Gold-Catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura Coupling Reaction

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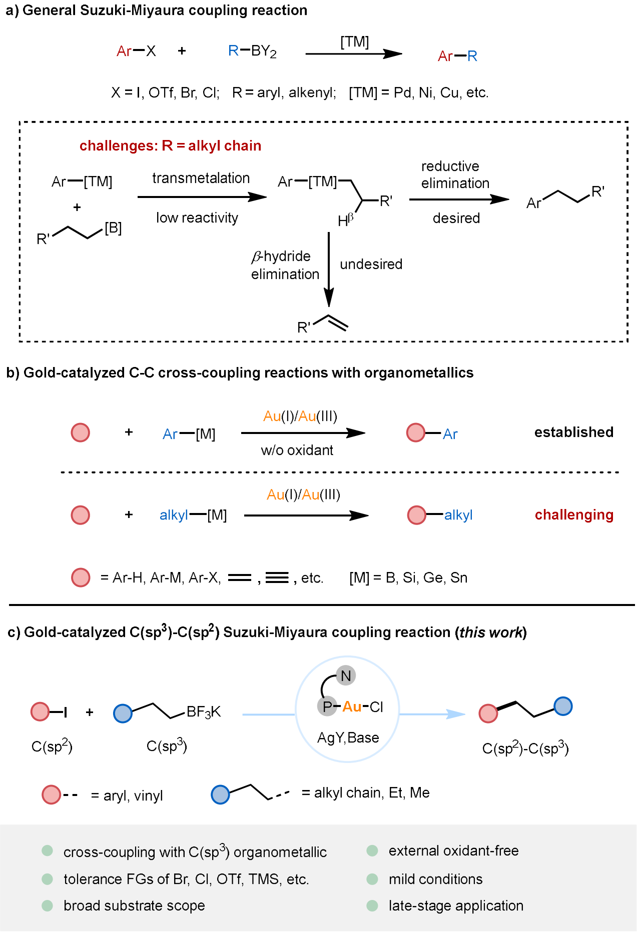
Abstract: A gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis was developed. The cross-coupling of alkyl organometallics was first realized in the redox catalytic cycle in gold chemistry, without the use of external oxidants. This gold-catalyzed C(sp^3)-C(sp^2) coupling reaction allows a variety of chain alkyl and useful methyl trifluoroborates to react with aryl and vinyl iodides under very mild conditions, which provides a complementary reactivity pattern for the challenging coupling with alkyl organometallics. The strong synthesis ability of this gold-catalyzed Suzuki-Miyaura coupling reaction is also demonstrated by its good functional-group compatibility and late-stage application of complicated biomolecules.

Introduction

Transition metal-catalyzed cross-coupling reactions have revolutionized the construction of C-C bonds, as demonstrated in several name reactions.[1] Among these cross-coupling processes, the Suzuki-Miyaura reaction is one of the most utilized methods for carbon-carbon bond formation owing to its extensive reaction scope, broad functional group tolerance, mild reaction conditions, as well as the stability and availability of organoboron reagents (Scheme 1a).[2] Despite the Suzuki reaction being commonly used for constructing C(sp^2)-C(sp^2) bonds, extending this process to form C(sp^3)-C(sp^2) bonds using alkyl-boron nucleophiles still presents a significant challenge.[3] The utilization of C(sp^3) coupling partners in transition metal-catalyzed reactions is hampered by slow metal transmetalation and the susceptibility of alkyl ligands to undergo β-hydride elimination. Furthermore, the palladium (or nickel or copper) catalyst's strong catalytic reactivity limits the tolerance of many functional groups in these cross-coupling products.



Scheme 1. Suzuki-Miyaura reaction: general overview and present work.

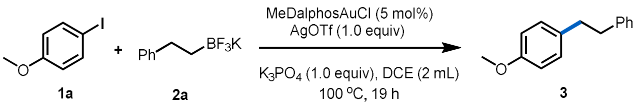
In the past two decades, homogeneous gold catalysis has emerged as an attractive research field for its high catalytic efficiency, favorable functional-group compatibility, and good biocompatibility.[4] Gold catalysts have been widely used for π-activation of unsaturated carbon-carbon bonds, particularly alkynes. Due to the higher redox potential of gold Au^{III}/Au^{I} (1.41) than that of Pd^{II}/Pd^{0} (0.99), achieving the cross-coupling reactions on gold is a nontrivial task. Recent studies have utilized external oxidants,[5a,5g] EBX reagents,[5b,5m] strain release,[5d] photochemistry,[5b,5c,5h] ligand design[5d,6] and electro photochemistry[7] to promote the otherwise sluggish oxidative addition to gold(I) complexes. Over the past decade, gold-catalyzed oxidative C-C cross-coupling reactions with aryl organometallics, such as B, Si, Ge, and Sn, have been developed as an attractive strategy to access various arylated products (Scheme 1b).[8] Under oxidant-free conditions, visible-light-assisted gold catalysis has also become an efficient method for promoting selective coupling reactions with aryl organometallics.[9] However, the inherent thermodynamic/kinetic instability and uncontrolled reactivity of many gold(III) complexes, like the β-hydride elimination, have posed additional challenges for the rational experimental design of gold-catalyzed cross-coupling reactions with alkyl organometallics (Scheme 1b).[10] The Suzuki-Miyaura reaction, which is well-known in the domain of traditional transition-metal catalysis (such as Pd, Ni, and Cu), has been developed by gold-catalysis from aryl diazonium salts or hindered aryl iodides and aryl organoboron reagents.[11] However, the typical gold-catalyzed C(sp^3)-C(sp^2) cross-coupling reaction of aryl halides and alkyl organoboron reagents, which is supposed to operate via Au(I)/Au(III) redox catalysis, has not been realized yet.

Recently, Patil and our group reported the gold-catalyzed Heck reaction with aliphatic alkenes and styrenes.[6i,12e] Following our continued interest in gold chemistry,[12] herein, we describe the first gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis, without the use of external oxidants. Considering the limitations of transition-metal catalyzed coupling reactions of alkyl organometallic reagents, such as slow metal transmetalation and β-hydride elimination, this gold-catalyzed Suzuki-Miyaura coupling reaction provides a complementary reactivity pattern for coupling with C(sp^3) coupling partners. In this gold-catalyzed coupling process, a variety of chain alkyl and useful methyl trifluoroborates were used as effective, stable, and available coupling partners, which can smoothly react with aryl and vinyl iodides under very mild conditions to build a C(sp^3)-C(sp^2) bond. The strong synthesis ability of this gold-catalyzed Suzuki-Miyaura coupling reaction is also demonstrated by its good functional group compatibility (such as Br, Cl, OTf, TMS, etc.) and its late-stage application of complicated biomolecules. Given the extensive reactivity profile of cross-coupling with alkyl organometallics, this work will open a new window in the field of gold chemistry.

Results and Discussion

We initiated the development of this gold-catalyzed Suzuki-Miyaura coupling reaction by using 4-iodoanisole **1a** and potassium phenethyltrifluoroborate **2a** as coupling partners in the presence of MeDalPhosAuCl (5 mol%), AgOTf (1.0 equiv), and K_3PO_4 (1.0 equiv) in DCE (0.1 M) at 100 °C (Table 1). The desired product **3** was obtained with a 56% yield (Entry 1). The screening of several bases revealed that Cs_2CO_3 is more suitable for this reaction (Entry 2 and supplementary Table S1 for details). Decreasing the equivalence of Cs_2CO_3 had a positive effect on the yield of the reaction (Entry 3). Decreasing the temperature from 100 °C to 60 °C just slightly reduces the yield, but no product is obtained at room temperature (25 °C) (Entries 1, 4, and 5). When 7.5 mol% of MeDalPhosAuCl was used, a best yield of 86% was obtained (Entry 6, 83% for isolated yield). In addition, the reaction time was reduced to 6 hours, resulting in a slightly lower yield of 72% (Entries 6 and 7). Control experiments indicated that gold catalyst and silver salts are necessary for this coupling reaction (see Entries 8-9 and Supporting Information Tables S2-S4 for details).

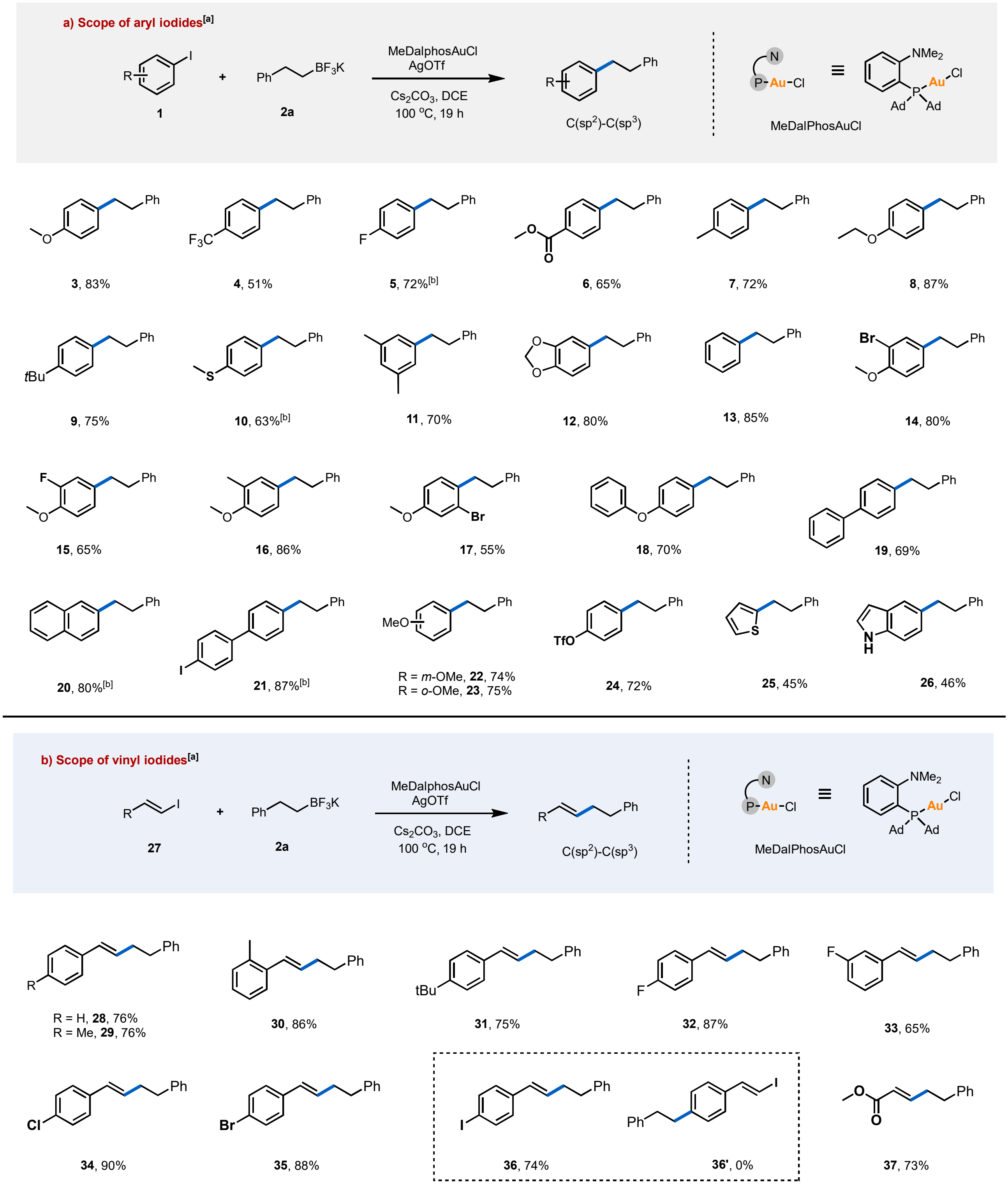
Table 1. Optimization of reaction conditions.[a]



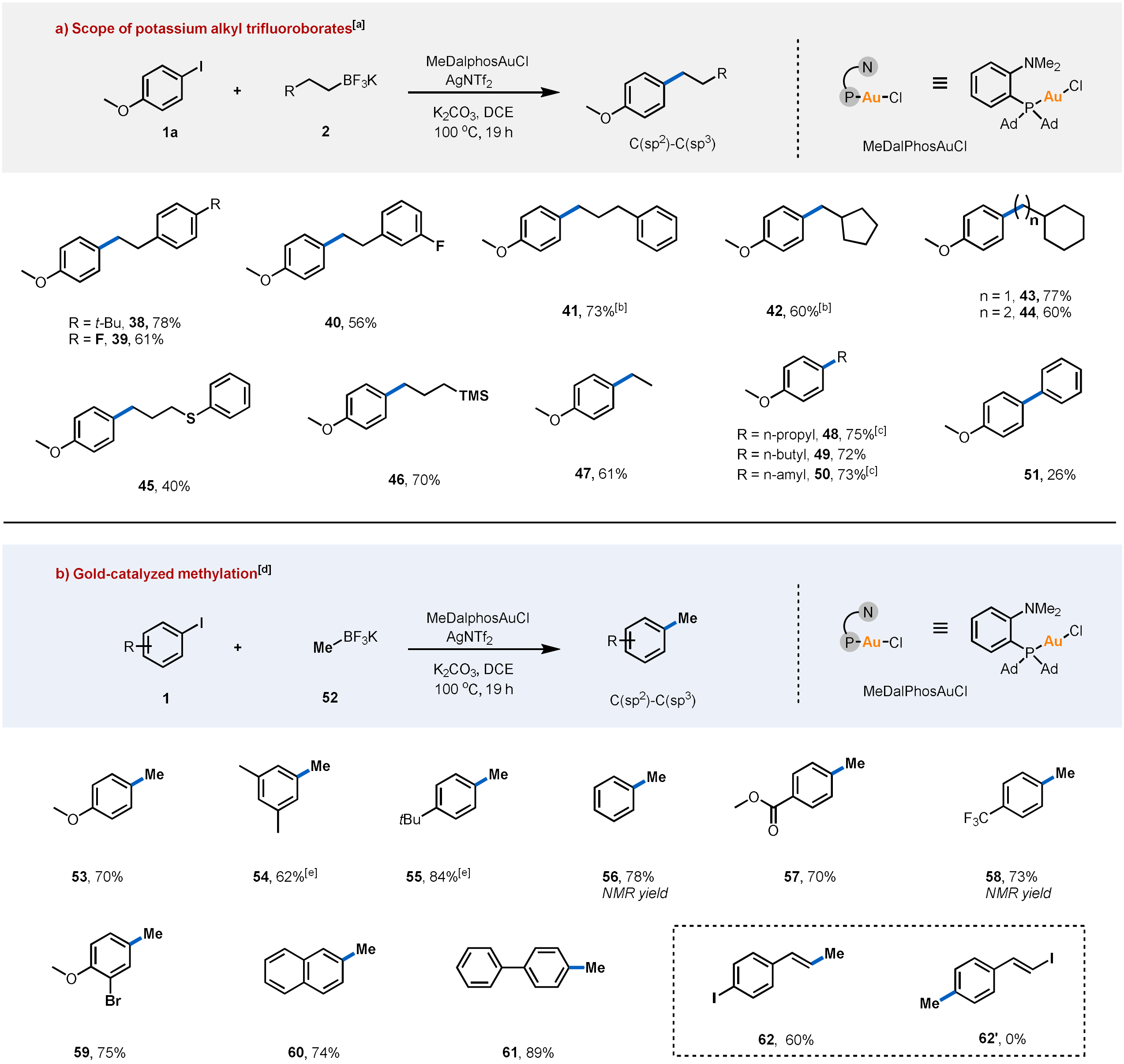
Entry	Deviation	Yield 3 [%]
1	None	56
2	Cs_2CO_3 (1.0 equiv)	66
3	Cs_2CO_3 (0.5 equiv)	78
4	60 °C	50
5	25 °C	ND
6	Cs_2CO_3 (0.5 equiv)/ MeDalphosAuCl (7.5 mol%)	86 (83)
7[b]	Cs_2CO_3 (0.5 equiv)/ MeDalphosAuCl (7.5 mol%)	72
8	No MeDalphosAuCl	ND
9	No AgOTf	ND

[a] Reaction conditions unless noted: **1a** (0.3 mmol), **2a** (0.2 mmol), MeDalphosAuCl (5 mol%), AgOTf (1.0 equiv), K_3PO_4 (1.0 equiv), DCE (0.1 M), 100 °C, 19 h. Product yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parentheses. [b] Reaction time for 6 h. ND=not detected.

We next investigated the scope of aryl iodide **1** with potassium phenethyltrifluoroborate **2a** under the optimal reaction conditions as described in Entry 6 of Table 1. As shown in Scheme 2a, the reactions proceeded smoothly when aryl iodides **1** carried electron-donating groups (-OMe, -Me, -OEt, -*t*-Bu, -SMe, -3,5-dimethyl) generating desired products **3** and **7-11** in good yields (63-87%). Next, aryl iodides bearing electron-withdrawing groups (-CF_3, -F, -CO_2Me) at the *para*-position also delivered the cross-coupling products **4-6** in slightly lower yields. 5-Iodo-1,3-benzodioxole and iodobenzene also reacted with **2a** to afford the desired products **12** and **13** in 80% and 85% yield, respectively. Next, 4-iodoanisole bearing Br, F, and methyl groups provided corresponding products **14-17** in moderate to good yields (55-86%). Moreover, phenoxyphenyl, biphenyl, and naphthyl iodides also



Scheme 2. Scope of aryl/vinyl iodides. [a] Reaction conditions unless noted: **1** or **27** (0.3 mmol), **2a** (0.2 mmol), MeDalphosAuCl (7.5 mol%), AgOTf (1.0 equiv), Cs_2CO_3(0.5 equiv), DCE (0.1 M), 100 °C, 19 h, and isolated yields. [b] **1** (0.6 mmol), **2a** (0.2 mmol).



Scheme 3. Scope of potassium alkyl trifluoroborates and gold-catalyzed methylation, functionalization of natural products. [a] Reaction conditions of scope of potassium alkyl trifluoroborates: **1a** (0.3 mmol), **2** (0.2 mmol), MeDalphosAuCl (7.5 mol%), $AgNTf_2$ (1.0 equiv), K_2CO_3(0.5 equiv), DCE (0.1 M), 100 °C, 19 h, and isolated yields; [b] AgOTf (1.0 equiv), Cs_2CO_3 (0.5 equiv); [c] K_3PO_4 (0.5 equiv). [d] Reaction conditions of gold-catalyzed methylation: **1** (0.4 mmol), **52** (0.2 mmol), MeDalphosAuCl (7.5 mol%), $AgNTf_2$ (1.0 equiv), K_2CO_3(0.5 equiv), DCE (0.1 M), 100 °C, 19 h, and isolated yields; [e] **1** (0.6 mmol).

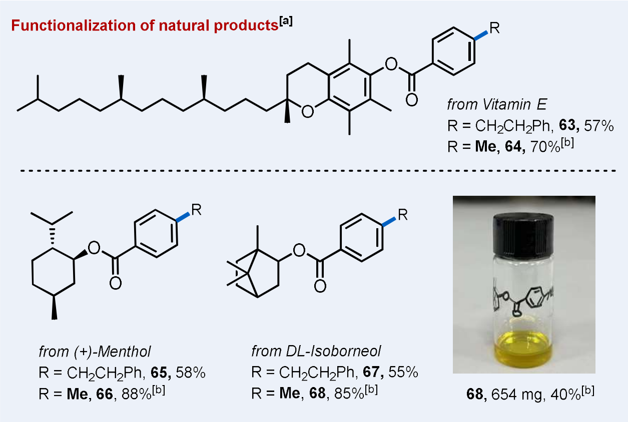
worked smoothly, furnishing target products **18**-**20** in satisfactory yields. Interestingly, 4,4'-diiodobiphenyl afforded a monosubstituted cross-coupling product **21** in 87% yield. The substituent position of aryl iodide displayed a slight effect on the reaction efficiency, as the *para*-, *meta*- and *ortho*-substituted iodoanisole delivered 83%, 74%, and 75% yield (**3**, **22**, and **23**), respectively. Delightedly, the gold catalyst showed excellent chemoselectivity for the $C(sp^2)$-I bond, as other (peso)halogen bonds, such as Br and OTf, remained fully unaffected during the process (see **14**, **15**, **17**, and **24**), which are valuable functional groups for further elaboration. And heteroaromatic scaffolds such as thiophene and indole-based iodo compounds successfully furnished corresponding products (**25**, **26**) and gave a more modest yield.

Additionally, a variety of vinyl iodine substrates **27** have been found to be suitable partners in this $C(sp^3)$-$C(sp^2)$ coupling reaction process, and the results are summarized in Scheme 2b. As can be seen, (*E*)-(2-iodovinyl)benzene could undergo this gold-catalyzed coupling reaction smoothly to furnish a good isolated yield (**28**). When the (*E*)-(2-iodovinyl)benzene bearing -Me, -*t*-Bu, and halogen (-F, -Cl, and -Br) substituents at *para*, *meta*, and *ortho* positions worked well to afford corresponding products **29**-**35** in good to excellent yields (65-90%). Interestingly, when a substrate contains both aryl iodide and vinyl iodide, the reaction preferentially proceeded with vinyl iodide to obtain vinyl-alkyl coupling products **36**, which indicated that the vinyl iodide has faster oxidative addition with MeDalphosAuCl than aryl iodide (**36** and **36'**). As shown in previous studies,[6d,6o] the reserved aryl iodide of **36** provides possibilities for the further diversification ofcross-coupling products. Furthermore, methyl (*E*)-3-iodoacrylate can afford the desired product **37** in 73% yield with good reaction selectivity.

Subsequently, the substrate's scope of potassium alkyl tri-fluoroborates **2** was also examined. As shown in Scheme 3a, different substituted phenethyltrifluoroborates successfully furnished corresponding products (**38**-**40**). Besides the phenethyltrifluoroborates, 3-phenylpropyltrifluoroborates also manifested good reactivity in this reaction, with a yield of 73% (**41**). Moreover, alkyl trifluoroborate salts, such as cyclopentylmethyl, cyclohexylmethyl, and cyclohexylethyl trifluoroborates, also reacted smoothly with **1a** to deliver the corresponding products **42**-**44** in 60-77% yields. Potassium alkyl trifluoroborates **2** bearing some of the useful functional groups, such as phenylthio and trimethylsilane, were also tolerated well (**45** and **46**). Compared with Pd, Cu, and Ni, Au exhibited good reaction selectivity with the C(sp^2)-I bond. The tolerance of substituted functional groups, such as Br, OTf, Cl, F, TMS, etc., provides possibilities for the diversification of further chemical transformation and highlights the orthogonal reactivity of gold redox catalysis. Gratifyingly, simple alkyl chain trifluoroborates, such as ethyl-, propyl-, butyl-, and amyltrifluoroborates, were also coupled in good yields (**47**-**50**). However, the potassium phenyltrifluoroborate resulted in product **51** with a much lower yield. Finally, we also tested secondary and tertiary alkyl potassium alkyl trifluoroborates, but they suffer from low reactivity, which might be due to their lower rate of transmetalation than the unhindered primary alkyl group. See Supporting Information for details.

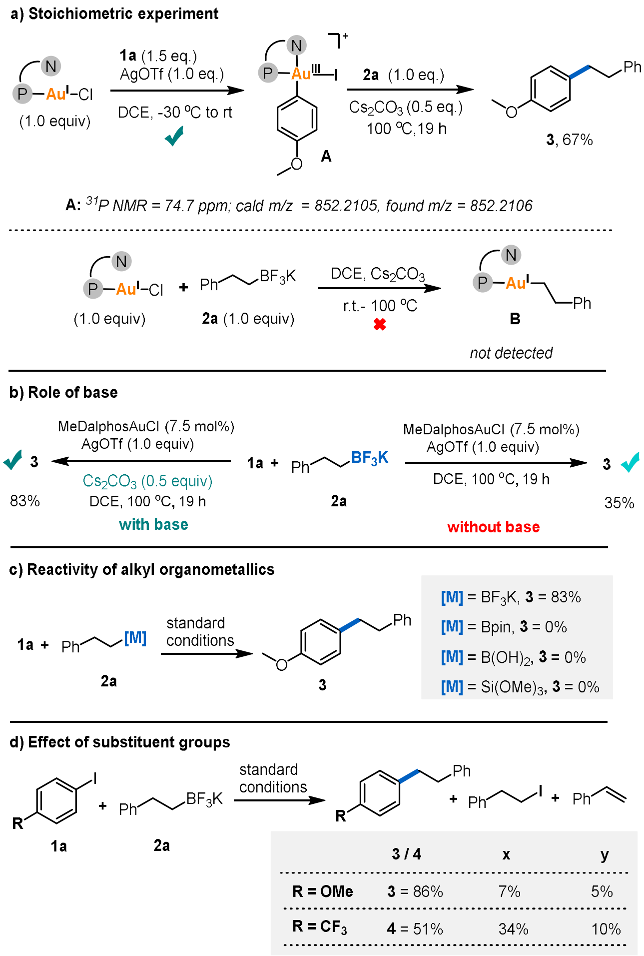
Methyl groups are thought to play a critical role in pharmaceutical molecules since they have been extensively utilized to increase the drug's potency, efficacy, or stability.[13] Therefore, the introduction of a methyl group is a particularly attractive approach for pharmacists and chemists. Compared with traditional transition metals, gold is generally considered to be green and biocompatible, which could be applied in food additives and pharmaceuticals. Inspired by the above results, we next considered the possibility of extending the gold-catalyzed Suzuki reaction to a useful methylation protocol from easily accessible methyltrifluoroborates **52**, the results of which are summarized in Scheme 3b. The reaction of methyltrifluoroborates **52** and various aryl iodides **1** bearing electron-rich groups (Me, OMe, *t*-Bu, Ph, naphthyl) or electron-withdrawing groups (CF_3, CO_2Me) proceeded smoothly to afford the corresponding products (**53**-**59**) in moderate to excellent yields. 2-Iodonaphthalene and 4-iodobiphenyl afforded the corresponding methylation products in good to excellent yields (**60** and **61**). Similarly, (*E*)-1-iodo-4-(2-iodovinyl) benzene was also tolerated well to deliver the product (*E*)-1-iodo-4-(prop-1-en-1-yl) benzene **62** in 60% yield, and no (*E*)-1- (2-iodoethyl) -4-methylbenzene product **62'** was found.

To further establish the utility of this reaction, we tested the gold-catalyzed C(sp^3)-C(sp^2) coupling reactions of potassium alkyl trifluoroborates with aryl iodides derived from natural products, such as menthol, isoborneol, and tocopherol (Scheme 4). The phenethylation and methylation products were obtained in good yields (**63**-**68**), which demonstrates the generality of the method. To illustrate the synthetic feasibility, a large-scale of methylated drug analogue **68** was prepared as 654 mg.



Scheme 4. Functionalization of natural products. [a] Reaction conditions: natural product iodide (0.2 mmol), **2a** (0.4 mmol), MeDalphosAuCl (7.5 mol%), AgOTf (1.0 equiv), Cs_2CO_3 (0.5 equiv), DCE (0.1 M), 100 °C, 19 h, and isolated yields; [b] natural product iodide (0.6 mmol), **52** (0.2 mmol), $AgNTf_2$ (1.0 equiv), K_2CO_3 (0.5 equiv).

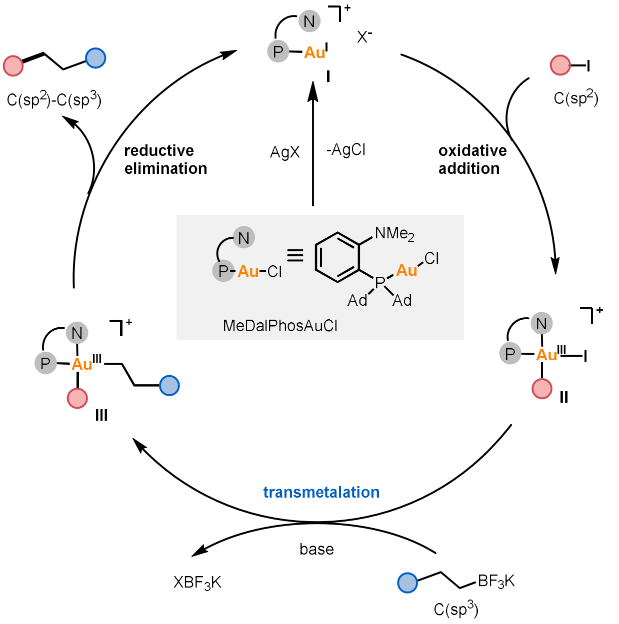
After exploring the reaction scope, we moved our attention toward mechanistic investigations (Scheme 5). Firstly, the Au(III) complex **A** could be formed smoothly from MeDalPhosAuCl and 4-iodoanisole **1a**, which is consistent with Bourissou and Patil's result.[6a,14] Then the *in situ* generated Au(III) complex **A** was treated with potassium alkyl trifluoroborates **2a**, and the desired product **3** was obtained in a 67% yield (Scheme 5a). While the transmetalation reaction between the MeDalphosAuCl and potassium alkyl trifluoroborates **2a** was difficult to occur (Scheme 5a). In fact, it was found that potassium alkyl trifluoroborate **2a** could not dissolve well in DCE solvent, even in base and heating conditions.



Scheme 5. Mechanistic investigations.

Therefore, it was suggested that the putative elementary reaction steps in this gold-catalyzed Suzuki reaction, which include oxidative addition, transmetalation, and reductive elimination, are analogous to those of cross-couplings catalyzed by Pd(0). Notably, it was found that the base was important in the gold-catalyzed Suzuki-Miyaura coupling reaction. The base is usually regarded as regenerating the active catalyst during the Suzuki-Miyaura reaction, as shown in Scheme 5b, adding 0.5 equiv. of Cs_2CO_3 would give 83% of the desired product **3**. While in the absence of a base, 35% of product **3** could be obtained, which might be attributed to the strong nucleophilicity and negatively charged base of potassium alkyl trifluoroborates. Apart from potassium alkyltrifluoroborate, we also tested other alkyl organometallics, such as boronic acid, boronic ester, and trimethoxy silane (Scheme 5c), and it was found that only potassium alkyltrifluoroborate works in this system, which might be due to its greater nucleophilicity in the transmetalation step. Moreover, compared with other alkyl organometallics, potassium trifluoroborate could be prepared easily on large scales, readily isolated for monomeric solids, and have long shelf lives. This result also suggested that the gold-catalyzed Suzuki reaction has good reaction selectivity for alkyl organometallics. Moreover, the control experiments suggested that the substituent group will affect the ratio distribution of the products (Scheme 5d), the electro-donating group (OMe) will favor the desired product **3**, whereas electron-poor aryl iodide gives higher side products **x** and **y**. This may be due to the electron-deficient intermediate gold(III) aryl complex being less susceptible to desired reductive elimination.

Based on our results, mechanistic investigations, and literature reports, a plausible mechanism for this gold-catalyzed Suzuki-Miyaura coupling reaction has been proposed in Scheme 6. First, the cationic Au(I) complex **I**, generated after the halide abstraction by silver salts (AgX), would undergo oxidative addition with iodoarene or iodoalkene to form the Au(III) intermediate **II**. Subsequently, under the action of the base, alkyl trifluoroborates undergo transmetalation with Au(III) intermediate **II** to form Au(III) intermediate **III**, which upon reductive elimination, leads to the formation of the C(sp^3)-C(sp^2) cross-coupling product and propagates the catalytic cycle. The reactive transmetalling species,[15] may be involved with the formation of hydroxyborate complexes from potassium alkyl trifluoroborates, or hydrolysis of Au(III)X to Au(III)OH, is not known yet, and detailed kinetic and mechanistic investigations are undergoing in our lab.



Scheme 6. Plausible mechanism.

Conclusion

In conclusion, we developed a gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction, which is facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis. Taking advantage of the hemilabile character of the MeDalphos (P^N) ligand, the cross-coupling of C(sp^3) organometallics has been realized in the redox catalytic cycle in gold chemistry, without the use of external oxidants. A wide range of structurally diverse chain alkyl trifluoroborates, including the simple and useful methyl trifluoroborate, are good alkyl coupling partners that can react smoothly with aryl and vinyl iodides in this gold-catalyzed C(sp^3)-C(sp^2) coupling reaction. The present methodology provides a complementary reactivity pattern for previously known transition-metal catalyzed coupling reactions of alkyl organometallic reagents, which suffer from the low reactivity of transmetalation and susceptibility to β-hydride elimination. The strong synthesis ability of this gold-catalyzed Suzuki-Miyaura allows for good functional group compatibility (such as Br, Cl, OTf, TMS, etc.) and late-stage application of complicated biomolecules. This work will open a new window in the field of gold chemistry, and promote more cross-coupling reactions with alkyl organometallics.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Gold Catalysis• Alkyl Trifluoroborates • C(sp^3)-C(sp^2) Coupling • Suzuki-Miyaura Reaction • Methylation

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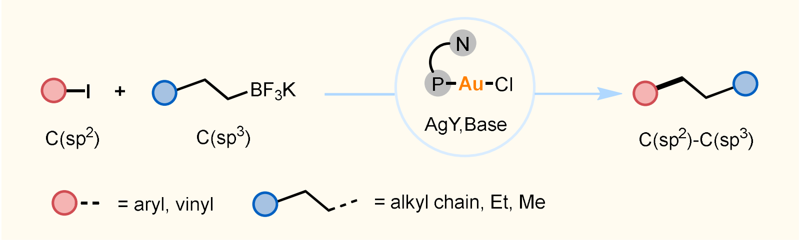

A gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis is reported. It allows a variety of chain alkyl and useful methyl trifluoroborates to react with aryl and vinyl iodides under very mild conditions. The strong synthesis ability of this gold-catalyzed Suzuki-Miyaura coupling reaction is demonstrated by its good functional-group compatibility and late-stage application of complicated biomolecules.