupling advantage of atom-economic triarylbismuth organometallic reagents has been of particular interest to us.[7] It paved the way to establish the rapid bis-coupling reactivity of *gem*-dibromoesters with triarylbismuth reagents under palladium-catalyzed conditions. Further, the developed method was applied in the step-economic convergent synthesis of quebecol natural product as elaborated here.

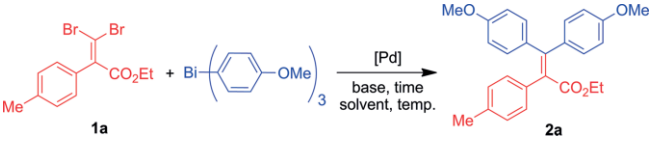


Scheme 1. BiAr3 based bis-coupling approach.

Results and Discussion

The bis-coupling reactivity of ethyl 3,3-dibromo-2-*p*-tolylacrylate (**1a**) was screened with tri(*p*-anisyl)Bi under palladium-catalyzed conditions (Table 1). This reaction was expected to provide ethyl 3,3-bis(4-methoxyphenyl)-2-*p*-tolylacrylate (**2a**) as bis-coupled product. As a trail reaction, it was initially screened with 1.5 equiv. of 3,3-dibromo-2-*p*-tolylacrylate (**1a**) and 1 equiv. of tri(*p*-anisyl)Bi using $Pd(PPh_3)_4$ and KOAc in *N*,*N*-dimethylformamide (DMF) at 110 °C for 2 hour conditions. Encouragingly, this protocol afforded bis-coupled product (**2a**) in 60 % yield (entry 1, Table 1). Further study with 1.7 equiv. of **1a** furnished bis-coupled product **2a** in 65 % yield (entry 2, Table 1). To our delight, the desired yield greatly improved to 86 % with 0.05 equiv. palladium catalyst conditions (entry 3, Table 1). Further screening with $Pd(dba)_2$/2 PPh_3 afforded bis-coupled product in 57 % yield (entry 4, Table 1). Moreover, this reaction with $Pd(PPh_3)_4$ (0.09 equiv.) did not improve the yield (entry 5, Table 1). The screening carried out with DMA (*N*,*N*-dimethylacetamide), NMP (*N*-methyl-2-pyrrolidone) and DMSO (dimethyl sulfoxide) afforded product **2a** in 70–79 % yields (entries 6–8, Table 1). Different bases investigated for their efficacy using K_2CO_3, $NaHCO_3$, K_3PO_4, and Cs_2CO_3 provided product **2a** in 65–83 % yields (entries 9–12, Table 1). This base screening thus proved KOAc as the more efficient one to provide a high bis-coupling yield (entry 3, Table 1). To find the optimum amount required, screening was carried out with 3 or 5 equiv. of KOAc and these two conditions afforded lowered yields (entries 13 and 14, Table 1). Further, different reaction times using 1 and 3 hour conditions gave 77 % and 85 % yields respectively

Table 1. Optimization conditions.[a]



1a 2a

Entry	Catalyst [equiv.]	Base [equiv.]	Solvent	Yield [%]
1	$Pd(PPh_3)_4$ [0.02]	KOAc [4]	DMF	60[b]
2	$Pd(PPh_3)_4$ [0.02]	KOAc [4]	DMF	65
3	**$Pd(PPh_3)_4$ [0.05]**	**KOAc [4]**	**DMF**	**86**
4	$Pd(dba)_2$/2 PPh_3 [0.05]	KOAc [4]	DMF	57
5	$Pd(PPh_3)_4$ [0.09]	KOAc [4]	DMF	83
6	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	DMA	79
7	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	NMP	79
8	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	DMSO	70
9	$Pd(PPh_3)_4$ [0.05]	K_2CO_3 [4]	DMF	65
10	$Pd(PPh_3)_4$ [0.05]	$NaHCO_3$ [4]	DMF	65
11	$Pd(PPh_3)_4$ [0.05]	K_3PO_4 [4]	DMF	75
12	$Pd(PPh_3)_4$ [0.05]	Cs_2CO_3 [4]	DMF	83
13	$Pd(PPh_3)_4$ [0.05]	KOAc [3]	DMF	75
14	$Pd(PPh_3)_4$ [0.05]	KOAc [5]	DMF	82
15	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	DMF	77[c]
16	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	DMF	85[d]
17	$Pd(PPh_3)_4$ [0.05]	KOAc [4]	DMF	70[e]
18	$Pd(PPh_3)_4$ [0.05]	–	DMF	13
19	–	KOAc [4]	DMF	–

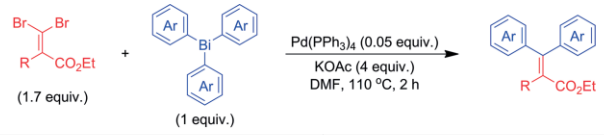
[a] Conditions: **1a** (0.212 mmol, 1.7 equiv.), tri(*p*-anisyl)bismuth (0.125 mmol, 1 equiv.), KOAc (0.5 mmol, 4 equiv.), $Pd(PPh_3)_4$ (0.0062 mmol, 0.05 equiv.), DMF (3 mL), 110 °C, 2 h. [b] **1a** (1.5 equiv.). [c] 1 h. [d] 3 h. [e] At 90 °C.

(entries 15 and 16, Table 1). The desired cross-coupling further screened at 90 °C gave 70 % yield (entry 17, Table 1). A couple of control reactions without base and catalyst conditions gave either poor and no product respectively (entries 18 and 19, Table 1). Overall, the above systematic investigation revealed an effective protocol comprising $Pd(PPh_3)_4$ (0.05 equiv.), KOAc (4 equiv.) in DMF at 110 °C with 2 hour conditions (entry 3, Table 1) to derive the desired bis-coupling in high yield.

The facile bis-coupling reactivity thus obtained above under the established conditions prompted us to further investigate for generalized reactivity of different *gem*-dibromoesters (**1a**–**1n**) with triarylbismuth reagents. It is worth mentioning that the cross-couplings carried out with different *gem*-dibromoesters and triarylbismuth reagents provided the broad substrate scope with good to excellent yields (Table 2).

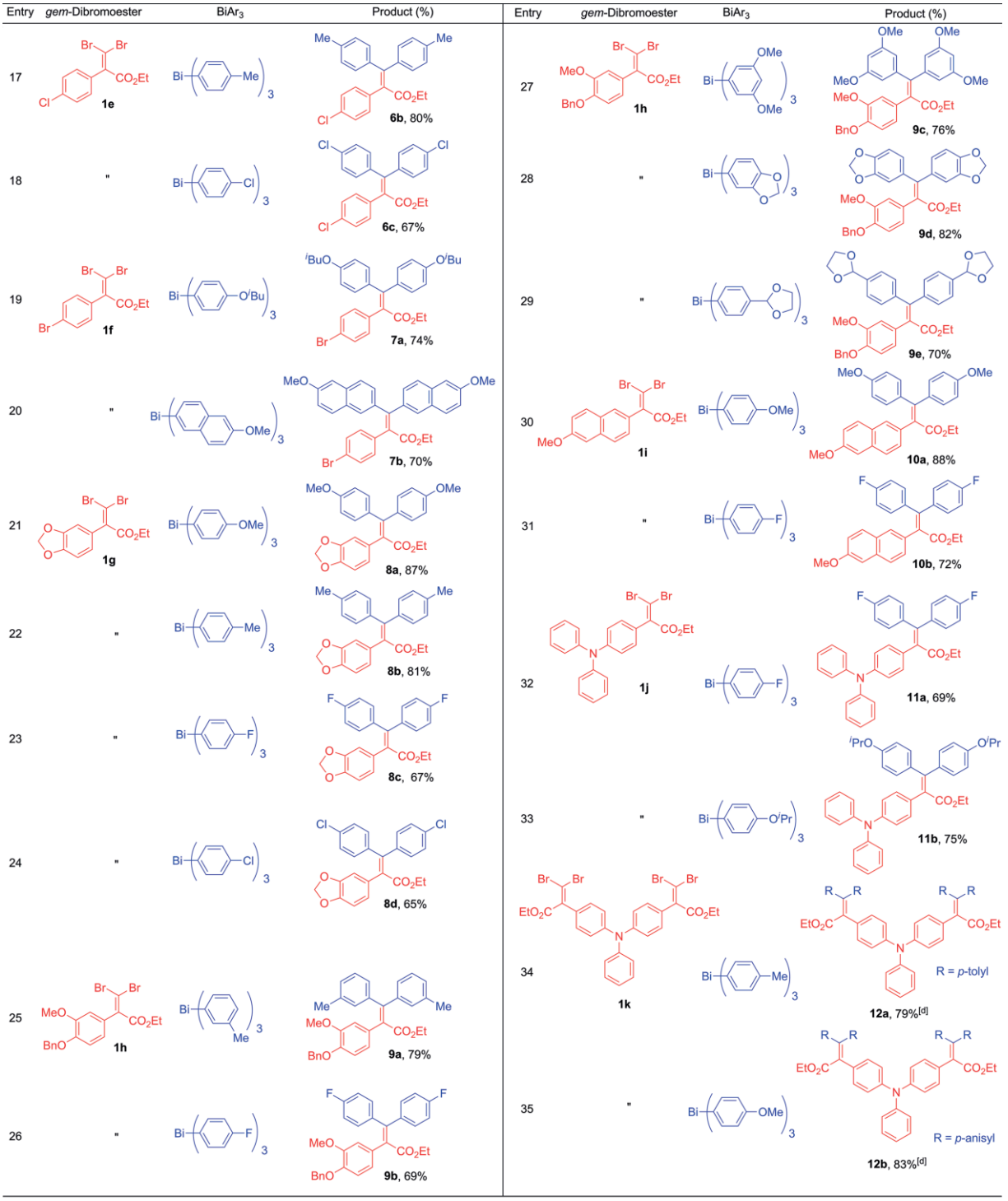
To elaborate, under the optimized protocol conditions, ethyl 3,3-dibromo-2-*p*-tolylacrylate (**1a**) reacted very efficiently with triarylbismuth reagents affording differently functionalized triarylated acrylates (**2a**–**2e**) in 67–86 % yields (entries 1–5, Table 2). This reactivity was extended further to different 3,3-

Table 2. Bis-arylation of *gem*-dibromoester derivatives with triarylbismuth reagents.[a–c]



Entry	*gem*-Dibromoester	$BiAr_3$	Product (%)	Entry	*gem*-Dibromoester	$BiAr_3$	Product (%)
1	**1a**	$Bi(C_6H_4OMe)_3$	**2a**, 86%	9	**1b**	$Bi(C_6H_4Cl)_3$	**3d**, 68%
2	"	$Bi(C_6H_4Me)_3$	**2b**, 79%	10	**1c**	$Bi(C_6H_4Me)_3$	**4a**, 76%
3	"	$Bi(C_6H_4Cl)_3$	**2c**, 67%	11	"	$Bi(C_6H_4OMe)_3$	**4b**, 79%
4	"	$Bi(C_6H_4O^iPr)_3$	**2d**, 84%	12	"	$Bi(C_6H_4Cl)_3$	**4c**, 70%
5	"	$Bi(C_6H_4O_2CH_2)_3$	**2e**, 80%	13	**1d**	$Bi(C_6H_4OMe)_3$	**5a**, 83%
6	**1b**	$BiPh_3$	**3a**, 73%	14	"	$Bi(C_6H_4Me)_3$	**5b**, 80%
7	"	$Bi(C_6H_4OMe)_3$	**3b**, 80%	15	"	$Bi(C_6H_4Cl)_3$	**5c**, 65%
8	"	$Bi(C_6H_4Me)_3$	**3c**, 81%	16	**1e**	$Bi(C_6H_4OMe)_3$	**6a**, 83%

Table 2. *(continued)*



[a] Conditions: *gem*-Dibromoester (0.212 mmol, 1.7 equiv.), $BiAr_3$ (0.125 mmol, 1 equiv.), KOAc (0.5 mmol, 4 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), DMF, 110 °C, 2 h. [b] Isolated yields. [c] Biaryl formed in minor amounts. [d] **1k** (0.106 mmol, 0.85 equiv.), 4 h.

dibromo-2-(aryl)acrylates (**1b**–**1f**) in couplings with triarylbismuth reagents (entries 6–20, Table 2). This study with electronically different *gem*-dibromoesters reacted smoothly to deliver the corresponding bis-arylated products (**3a**–**3d**, **4a**–**4c**, **5a**–**5c, 6a**–**6c, 7a,** and **7b**) in high yields. Gratifyingly, 4-bromophenyl-substituted *gem*-dibromoester (**1f**) participated in a chemo-selective coupling involving *gem*-dibromo terminus. It afforded the corresponding **7a** and **7b** products in good yields (entries 19 and 20, Table 2). To our delight, the bis-coupling reactivity carried out with other *gem*-dibromoesters (**1g**–**1i**) also showed

facile reactivity under the established conditions delivering the corresponding bis-arylated products (**8a**–**8d**, **9a**–**9e**, **10a** and **10b**) in good to high yields (entries 21–31, Table 2).

Importantly, triphenylamine derivatives with core extended conjugated system are well known for their photophysical properties as some of these compounds were earlier studied in aggregation-induced emission (AIE) and intramolecular charge transfer (ICT) behavior.[1f–1i] Keeping this in mind, it was of interest to extend the present study to bis-coupling of triphenylamine derived *gem*-dibromoester (**1j**) with triarylbismuth reagents (entries 32 and 33, Table 2). Amazingly, this substrate also demonstrated an excellent reactivity under the established cross-coupling conditions to deliver the corresponding bis-arylated products (**11a** and **11b**) in high yields. It was further extended to triphenylamine derived bis-*gem*-dibromo compound **1k** and it was cross-coupled for tetraarylation with triarylbismuth reagents (entries 34 and 35, Table 2). In this attempt, the corresponding triarylated products (**12a** and **12b**) were obtained in high yields. The literature known methods[1c–1f] to prepare this type of compounds required C-N coupling procedures. The present method thus proved to be very useful to access triphenylamine based molecules (Figure 1) in a facile manner and may serve as a viable alternative.

The broad spectrum of reactivity obtained above prompted our further studies with differently functionalized *gem*-dibromoesters (Table 3). As part of this, the bis-coupling reactivity of *gem*-dibromoesters functionalized with alkyl, alkenyl and alkyne moieties (**1l**–**1n**) were investigated. The alkyl functionalized *gem*-dibromoester (**1l**) reacted efficiently (entries 1–4, Table 3) with triarylbismuth reagents providing the corresponding trisubstituted acrylates (**13a**–**13d**) in good yields. Similarly, alkenyl derived *gem*-bromoester (**1m**) also fared well in bis-couplings (entries 5–7, Table 3) to furnish the corresponding functionalized 1,3-dienes (**14a**–**14c**) in high yields. This encouraging reactivity was continued with alkynyl derived *gem*-dibromoester (**1n**) in couplings with triarylbismuth reagents (entries 8–13, Table 3). These reactions afforded the corresponding functionalized 1,3-eneynes (**15a**–**15f**) in good yields. This attempt demonstrated further scope and utility of the developed methodology in the preparation of novel functional scaffolds. Overall, an excellent and broad spectrum of bis-coupling reactivity of *gem*-dibromoesters with triarylbismuth reagents was obtained under the established palladium-catalyzed conditions.

The applicability of our methodology was then assessed in the synthesis of quebecol (**22**) natural product. For this, a concise strategy was envisaged as given in Scheme 2, from guaiacol (**16**). A retrosynthetic plan comprising the bis-coupling of *gem*-dibromoester (**1h**) with triarylbismuth reagent (**TAB-1**) is a key step involved to achieve the synthesis of quebecol (**22**) (Scheme 3). Accordingly, aryl bromide (**18**) required for the preparation of **TAB-1** could be obtained from guaiacol (**16**). In turn, the aryl bromide (**18**) could also be utilized in the preparation of *gem*-dibromoester (**1h**) through keto ester (**19**).

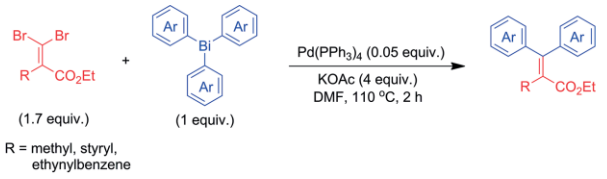
Thus, the proposed synthetic effort was started with the bromination of guaiacol (**16**) using NBS/PTSA to obtain aryl bromide (**17**) in 88 % yield.[8a] It was then benzylated to prepare the corresponding benzyl protected aryl bromide (**18**) in 76 % yield.[8b] This bromide (**18**) was further used in the preparation of triarylbismuth reagent (**TAB-1**) through lithiation and reaction with bismuth trichloride. This afforded triarylbismuth reagent (**TAB-1**) in 64 % yield (Scheme 3).[4d] Further aryl bromide (**18**) was subjected to lithiation followed by reaction with diethyloxalate and this afforded the corresponding keto ester (**19**) in 81 % yield. This keto ester was then used to prepare *gem*-dibromoester (**1h**) using CBr_4/PPh_3 reagent in high yield. This way, the two crucial fragments namely, *gem*-dibromoester (**1h**) and triarylbimsuth reagent (**TAB-1**) were obtained in a concise manner starting from guaiacol (**16**).

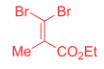
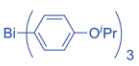
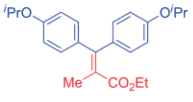
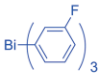
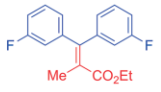
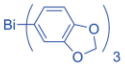
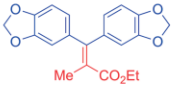
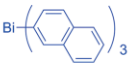
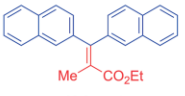
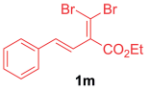
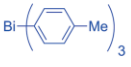
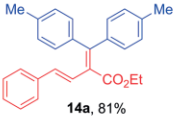
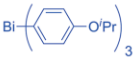
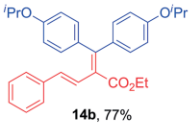
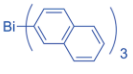
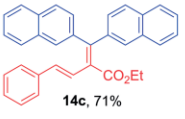
To take forward the proposed synthetic process, the cross-coupling reaction of *gem*-dibromoester (**1h**) was carried out with triarylbismuth reagent (**TAB-1**) under the established palladium-catalyzed conditions (Scheme 4). This step furnished the bis-arylated product (**20**) in 81 % high yield. This product was then subjected to a few known steps to arrive at quebecol (**22**). It involved initially the hydrogenolysis step under Pd/C conditions. However, under these conditions employed, benzyl deprotection was also witnessed along with the reduction of a double bond. This cumulatively afforded the formation of saturated ester **21** in 90 % yield. The final step of the reduction of ester was carried out using lithium aluminum hydride under reflux conditions. It afforded the quebecol (**22**) in overall good yield.

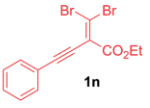
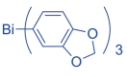
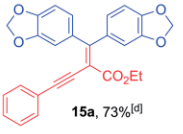
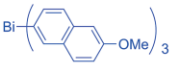
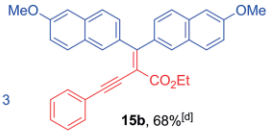
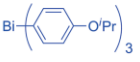
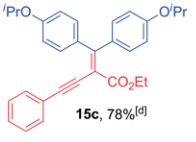
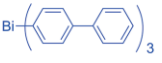
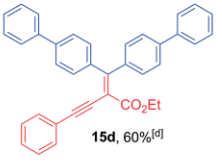
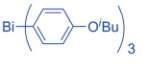
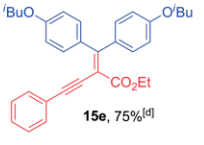
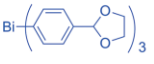
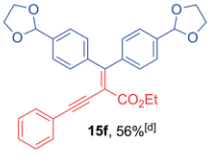
To note, the bis-arylation of *gem*-dibromoester under the Suzuki cross-coupling was applied earlier by Voyer et al. in the synthesis of quebecol.[9] However, it involved the preparation of two coupling partners from two different starting materials (Scheme 5). In comparison, the present convergent method starting from guaiacol (**16**) delivered an efficient and step-economic protocol (Scheme 3 and Scheme 4) with high synthetic viability. Additionally, our cross-couplings involving triarylbismuth reagent furnished atom-economic couplings with improved cross-coupling reactivity and in shorter reaction time with sub-stoichiometric loading of organometallic reagent. As mentioned above, *gem*-dibromoester (**1h**) utilized in quebecol (**22**) synthesis, was also involved in efficient cross-couplings with different triarylbismuth reagents (entries 25–29, Table 2). These couplings afforded the corresponding triarylated acrylates (**9a**–**9e**) in good to high yields.

As proposed, the formation of bis-coupling product from *gem*-dibromoester was expected to follow the general cross-coupling steps involving oxidative addition, transmetallation and reductive elimination under Pd-catalyzed conditions (Scheme 6).[4a,7] As known, the bromide terminus *trans* to aryl group in *gem*-dibromoester (**p**) preferentially involves the cross-coupling process to give the product (**s**).[3g,10] The second cross-coupling involving intermediate **s** was expected to provide the desired bis-coupling product (**v**). To note, experimentally both these couplings were completed very fast in 2 h shorter time under our simple and routinely used palladium protocol conditions. Importantly, the intermediate (**s**) could not be isolated, probably be due to the faster bis-coupling reactivity under the conditions employed. However, analysis of the crude product mixture by mass spectroscopy revealed the presence of mono-

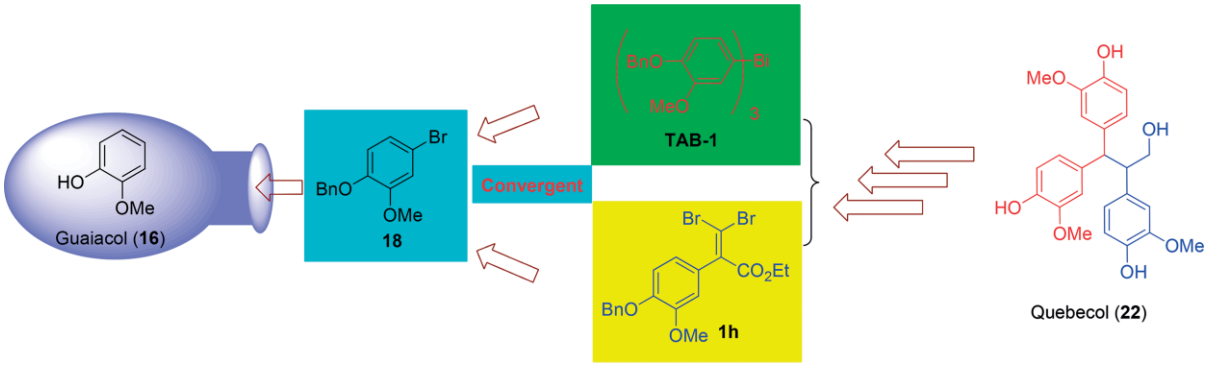
Table 3. Bis-arylation of *gem*-dibromoester derivatives with triarylbismuth reagents.[a–c]



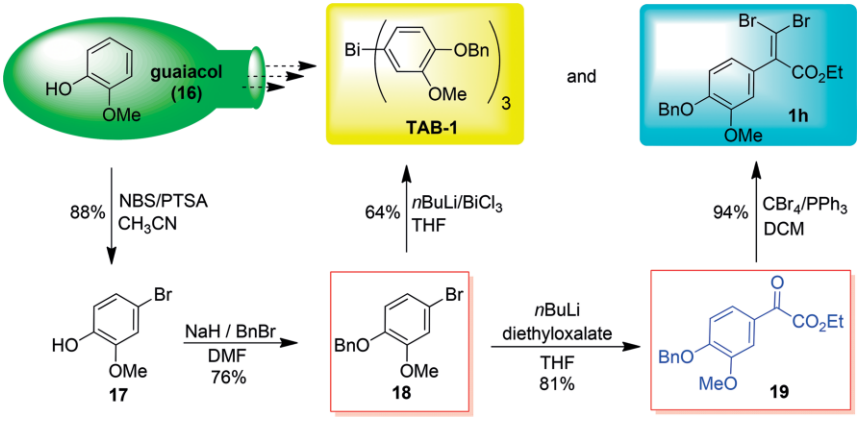
Entry	*gem*-Dibromoester	$BiAr_3$	Product (%)
1	 **1l**		 **13a**, 72%
2	"		 **13b**, 60%
3	"		 **13c**, 75%
4	"		 **13d**, 71%
5	 **1m**		 **14a**, 81%
6	"		 **14b**, 77%
7	"		 **14c**, 71%

Entry	*gem*-Dibromoester	$BiAr_3$	Product (%)
8	 **1n**		 **15a**, 73%[d]
9	"		 **15b**, 68%[d]
10	"		 **15c**, 78%[d]
11	"		 **15d**, 60%[d]
12	"		 **15e**, 75%[d]
13	"		 **15f**, 56%[d]

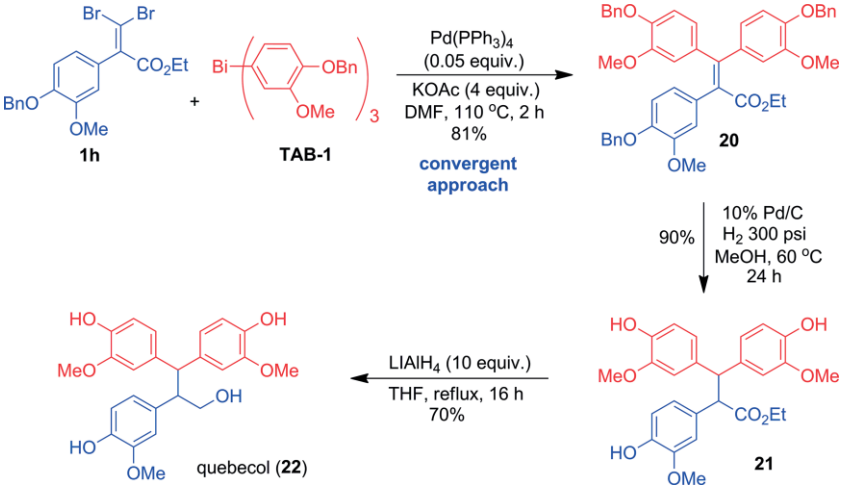
[a] Conditions: *gem*-Dibromoester (0.212 mmol, 1.7 equiv.), $BiAr_3$ (0.125 mmol, 1 equiv.), KOAc (0.5 mmol, 4 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), DMF, 110 °C, 2 h. [b] Isolated yields. [c] Biaryl formed in minor amounts. [d] **1n** (0.25 mmol, 2 equiv.).



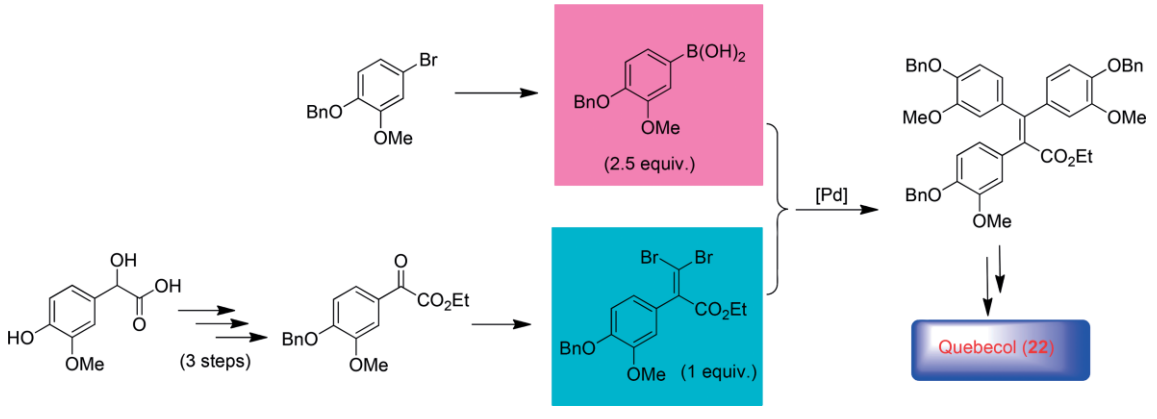
Scheme 2. Retrosynthetic analysis of quebecol (**22**).



Scheme 3. Synthesis of triarylbismuth **TAB-1** and *gem*-dibromoester (**1h**).

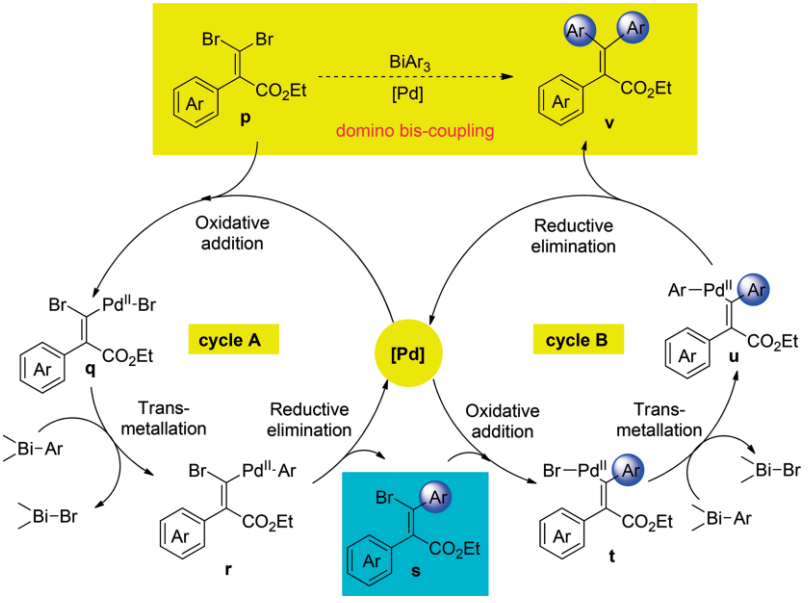


Scheme 4. Synthesis of quebecol.



Scheme 5. Synthesis by Voyer et al.[9]

coupled intermediate (**s**) in trace amount. Further, a reaction was carried out with 2 equiv. of *gem*-dibromide **1a** and 0.3 equiv. of Bi(*p*-anisyl)$_3$ to check the possibility for the isolation of the mono-coupled intermediate (**s**). However, under these conditions also bis-coupled product **2a** was isolated in 66 % yield along with the recovery of the unreacted *gem*-dibromide quantitatively. Overall, the present methodology presents more than one advantage with triarylbismuth reagents such as (a) sub-stoichiometric loadings (b) atom-economic threefold reactivity (c) shorter reaction time for bis-arylations. Moreover, the synthesis of quebecol (**22**) was achieved in a step-economic manner from guaiacol (**16**).



Scheme 6. Mechanistic proposal.

Conclusions

We have successfully developed the bis-coupling reactivity of *gem*-dibromoesters with triarylbismuth reagents under palladium coupling conditions. These couplings provided a facile synthesis of various multi-functional trisubstituted acrylates embedded with aryl, alkene and alkyne scaffolds in high yields. This study of bis-couplings opened up a viable approach for the synthesis of various triarylated acrylates and functionalized 1,3-dienyl and 1,3-enyne esters. The present method was also applied in the concise and convergent synthesis of quebecol natural product in good yield starting from guaiacol.

Acknowledgments

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Keywords: Cross-coupling · Palladium catalysis · Triarylbismuth reagents · Trisubstituted acrylates · Quebecol synthesis

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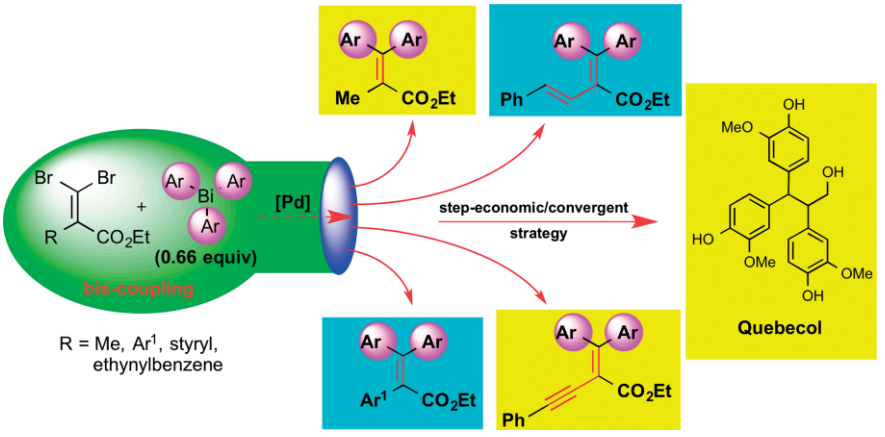
Cross-Coupling



The cross-coupling study of *gem*-dibromoesters with triarylbismuths furnished a variety of multi-functional trisubstituted acrylates embedded with aryl, alkene and alkyne scaffolds in high yields under palladium catalysis. Further, the established method was applied in the step-economic and convergent synthesis of quebecol natural product in good yield.

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