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Facile access to sterically hindered aryl ketones via carbonylative cross-coupling: application to the total synthesis of luteolin

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ABSTRACT

A general and mild protocol for achieving the carbonylative cross-coupling of sterically hindered, *ortho*-disubstituted aryl ketones is reported. The commercially available PEPPSI-IPr catalyst is shown to efficiently promote the carbonylative cross-coupling of hindered *ortho*-disubstituted aryl iodides to give diaryl ketones; traditional phosphine catalysts are less effective. Carbonylative Suzuki-Miyaura cross-couplings provide a diverse array of biaryl ketones in good to excellent yields. The same catalyst is also shown to catalyze a carbonylative Negishi cross-coupling reaction, utilizing a variety of alkynyl-zinc reagents to give the corresponding alkynyl aryl ketones. Application of this new methodology to the synthesis of the natural product luteolin is reported.

1. Introduction

Flavanoids and aryl ketones are common substructures found in many natural products.[1] Many of these biologically relevant molecules possess substitution at both positions *ortho* to the ketone moiety. For example, kidamycin (**1**), a potent anti-cancer antibiotic, contains a benzopyranone motif that possesses this substitution pattern,[2] as do simpler natural products, including luteolin (**2**) and aureusidin (**3**) (Fig. 1).[3] An efficient approach toward the total synthesis of any of these natural products will necessarily mandate installing the *ortho*-disubstituted aryl ketone functional group with minimal synthetic manipulations.

Numerous methods exist for the construction of *ortho*-disubstituted aryl ketones. Of these, the more common procedures are the Friedel–Crafts reaction,[4] the Fries rearrangement,[5] and additions of organometallic reagents to acyl electrophiles,[6] but these procedures utilize stoichiometric amounts of strongly basic or acidic reagents. Moreover, the inherent bias of the Friedel–Crafts reaction is to form the sterically less encumbered ketone,[7] and the Fries rearrangement is limited to phenol derivatives, therefore limiting the scope and applicability of the process to only selected targets.

Transition metal catalysis has emerged as an efficient and viable means for constructing new carbon–carbon bonds that would otherwise be difficult to create. For example, the three component coupling of aryl halides or triflates with organometals and carbon monoxide is a powerful method for preparing aryl ketones, as two new carbon–carbon bonds are formed in a single step.[8] Since the initial discovery by Heck,[9] numerous variants of carbonylative cross-couplings have been disclosed. Competent coupling partners

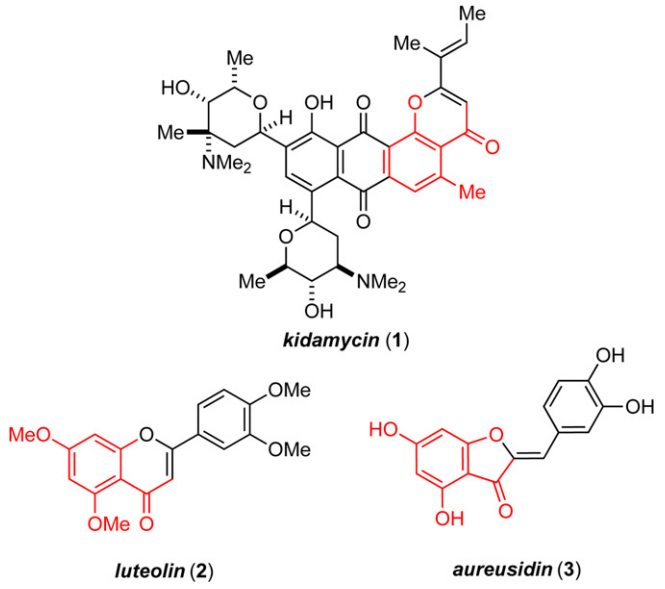

Fig. 1. Natural products containing *ortho*-disubstituted aryl ketones.

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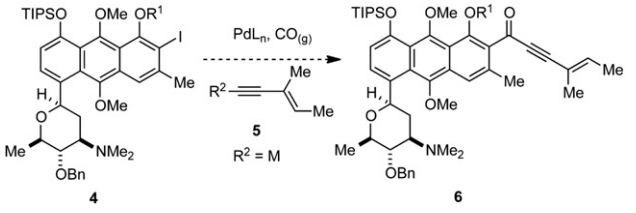
include aryl, alkenyl, alkynyl, and alkyl organometallic reagents that may be derived from tin,[10] copper,[11] boron,[12] zinc,[13] aluminum,[14] magnesium,[15] and silicon.[16] Recent developments in carbonylative cross-coupling technology have enabled the use of alkyl halides in the reaction.[17] Further advancements have been made in the field with immobilization of the catalyst on solid supports,[18] as well as the involvement of ionic liquids in the cross-coupling process;[19] however, most carbonylative cross-coupling reactions proceed under harsh conditions. Furthermore, the vast majority of carbonylative cross-coupling technologies reported are not applicable to the synthesis of *ortho*-disubstituted aryl ketones. A general process for the preparation of these hindered ketones under mild conditions would thus be a valuable addition to the synthetic chemist's toolbox.

During the course of our studies directed toward the total synthesis of isokidamycin,[20] we required an effective method for preparing ketone **6** from the hindered aryl halide **4** (Eq. 1). Although several methods have been reported for the synthesis of aryl alkynyl ketones,[12] including *ortho*-monosubstituted aryl ketones,[21] we found only one example of a carbonylative cross-coupling of an *ortho*, *ortho*-disubstituted aryl iodide that was reported by Suzuki and Miyaura.[12b] They coupled a range of boronic acids with a variety of aryl iodides in the presence of $PdCl_2(PPh_3)_2$ and K_2CO_3 in anisole as solvent under a balloon of CO. They were able to utilize aryl bromides if the reaction conditions were changed to include $Pd_2(dppf)$, K_2CO_3, and KI. We attempted to apply these conditions to the synthesis of ketone **6**, as well as other hindered aryl ketones; however, these endeavors were unsuccessful. It was thus apparent that there was a significant gap in synthetic methodology for effecting the efficient, carbonylative cross-coupling of an *ortho*-disubstituted aryl halide with organometallic nucleophiles. We now report the details of our studies to solve this problem and develop such a process.[22]

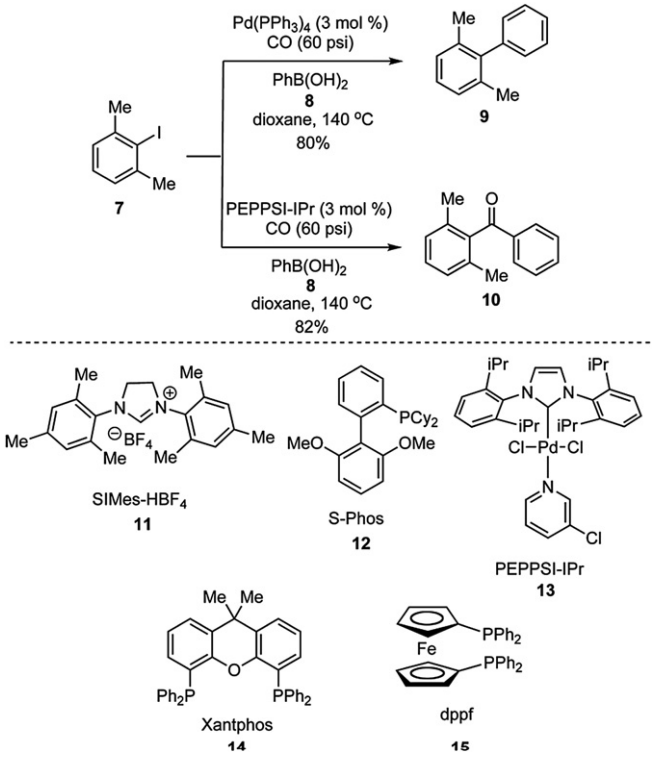


(1)

2. Results and discussion

2.1. Aryl nucleophiles

Drawing on work disclosed by Suzuki, we first examined the carbonylative cross-coupling of *ortho*-disubstituted aryl iodides with aryl boronic acids, which are readily available with diverse substitution patterns. Our campaign to discover appropriate conditions began by screening phosphine ligands in the carbonylative cross-coupling of 2-iodo-*m*-xylene (**7**) and phenyl boronic acid (**8**) (Scheme 1). Phosphine-based palladium catalysts were first selected because they have been widely used in carbonylative cross-coupling processes and have been shown to be effective in catalyzing cross-couplings of sterically congested systems.[23] When 2-iodo-*m*-xylene (**7**) was heated to 140 °C with either $Pd(PPh_3)_4$ or $PdCl_2(dppf)$, phenyl boronic acid (**8**), and cesium carbonate (Cs_2CO_3) at 60 psi of CO, complete conversion of the starting material was observed. However, the ratio of the desired ketone **10** to the undesired biaryl side-product **9** was typically 1:8; based on analysis of the ^1H NMR spectrum of the mixture; the biaryl **9** was typically isolated in excellent yield. This side-reaction, which is common in carbonylative cross-coupling processes, can sometimes be suppressed by increasing the CO pressure.



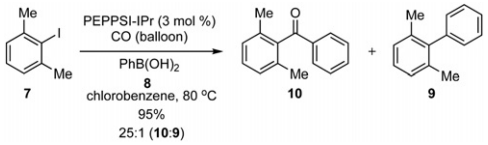
Scheme 1.

Unfortunately, this tactic was not productive in our case, and increasing the CO pressure merely led to lower conversions of iodide **7**. We examined numerous other phosphine ligands, such as *S*-Phos (**12**), Xantphos (**14**), and dppf (**15**), as well as arsine-ligated palladium catalysts, but the ratio of ketone **10** to biaryl **9** could not be improved. Based on the failure of phosphine-ligated palladium catalysts, we examined other supporting ligands.

N-Heterocyclic carbenes (NHC) have been used as ligands in many different cross-coupling reactions, including carbonylative cross-coupling reactions.[12c,24] Moreover, NHC-bound palladium complexes have been shown to be highly active in cross-couplings of hindered systems. However, to the best of our knowledge, they have not been applied to the carbonylative cross-coupling of more hindered *ortho*, *ortho*-disubstituted haloaromatics. NHCs have become popular in transition metal catalyzed cross-coupling reactions for several reasons. Firstly, they are strong ligands on palladium because they increase the electron density on the metal center, a property that may facilitate oxidative addition.[25] They also enhance the thermal stability of the metal complex, so higher reaction temperatures can be employed. When the NHC ligand SIMes-HBF_4 **11** was used as the catalyst for the carbonylative cross-coupling of **7**, ketone **10** was obtained in 50% yield, and the biaryl **9** was now the minor product. Upon switching to the commercially available PEPPSI-IPr catalyst **13**,[26] the yield increased to 82% (Scheme 1). Although this was an encouraging finding, the method was still limited by the requirement to conduct the reaction at 60 psi of CO in order to obtain the ketone **10** as the major product. When the reaction was performed under a balloon pressure of CO, the biaryl **9** was the major product.

A solvent screen was initiated, whereupon we discovered that use of aromatic solvents led to the formation of the ketone **10** as the major product, even under balloon pressure of CO. Use of non-aromatic solvents uniformly gave biaryl **9** as the major product. Toluene, α,α,α-trifluorotoluene, nitrobenzene, and anisole were examined as solvents, and ketone **10** was the major product in all of these reactions; however, significant amounts of starting aryl iodide **7** were also present. After additional experimentation, we found that when

chlorobenzene (PhCl) was used as a solvent, excellent conversion of **7** was observed, and ketone **10** was isolated in 95% yield (Eq. 2).



(2)

Various catalyst/ligand combinations were then reexamined in chlorobenzene in order to ascertain whether it was the PEPPSI-IPr catalyst or the chlorobenzene that was responsible for the excellent isolated yield of ketone **10**. When $Pd(PPh_3)_4$, $PdCl_2(dppf)$, $Pd(OAc_2)$/*S*-Phos, and $Pd(OAc)_2$/Xantphos were used as catalysts, starting material was consumed, but the major product of the reaction was the biaryl **9**. This lends support to the working hypothesis that the NHC ligands on palladium are essential for obtaining excellent product ratios and that chlorobenzene is the optimal solvent for conducting the reaction under a balloon pressure of CO.

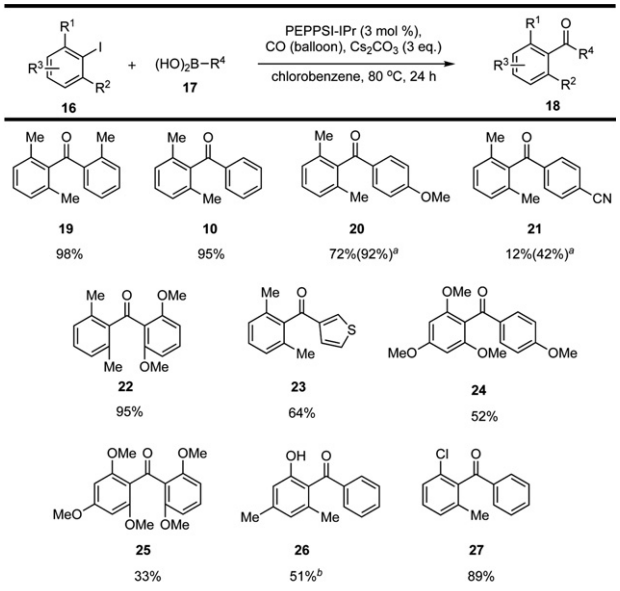
It is interesting that chlorobenzene was the optimal solvent for the reaction, since the PEPPSI-IPr catalyst has been shown to effectively catalyze the Suzuki coupling of aryl chlorides.[24d] Fortunately, no products arising from participation of the solvent were observed, perhaps because the electron withdrawing character of the CO ligands on palladium renders oxidative addition more difficult so aryl chlorides are unreactive.[24d] Furthermore, the ability to conduct the carbonylative cross-coupling under a simple balloon of CO when chlorobenzene was used as the solvent might arise from the increased solubility of CO in chlorobenzene over that of 1,4-dioxane, even at elevated temperatures.[27]

With optimized conditions in hand, we explored the scope of the reaction using several boronic acids (Table 1). Electron neutral and electron rich boronic acids were well tolerated, and the diaryl ketones **10**, **19**, **20**, and **22** were isolated in excellent yields. The carbonylative cross-coupling of electron deficient boronic acids was more difficult. For example, the ketone **21** was obtained in only 12% yield under the standard conditions. Although this was initially disappointing, electron deficient boronic acids are known to undergo more side reactions, such as homocoupling, and they undergo transmetalation to palladium much more slowly than electron rich boronic acids.[28] Nevertheless, the yield increased to 42% when the reaction was run at a higher temperature and pressure.

Heterocyclic boronic acids could also be employed as illustrated by the synthesis of the thiophenyl ketone **23** in 64% yield. Utilization of more electron rich aryl iodides resulted in somewhat diminished yields (cf. ketones **24**–**25**). Although the yields were not as high as some of the previous examples, the results were still promising as oxidative addition is presumably more difficult in these cases due to the highly electron rich nature of the aryl iodide. Phenolic protecting groups were not required as evidenced by the preparation of the ketone **26**. In this reaction, we found that use of K_2CO_3 as the base instead of Cs_2CO_3 improved the yield of **26** from 18% to 51%.

Although one might presume that oxidative addition should be easier on a more electron deficient aryl iodide, it is also known that electron withdrawing groups on the aryl ring can slow down the migratory insertion of CO into the palladium–aryl carbon bond.[29] We thus examined an aryl iodide bearing a chlorine atom, which would be mildly electron withdrawing. In the event, ketone **27** was isolated in an 89% yield. Ketone **27** is particularly valuable, as the chlorine substituent is suitable for further functionalization by numerous methods, including additional transition metal catalyzed cross-couplings.

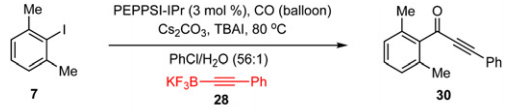
Table 1
Scope of suzuki carbonylative cross-coupling reactions



Reaction conditions: 3 mol % PEPPSI-IPr, 1.0 mmol aryl iodide, 2.0 mmol boronic acid, and 3.0 mmol Cs_2CO_3 in chlorobenzene (5.0 mL) at 80 °C for 24 h. Isolated yields are an average of two runs. [a]Dioxane was used as the solvent; CO pressure increased to 60 psi; temp. increased to 140°C. [b]K_2CO_3 used as the base.

2.2. Alkynyl nucleophiles

Having demonstrated that aryl boronic acids participated in cross-coupling reactions to give diaryl ketones, we next sought to incorporate alkynyl nucleophiles, as the product alkynyl ketones are valuable synthetic intermediates in the synthesis of benzopyranone containing natural products. However, we quickly discovered that using alkynyl nucleophiles in carbonylative cross-couplings was significantly more difficult than expected. Boronic acids derived from alkynes are notoriously unstable, as they suffer facile protiodeboronation in the presence of a protic solvent.[30] Isopropyl boronic esters of alkynes are known to be moderately stable and are isolable. Potassium alkynyltrifluoroborate salts are also stable alkynyl boron reagents and have been successfully utilized in palladium-catalyzed cross-coupling reactions; however, to our knowledge, they have not been used in *carbonylative* processes. Unfortunately, use of alkynyl potassium trifluoroborate **28** and boronic ester **29** in such cross-couplings with **7** delivered ketones **30** and **31** in only 25% and 49% yields, respectively, under optimized conditions (Eqs. 3 and 4).



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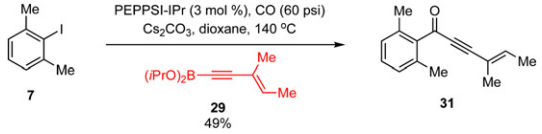
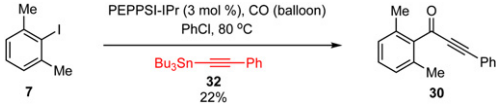


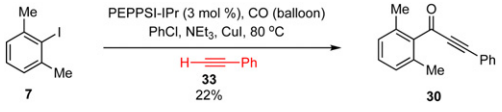
(4)

In light of these results, we examined other alkynyl nucleophiles in the cross-coupling reaction to ascertain whether better yields of alkynyl aryl ketones might be obtained. When iodide **7** was treated with alkynyl stannane **32** under similar conditions, a 22% yield of ketone **30** was obtained; slow addition of the stannane was required to observe any of the desired ketone (Eq. 5). Although transmetalation is frequently assumed to be the rate determining step in Stille cross-coupling reactions, it appears that transmetalation competes favorably with the migratory insertion of CO in this reaction. The toxicity of alkynyl stannanes prompted us to search further for alternative acetylenic nucleophiles.

We next examined a carbonylative Sonogashira cross-coupling, as there are numerous examples in the literature of similar processes on sterically unencumbered substrates.[11d,12a] Iodide **7** and phenylacetylene (**33**) were exposed to a variety of carbonylative Sonogashira cross-coupling conditions, but low yields of ketone **30** were invariably obtained, with the remainder of the mass balance being alkyne **35** (Eq. 6); increasing the CO pressure resulted in an increase in the formation of aryl alkyne **35**. We also examined placing a trimethylsilyl group on the alkyne in an attempt to effect a carbonylative Hiyama coupling, but aryl alkyne **35** was again the major product in all of our efforts (Eq. 7).



(5)



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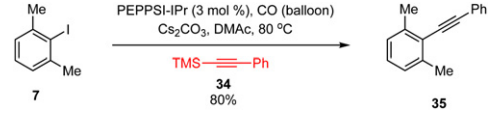
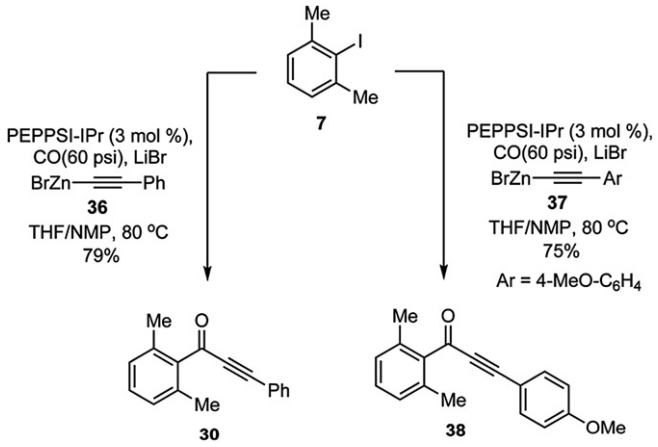


(7)

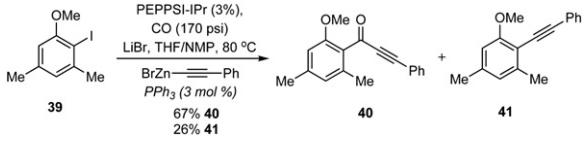
We then turned our attention to examining the possible utility of alkynyl-zinc reagents in carbonylative cross-couplings. Initial experiments involved heating **7** with the alkynyl-zinc reagent **36** and PEPPSI-IPr under a balloon of CO (Scheme 2). These experiments returned mostly the direct coupling product **35** and large amounts of alkyne dimer. We eventually discovered that treatment of **7** with 2 equiv of **36** and 3 equiv of lithium bromide (LiBr) in the presence of PEPPSI-IPr in a mixture (1:1) of THF/*N*-methylpyrrolidinone (NMP) gave **30** in 79% yield (Scheme 2). These conditions are similar to the conditions reported by Organ for a non-carbonylative, Negishi cross-coupling reaction utilizing the PEPPSI-IPr catalyst.[31] Efforts to further optimize the reaction or to reduce the CO pressure were unsuccessful. Substituted aryl acetylenes were also good substrates in this reaction as evidenced by the preparation the ketone **38** in good yield.

When the more electron rich aryl iodide **39** was employed as a substrate, a 35% yield of ketone **40** was obtained, with the remainder of the mass balance being unreacted starting iodide. After significant optimization, we found that varying the additives in the reaction dramatically affected the product distribution, and



Scheme 2.

a variety of phosphine, phosphite, arsine, and substituted pyridine additives were screened. We thus discovered that the addition of 3 mol % of PPh_3 to the reaction mixture and increasing the CO pressure led to a 100% conversion of the starting material and the isolation of the desired ketone **40** in 67% yield (Eq. 8). The addition of a phosphine ligand to the PEPPSI-IPr catalyst system most likely results in the formation of a mono-NHC/mono-phosphine-ligated palladium complex, as this has been observed in similar catalyst complexes.[25c] Furthermore, NHC/phosphine palladium complexes have been shown to be active catalysts in cross-coupling processes.[25c] They have also been shown to be thermally more stable than their mono-NHC ligated counterparts.[24b] It is noteworthy that the product distribution of **40** and **41** relied heavily on the nature of the phosphine ligand. For example, we observed that use of bulky, electron-rich phosphines, such as PCy_3 gave alkyne **41** as the major product (13:1).

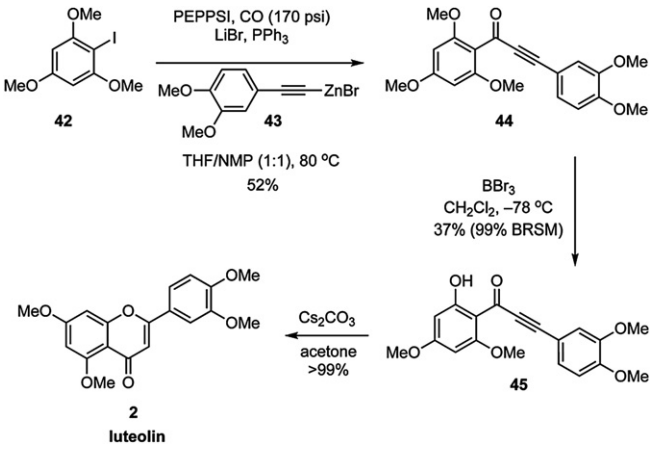


(8)

2.3. The total synthesis of luteolin

A key test of any new synthetic method lies in its practical application to the preparation of compounds of interest. In order to establish the utility of our procedure for effecting the carbonylative Negishi cross-coupling of sterically hindered aryl iodides, we set to apply this technology to the synthesis of luteolin (**2**), a flavanoid natural product, that is, found in teas, onions and apples.[3] Luteolin (**2**) also has been shown to exhibit anti-cancer, anti-bacterial, anti-inflammatory, and anti-oxidant properties. It has previously been synthesized by several groups; however, these routes relied on multi-step sequences involving harsh acidic conditions to promote the formation of the pyranone ring.[32] A more concise synthesis of these flavanoid natural products would be desirable.

Our synthesis of **2** commenced by subjecting aryl iodide **42** to our optimized Negishi cross-coupling conditions to furnish the ketone **44** in 52% yield (Scheme 3). Selective removal of one methyl group *ortho* to the ketone moiety was accomplished by treating **44** with 1 equiv of boron tribromide (BBr_3) in CH_2Cl_2 at



Scheme 3.

−78 °C for 1 min to afford phenol **45** in 37% yield; 62% of unreacted **44** that could be easily recycled was also obtained. When the reaction was conducted with excess BBr_3 or at elevated temperatures (0 °C), the yield of **45** decreased to <10%. We explored a number of other Lewis acids and conditions to induce this transformation, but all of these experiments were either lower yielding or provided complex mixtures of unidentifiable products. Finally, treatment of **45** with Cs_2CO_3 in acetone delivered a quantitative yield of luteolin (**2**), which had spectral characteristics (^1H and ^{13}C NMR, IR, mass spectrum) consistent in all respects with those reported.[33] This concise, three-step synthesis of luteolin (**2**) is the shortest reported to date.

3. Conclusion

In summary, novel variants of carbonylative Suzuki and Negishi cross-coupling reactions were developed that allow efficient coupling of *ortho*-disubstituted aryl iodides with substituted aryl boronic acids and zinc acetylides, respectively, using the commercially available PEPPSI-IPr catalyst. The cross-coupling reactions were shown to be rather general for a variety of aryl iodides. The utility of this transformation has been further exemplified with a concise synthesis of the naturally occurring flavanoid luteolin (**2**). Further development and applications of this reaction are underway, and the results will be reported in due course.

4. Experimental

4.1. General

Unless otherwise noted, solvents, and reagents were used without further purification. Tetrahydrofuran was dried by filtration through two columns of activated, neutral alumina. Dioxane was distilled from sodium metal and benzophenone prior to use. *N*-Methylpyrrolidinone was dried over 4 Å MS before use. Dimethylformamide was dried by filtration through two columns of activated molecular sieves. $ZnBr_2$ was sublimed under reduced pressure before use and stored in a desiccator. Cs_2CO_3 powder was purchased from Alfa Aesar and stored in a desiccator. $CO_{(g)}$ (99.9%) was obtained from Praxair. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Thin layer chromatography was run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60 F-254 indicator (Merck) unless otherwise noted. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 230–400 mesh silica gel (E. Merck reagent silica gel 60) unless otherwise noted.

Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on either a 600 MHz, 500 MHz, 400 MHz, or 300 MHz spectrometer as solutions in the indicated solvent. Chemical shifts are reported in parts per million (ppm) and are referenced to the indicated deuterated solvent. Coupling constants (J) are reported in hertz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; app, apparent. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained using the above-mentioned instruments operating at 150 MHz, 125 MHz, 100 MHz, or 75 MHz using the solvent indicated as the internal reference. Reaction temperatures refer to the temperature of the cooling bath.

5. Experimental procedures

5.1. Carbonylative Suzuki cross-coupling of *ortho*-disubstituted aryl iodides (method A)

The aryl iodide (1.0 mmol), boronic acid (2.0 mmol), PEPPSI-IPr (0.03 mmol), and Cs_2CO_3 (2.5 mmol) were placed into a 10 mL glass sleeve fitted with a rubber septum. The sleeve was then evacuated and backfilled with $CO_{(g)}$ three times. Dioxane (5.0 mL) was added, and the mixture was sparged with $CO_{(g)}$ for 2 min. The rubber septum was then removed, and the glass sleeve was quickly sealed in a stainless steel pressure reactor. The reactor was evacuated and backfilled with $CO_{(g)}$ (three cycles, 60 psi). The reactor was heated at 140 °C (oil bath) with stirring for 24 h at 60 psi of $CO_{(g)}$. The reaction mixture was filtered through a pad of Celite, washing with EtOAc. The filtrate was washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with the indicated solvent to afford the product benzophenone.

5.2. Carbonylative Suzuki cross-coupling of *ortho*-disubstituted aryl iodides (method B)

The aryl iodide (1.0 mmol), boronic acid (2.0 mmol), PEPPSI-IPr (0.03 mmol), and Cs_2CO_3 (3.0 mmol) were placed into a 25 mL round-bottomed flask that was fitted with a reflux condenser. Chlorobenzene (5 mL) was added, and the flask was evacuated and backfilled with $CO_{(g)}$ (three cycles). The mixture was heated to 80 °C (oil bath) with stirring for 24 h under a balloon of $CO_{(g)}$. The reaction mixture was filtered through a pad of Celite, washing with EtOAc. The filtrate was washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with the indicated solvent to afford the desired benzophenone.

5.3. Carbonylative Negishi coupling of *ortho*-disubstituted aryl iodides with alkynyl-zinc reagents (method C)

n-BuLi (0.63 mmol, 2.12 M solution in hexanes) was added dropwise to a solution of the alkyne (0.60 mmol) in THF (1.0 mL) at −78 °C. The resultant solution was stirred for 30 min, whereupon a solution of $ZnBr_2$ (0.63 mmol) in THF (0.65 mL) was added. The cooling bath was removed, and the solution was warmed to ambient temperature. The aryl iodide (0.30 mmol), PEPPSI-IPr (0.009 mmol), and LiBr (0.90 mmol) were placed into a dry, 10 mL glass sleeve. The

sleeve was placed into the metal jacket of the stainless steel pressure reactor, fitted with a rubber septum, and placed under nitrogen. NMP (2 mL) was added, and the mixture was cooled to −78 °C, whereupon the previously prepared zinc acetylide solution (2 mL, 0.3 M) was added dropwise. The jacket was removed from the bath, and the pressure reactor was sealed. The reactor was evacuated and backfilled with $CO_{(g)}$ (three cycles, 60 psi). The reactor was heated to 80 °C (oil bath) with stirring for 24 h at 60 psi of $CO_{(g)}$. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and brine (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with the indicated solvent to deliver the desired ketone.

*5.3.1. 2,6-Dimethylbenzophenone (**10**).* Method A: 0.27 g, 82%. Method B: 0.32 g, 95% of **10** as an off-white solid (98:2 hexanes/EtOAc); mp=64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J=7.2 Hz, 2H), 7.57 (m, 1H), 7.43 (t, J=7.9 Hz, 2H), 7.22 (t, J=7.0 Hz, 1H), 7.06 (d, J=7.0 Hz, 2H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 139.6, 136.9, 134.1, 133.7, 129.4, 128.8, 128.7, 127.5, 19.4; IR (neat) 3061, 1673 cm^{-1}; mass spectrum (CI) m/z 211.1123 [$C_{15}H_{15}O$ (M+1) requires 211.1123], 421, 212, 211.

*5.3.2. 2,2′,6-Trimethylbenzophenone (**19**).* Method A: 0.21 g, 93%. Method B: 0.22 g, 98% of **19** as a white solid (98:2 hexanes/EtOAc): mp=68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (comp, 2H), 7.31 (d, J=7.2 Hz, 1H), 7.24–7.20 (m, 1H), 7.16 (t, J=7.5 Hz, 1H), 7.06 (d, J=7.5 Hz, 2H), 2.73 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 141.1, 140.1, 136.4, 134.1, 132.3, 132.2, 131.9, 128.6, 127.6, 125.9, 21.8, 19.3; IR (neat) 2922, 1665, 1454 cm^{-1}; mass spectrum (CI) m/z 225.1280 [$C_{16}H_{17}O$ (M+1) requires 225.1279], 253, 226, 225.

*5.3.3. 2,6-Dimethyl-4′-methoxybenzopheone (**20**).* Method A: 0.22 g, 92%. Method B: 0.17 g, 72% of **20** as a yellow oil that solidified on standing (9:1 hexanes/EtOAc): mp=37–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (comp, 2H), 7.19 (t, J=7.7 Hz, 1H), 7.03 (d, J=7.7 Hz, 2H), 6.89 (d, J=8.9 Hz, 2H), 3.82 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 163.9, 139.8, 133.9, 131.6, 130.0, 128.4, 127.4, 113.9, 55.3, 19.2; IR (neat) 2954, 1665 cm^{-1}; mass spectrum (CI) m/z 241.1228 [$C_{16}H_{17}O_2$ (M+1) requires 241.1229], 481, 242, 241.

*5.3.4. 4′-Cyano-2,6-dimethylbenzophenone (**21**).* Method A: 0.10 g, 42%. Method B: 0.03 g, 12% of **21** as an off-white solid (9:1 hexanes/EtOAc): mp=90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=8.4 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H), 7.25 (t, J=7.5 Hz, 1H), 7.07 (d, J=7.5 Hz, 2H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 139.7, 138.2, 134.1 (2C), 132.7 (2C), 129.5 (2C), 129.3, 127.8 (2C), 117.8, 116.8, 19.3 (2C); IR (neat) 2922, 2231, 1676 cm^{-1}; mass spectrum (CI) m/z 236.1079 [$C_{16}H_{13}NO$ (M+1) requires 236.1075], 268, 264, 236.

*5.3.5. 2,6-Dimethyl-2′,6′-dimethoxybenzophenone (**22**).* Method A: 0.17 g, 62%. Method B: 0.26 g, 95% of **22** as an off-white solid (9:1→0:1 hexanes/EtOAc): mp=139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J=8.4 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 6.94 (d, J=7.6 Hz, 2H), 6.52 (d, J=8.4 Hz, 2H), 3.63 (s, 6H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 158.5, 142.2, 135.1, 132.0, 128.4, 127.6, 120.4, 104.4, 55.8, 19.5; IR (neat) 2951, 1666 cm^{-1}; mass spectrum (CI) m/z 271.1337 [$C_{17}H_{19}O_3$ (M+1) requires 271.1334], 272, 271, 239, 165.

*5.3.6. 3-(2′,6′-Dimethylbenzoyl)thiophene (**23**).* Method B: 0.14 g, 64% of **23** as a pale orange/pink solid (9:1 hexanes/EtOAc): mp=65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J=2.9, 1.2 Hz, 1H), 7.53 (dd, J=5.1, 1.2 Hz, 1H), 7.32 (dd, J=5.1, 2.9 Hz, 1H), 7.20 (t, J=7.6 Hz, 1H), 7.04 (d, J=7.6 Hz, 2H), 2.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 143.0, 140.4, 135.1, 133.9, 128.7, 127.5, 127.0, 126.9, 19.3; IR (neat) 2921, 1659 cm^{-1}; mass spectrum (CI) m/z 217.0692 [$C_{13}H_{12}OS$ (M+1) requires 217.0687], 433, 327, 245, 218, 217.

*5.3.7. 2,4,4′,6-Tetramethoxybenzophenone (**24**).* Method B: 0.16 g, 52% of **24** as a white solid (9:1→4:1 hexanes/EtOAc): mp=144 °C (EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (comp, 2H), 6.88–6.84 (comp, 2H), 6.14 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 163.4, 162.1, 158.4, 131.7, 131.3, 113.4, 111.1, 90.6, 55.7, 55.37, 55.33; IR (neat) 2940, 1661 cm^{-1}; mass spectrum (ESI) m/z 303.12270 [$C_{17}H_{19}O_5$ (M+1) requires 303.1231], 331, 304, 303.

*5.3.8. 2,2′,4,6,6′-Pentamethoxybenzophenone (**25**).* Method B: 0.11 g, 33% of **25** as a tan solid (9:1→0:1 hexanes/EtOAc): mp=142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, J=8.3 Hz, 1H), 6.49 (d, J=8.3 Hz, 2H), 6.04 (s, 2H), 3.79 (s, 3H), 3.67 (s, 6H), 3.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 162.6, 160.3, 157.91, 130.1, 122.9, 115.0, 104.4, 91.0, 56.25, 56.28, 55.3; IR (neat) 2939, 1673 cm^{-1}; mass spectrum (ESI) m/z 333.13327 [$C_{18}H_{21}O_6$ (M+1) requires 333.1338], 361, 334, 333.

*5.3.9. 2-Hydroxy-4,6-dimethylbenzophenone (**26**).* Method B (K_2CO_3 was used as the base): 0.12 g, 51% of **26** as an off-white solid (9:1 hexanes/EtOAc): mp=138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.66–7.63 (comp, 2H), 7.56–7.52 (m, 1H), 7.45–7.41 (comp, 2H), 6.69 (s, 1H), 6.55 (s, 1H), 2.30 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 159.4, 144.6, 140.4, 138.8, 132.6, 128.8, 128.6, 124.0, 120.2, 115.4, 22.6, 21.6; IR (neat) 3352 (br), 2922, 1651 cm^{-1}; mass spectrum (ESI) m/z 249.08860 [$C_{15}H_{14}O_2Na$ (M+Na) requires 249.0891], 255, 228, 227.

*5.3.10. 2-Chloro-6-methylbenzophenone (**27**).* Method B: 0.21 g, 89% of **27** as a colorless oil that solidified upon standing (9:1 hexanes/EtOAc): mp=54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.79 (comp, 2H), 7.59–7.54 (m, 1H), 7.46–7.41 (comp, 2H), 7.26–7.23 (comp, 2H), 7.15–7.13 (m, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 138.4, 136.8, 136.1, 133.9, 130.2, 129.8, 129.4, 128.8, 128.6, 126.7, 19.2; IR (neat) 3061, 1674 cm^{-1}; mass spectrum (CI) m/z 231.0579 [$C_{14}H_{12}ClO$ (M+1) requires 231.0577], 233, 232, 231.

*5.3.11. (E)-1-(2′,6′-Dimethylphenyl)-4-methylhex-4-en-2-yn-1-one (**31**).* Method A: 0.03 g, 49% of **31** as a yellow oil (9:1 hexanes/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J=7.7 Hz, 1H), 7.01 (d, J=7.7 Hz, 2H), 6.27 (qq, J=7.2, 1.7 Hz, 1H), 2.35 (s, 6H), 1.82 (comp, 3H), 1.75 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 141.1, 140.5, 134.6, 129.3, 128.1, 117.1, 97.6, 86.8, 19.6, 16.1, 14.7; IR (neat) 2924, 2180, 1646 cm^{-1}; mass spectrum (CI) m/z 213.1276 [$C_{15}H_{17}O$ (M+1) requires 213.1279], 213, 213.

*5.3.12. 1-(2′,6′-Dimethylphenyl)-3-phenylprop-2-yn-1-one (**30**).* Method C: 0.06 g, 79% of **30** as a light yellow oil (9:1 hexanes/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (comp, 2H), 7.47–7.42 (m, 1H), 7.39–7.34 (comp, 2H), 7.21 (t, J=7.7 Hz, 1H), 7.06 (d, J=7.7 Hz, 2H), 2.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 140.1, 134.8, 133.2, 130.9, 129.6, 128.6, 128.2, 119.9, 93.6, 89.3, 19.6; IR (neat) 2959, 2191, 1645 cm^{-1}; mass spectrum (CI) m/z 235.1126 [$C_{17}H_{14}O$ (M+1) requires 235.1123], 470, 469, 236, 235, 133.

*5.3.13. 1-(2′,6′-Dimethylphenyl)-3-(4″-methoxyphenyl)prop-2-yn-1-one (**38**).* Method C: 0.06 g, 75% of **38** as a yellow oil (9:1 hexanes/EtOAc): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.50 (comp, 2H), 7.20 (t, J=7.7 Hz, 1H), 7.05 (d, J=7.7 Hz, 2H), 6.89–6.85 (comp, 2H), 3.82 (s, 3H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 161.8, 140.4,

135.3, 134.7, 129.4, 128.1, 114.3, 111.7, 95.0, 89.4, 55.4, 19.6; IR (neat) 2961, 2183, 1643 cm^{-1}; mass spectrum (CI) *m/z* 265.1229 [$C_{18}H_{17}O_2$ (M+1) requires 265.1229], 529, 266, 265.

*5.3.14. 1-(2′-Methoxy-4′,6′-dimethylphenyl)-3-phenylprop-2-yn-1-one (**40**).* Method C (3 mol % PPh_3 was added to the reaction mixture and the pressure was increased to 170 psi of CO): 0.05 g, 67% of **40** as a yellow oil (9:1 hexanes/EtOAc): ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.53 (comp, 2H), 7.43–7.39 (m, 1H), 7.36–7.32 (comp, 2H), 6.64 (s, 1H), 6.62 (s, 1H), 3.85 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 158.0, 141.9, 137.5, 133.0, 130.4, 128.5, 126.7, 124.0, 120.6, 110.0, 90.9, 90.1, 55.8, 21.7, 19.5; IR (neat) 2925, 2193, 1644 cm^{-1}; mass spectrum (ESI) *m/z* 265.12231 [$C_{18}H_{17}O_2$ (M+1) requires 265.1228], 288, 265, 163.

*5.3.15. 2-Iodo-1-methoxy-3,5-dimethylbenzene (**39**).* Sodium hydride (0.32 g, 8.1 mmol) was added in one portion to a solution of 2-iodo-3,5-dimethylphenol (1.0 g, 4.0 mmol) and methyl iodide (1.3 mL, 20.2 mmol) in DMF (20 mL) at 0 °C. After gas evolution had subsided, the cooling bath was removed, and the mixture was stirred at ambient temperature for 30 min. The mixture was recooled to 0 °C, whereupon saturated NH_4Cl (10 mL) was slowly added. The mixture was diluted with EtOAc (50 mL), and the layers were separated. The organic layer was washed with H_2O (4×50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash column chromatography, eluting with hexanes/ethyl acetate (9:1), to afford 0.95 g (90%) of **39** as a white solid: mp=43–44 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.46 (s, 1H), 3.85 (s, 3H), 2.43 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 142.7, 138.7, 123.2, 109.0, 88.8, 56.2, 28.4, 21.1; IR (neat) 2936, 1572, 1457 cm^{-1}; mass spectrum (ESI) *m/z* 262.99273 [$C_9H_{12}IO$ (M+1) requires 262.9927], 263, 262.

*5.3.16. 3-(3′,4′-Dimethoxyphenyl)-1-(2″,4″,6″-trimethoxyphenyl) prop-2-yn-1-one (**44**).* Method C: (3 mol % PPh_3 was added to the reaction mixture and the pressure was increased to 170 psi of CO): 0.06 g, 52% of **44** as a yellow oil (9:1 hexanes/EtOAc): ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J*=8.2, 1.7 Hz, 1H), 7.03 (d, *J*=1.7 Hz, 1H), 6.80 (d, *J*=8.2 Hz, 1H), 6.11 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 160.1, 151.1, 148.6, 127.1, 115.4, 112.9, 112.5, 110.9, 90.7, 56.1, 55.9, 56.1, 55.9; IR (neat) 2960, 2190, 1643 cm^{-1}; mass spectrum (CI) *m/z* 357.1337 [$C_{20}H_{21}O_6$ (M+1) requires 357.1338].

*5.3.17. 3-(3′,4′-Dimethoxyphenyl)-1-(2″-hydroxy-4″,6″-dimethoxyphenyl)prop-2-yn-1-one (**45**).* BBr_3 (0.004 mL, 0.043 mmol) was added dropwise to a solution of **44** (0.015 g, 0.042 mmol) in CH_2Cl_2 (1 mL) at −78 °C. Stirring was continued for 1 min, whereupon MeOH was added. The cooling bath was removed and the solution was warmed to room temperature. The mixture was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were washed with H_2O (3 mL), brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with CH_2Cl_2, to afford 0.0042 g (37%) of **45** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 13.65 (s, 1H), 7.25–7.23 (m, 1H), 7.11 (d, *J*=1.8 Hz, 1H), 6.86 (d, *J*=8.2 Hz, 1H), 6.05 (d, *J*=2.2 Hz, 1H), 5.92 (d, *J*=2.2 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 168.2, 167.2, 162.5, 151.4, 148.8, 127.2, 115.4, 113.0, 111.0, 107.0, 96.1, 93.4, 91.0, 89.3, 56.0, 55.70, 55.66; IR (neat) 3350, 1645 cm^{-1}; mass spectrum (CI) *m/z* 343.1183 [$C_{19}H_{18}O_6$ (M+1) requires 343.1182].

*5.3.18. Luteolin (**2**).* Cs_2CO_3 (0.043 g, 0.131 mmol) was added in one portion to a solution of **45** (0.015 g, 0.044 mmol) in acetone (0.44 mL) at ambient temperature. Stirring was continued for 10 min, whereupon the mixture was diluted with H_2O (1 mL). Saturated NH_4Cl (1 mL) was added, and the resultant mixture was extracted with EtOAc (3×1 mL). The combined organic layers were washed with brine (4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 0.015 g, >99% of **2** as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.31 (comp, 2H), 6.96 (d, *J*=7.0 Hz, 1H), 6.63 (s, 1H), 6.58 (d, *J*=1.8 Hz, 1H), 6.40 (d, *J*=1.8 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.4, 164.0, 160.9, 160.3, 159.8, 151.7, 149.0, 123.9, 119.2, 111.1, 108.6, 108.0, 106.0, 96.0, 92.8, 56.2, 56.1, 56.0, 55.6; mass spectrum (CI) *m/z* 343.1182 [$C_{19}H_{19}O_6$ (M+1) requires 343.1182].

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