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

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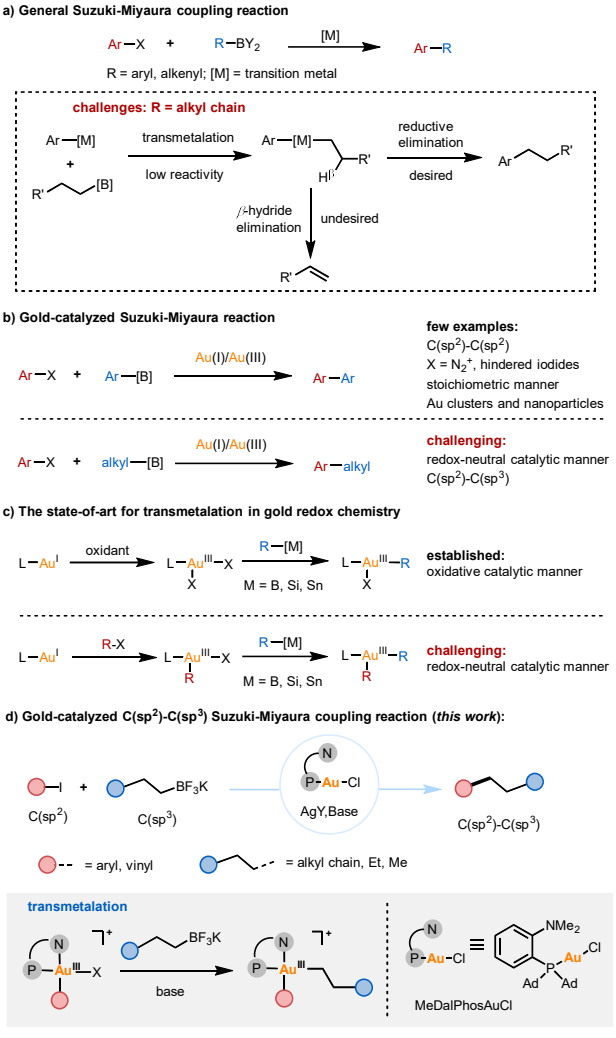
ABSTRACT: A gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis was developed. The elementary organometallic step of transmetalation has been realized in the redox catalytic cycle in gold chemistry, and overcome the limitations of previously known transition-metal catalyzed coupling reactions of alkyl organometallic reagents, such as the low reactivity of transmetalation and susceptibility to *β*-hydride elimination. This gold-catalyzed C(sp^3)-C(sp^2) coupling reaction allows a variety of chain alkyl and methyl trifluoroborates to react with aryl and vinyl iodides under very mild conditions, which has the promise for late-stage application of complicated biomolecules.

Transition metal-catalyzed cross-coupling reactions have revolutionized the construction of C-C bonds. which is demonstrated in several name reactions.[1] Among these cross-coupling processes, the Suzuki-Miyaura reaction is one of the most utilized method for carbon-carbon bond formation owing to its extensive reaction scope, broad functional groups tolerance, mild reaction conditions, as well as the stability, availability, and low toxicity 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. 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.

In the past two decades, homogeneous gold catalysis has emerged as a research field for its capacity to activate unsaturated carbon-carbon bonds, particularly alkynes.[3] Gold redox chemistry holds the promise of unique reactivities and selectivities that are distinct from those of other transition metals, has raised significant interest in recent years.[4] The putative elementary reaction steps in a potential redox gold cycle, which include oxidative addition, transmetalation, and reductive elimination, are analogous to those of cross-couplings catalyzed by Pd(0). Recent studies have utilized external oxidants,[4a,4g] EBX reagents[4b,4m,] strain release,[4d] photochemistry, [4b,4c,4h] and ligand design[4d,5] to promote the otherwise sluggish oxidative addition to Au(I) complexes. In particular, the MeDalphosAuCl with a hemilabile P, N-ligand, has allows the bottleneck oxidative addition of aryl halides to readily proceed under mild conditions.[4d,5] Moreover, it was found that the electrochemical strategy become a promising method to achieve gold redox catalysis, under external-oxidant-free conditions.[6] In spite of such significant advancements, the gold-catalyzed Suzuki-Miyaura reaction from aryl halides and organoboron reagents, which is supposed to operate via the typical Au(I)/Au(III) redox catalysis, is still very challenging, especially for alkylboron nucleophiles (Scheme 1b). Although there are few examples of gold-catalyzed C(sp^2)-C(sp^2) Suzuki-Miyaura reaction,[7] which rely on

Scheme 1. Suzuki-Miyaura Reaction: General Overview and Present Work



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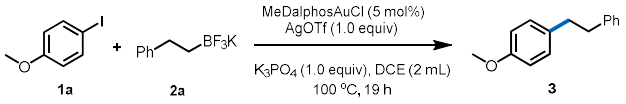
aryl diazoniums salts or hindered aryl iodides, in a stoichiometric manner, or special Au clusters and nanoparticles, the typical gold-catalyzed Suzuki-Miyaura reaction lags behind those of other gold-catalyzed redox catalysis. This might be attributed to the transmetalation,[8] which is the key elementary step in the Suzuki-Miyaura reaction, however, is less well understood in gold redox chemistry (Scheme 1c). Although the transmetalation to gold in an oxidative catalytic manner[4a,4g,9] has been established, and many examples of gold complexes for stoichiometric manner[10] are reported, the more valuable redox-neutral catalytic manner, to the best of our knowledge, is uncommon in gold chemistry.

Recently, Patil and our group reported the gold-catalyzed Heck reaction with aliphatic alkenes and styrenes.[5i,11e] Following our continued interest in gold chemistry,[11] herein, we describe a gold-catalyzed C(sp^3)-C(sp^2) Suzuki-Miyaura coupling reaction facilitated by the ligand-enabled Au(I)/Au(III) redox catalysis. The elementary organometallic step of transmetalation has been achieved in gold(I)/gold(III) redox catalysis without the use of external oxidants. Beyond the limitations of transition-metal catalyzed coupling reaction of alkyl organometallic reagents, such as slow metal transmetalation and β-hydride elimination, this gold-catalyzed Suzuki-Miyaura coupling reaction provides an efficient method for coupling with C(sp^3) coupling partners. In this gold-catalyzed coupling process, a variety of chain alkyl and methyl trifluoroborates were used as effective coupling partners, which can smoothly react with aryl and vinyl iodides under very mild conditions to build C(sp^3)-C(sp^2) bond. Its strong synthetic capabilities are demonstrated by its good functional group compatibility and late-stage application of complicated biomolecules.

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	Cs_2CO_3(0.5 equiv) / MeDalphosAuCl (7.5 mol%)	86 (83)
5[b]	Cs_2CO_3 (0.5 equiv) / MeDalphosAuCl (7.5 mol%)	72
6	r.t.	NR
7	no MeDalphosAuCl	NR
8	no AgOTf	NR
9	no base	35

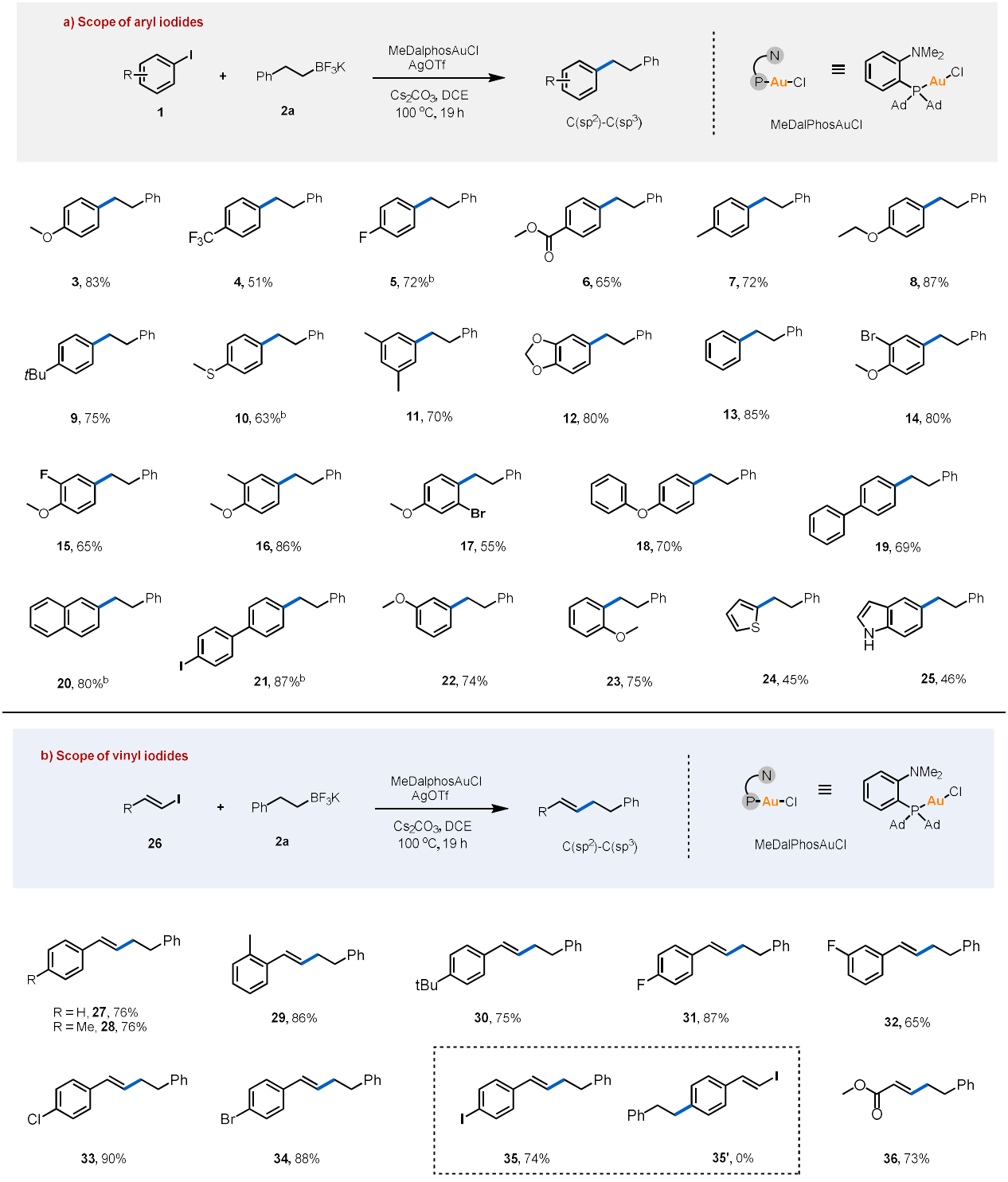
[a]Reaction conditions unless noted: **1a** (0.3 mmol), **2a** (0.2 mmol), MeDalphosAuCl (5 mol%), AgOTf (1.0 equiv), K_3PO_4 (1.0 equiv), DCE (0.1 M), 100 °C, 19 h. Product yield was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parentheses. [b]Reaction time for 6 h.

We initiated the development of a 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 in 56% yield (entry 1). We also tested other organoborane alkyl reagents, such as boronic acids or esters, and it was found that only potassium alkyltrifluoroborate works in this system, which might be attributed to its greater nucleophilicity. Moreover, compared with boronic acids or esters, the potassium trifluoroborate could be prepared easily on large scales, readily isolated for monomeric solids and long shelf lives. 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). When 7.5 mol% of MeDalPhosAuCl was used, a best yield of 86% was obtained (entry 4, 83% for isolated yield). In addition, the reaction time was reduced to 6 hours, resulting in a slightly lower yield of 72% (entry 5). Control experiments indicated that heating, gold catalyst, and silver salts are necessary for this coupling reaction, and the absence of base will dramatically lead to low yield (entries 6-9 and supplementary Tables S2-S4 for details).

We next investigated the scope of aryl iodide **1** with potassium phenethyltrifluoroborate **2a** under the optimal reaction conditions as described in entry 4 of Table 1. As shown in Scheme 2a, the reactions proceeded smoothly when aryl iodides **1** carried electron-withdrawing groups (-CF_3, -F, -CO_2Me) at the *para*-position generating desired products **4-6** in good yields (51-72%). Next, aryl iodides bearing electron-donating groups (-OMe, -Me, -OEt, -*t*-Bu, -SMe, -3,5-dimethyl) also delivered the cross-coupling product (**3** and **7-11**). 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, bulkier polycyclic aryl substrates (phenoxyphenyl, biphenyl, and naphthyl) also 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. Notably, heteroaromatic scaffolds such as thiophene and indole-based iodo compounds successfully furnished corresponding products (**24**, **25**) and gave a more modest yield. So compared with Pd and Ni, Au exhibited a good reaction selectivity with the C-I bond, this result highlighted an orthogonal reactivity of gold redox catalysis.

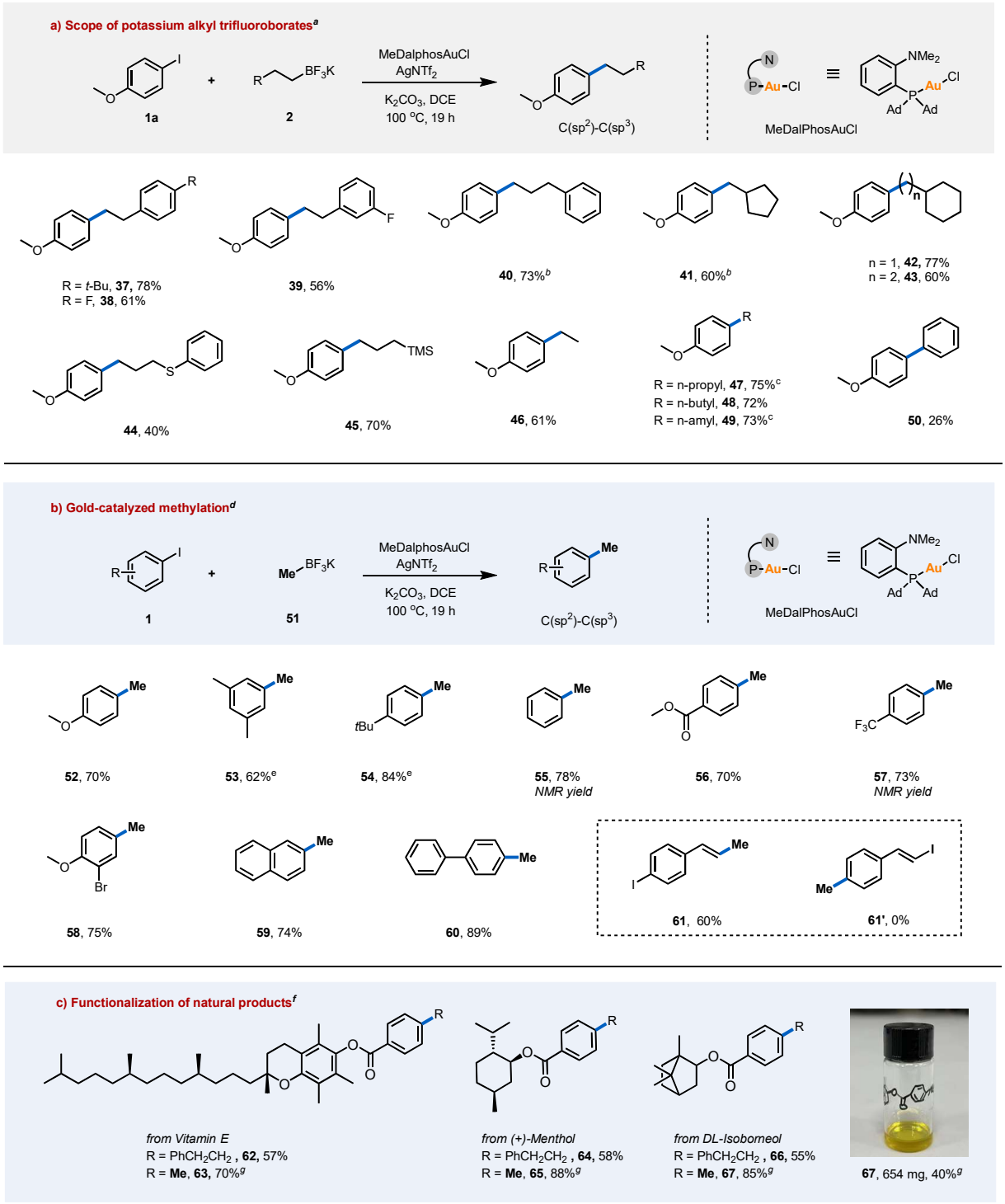
Additionally, a variety of vinyl iodine substrates **26** have been found to be suitable partners in this C(sp^3)-C(sp^2) coupling reaction process, and the results are summarized in Scheme 2b. As can be seen, (*E*)-(2-iodovinyl)benzene could undergo smooth this gold-catalyzed coupling reaction to furnish a good

Scheme 2. Scope of aryl/vinyl iodides[a]



[a]Reaction conditions unless noted: **1** or **26** (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), **51** (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). [f] Reaction conditions of functionalization of natural products: 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; [g] natural product iodide (0.6 mmol), **51** (0.2 mmol), $AgNTf_2$ (1.0 equiv), K_2CO_3(0.5 equiv).

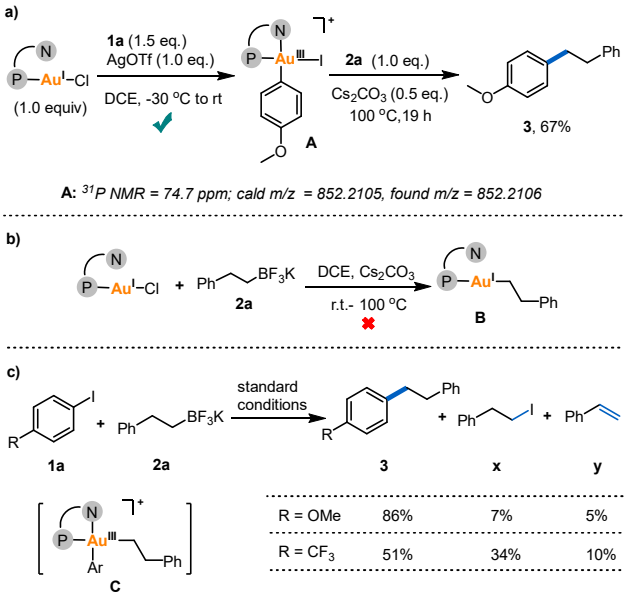
isolated yield (**27**). When the (*E*)-(2-iodovinyl)benzene bearing -Me, -*t*-Bu, and halogen (-F, -Cl, and -Br) substituents at *para*, *meta*, and *ortho* positions worked well to afford corresponding products **28-34** in good to excellent yields (65-90%). Interestingly, when a substrate contains both aryl iodide and vinyl iodide, the reaction preferentially proceeded with vinyl iodide to obtain vinyl-alkyl coupling products **35**, which indicated that the vinyl iodide has faster oxidative addition with MeDalphosAuCl than aryl iodide.[5d,5o] Also, the reserved aryl iodide of **35** provides possibilities for the further diversification of cross-coupling products. Furthermore, methyl (*E*)-3-iodoacrylate can afford the desired product **36** in 73% yield with good reaction selectivity.

Subsequently, the substrates scope of potassium alkyl trifluoroborates **2** was also examined. As shown in Scheme 3a, both electron-rich and electron-deficient substituted phenethyltrifluoroborates successfully furnished corresponding products (**37** and **38**) in good yields (78% and 61%). The substituent positions displayed negligible effects on the reaction efficiency, as the comparable yield was obtained for the *para*- and *meta*-substituted phenethyltrifluoroborates (**38** vs. **39**). Beside the phenethyltrifluoroborates, 3-phenylpropyltrifluoroborates also manifested good reactivity in this reaction with a yield of 73% (**40**). Moreover, alkyl trifluoroborate salts, such as cyclopentylmethyl, cyclohexylmethyl, and cyclohexylethyl trifluoroborates, also reacted smoothly with **1a** to deliver the corresponding products **41-43** in 60-77% yields. Potassium alkyl trifluoroborates **2** bearing some of the useful functional groups, such as phenylthio and trimethylsilane, were also tolerated well (**44** and **45**). Gratifyingly, simple alkyl trifluoroborates, such as ethyl-, propyl-, butyl- and amyl-trifluoroborates, were also coupled in good yields (**46-49**). However, the potassium phenyltrifluoroborate resulted product **50** in a much lower yield. Finally, we also tested secondary and tertiary alkyl potassium alkyl trifluoroborates, but it suffers from low reactivity. 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.[12] Therefore, the introduction of a methyl group is a particularly attractive approach for pharmacists and chemists. 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 **51**, the results of which are summarized in Scheme 3b. The reaction of methyltrifluoroborates **51** and various aryl iodides **1** bearing electron-rich groups (Me, OMe, t-Bu, Ph, naphthyl) or electron-donating groups (CF_3, CO_2Me) proceeded smoothly to afford the corresponding products (**52-58**) in moderate to excellent yields. Similarly, 2-iodonaphthalene and 4-iodobiphenyl also afforded the corresponding methylation products in good to excellent yields (**59** and **60**). Similarly, (*E*)-1-iodo-4-(2-iodovinyl) benzene was also tolerated well to afford the product (*E*)-1-iodo-4-(prop-1-en-1-yl) benzene **61** in 60% yield, and no (*E*)-1- (2-iodoethyl) -4-methylbenzene product **61'** was found.

To further demonstrate 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 3c). The phenethylation and methylation products were obtained in good yields (**62-67**), which demonstrates the generality of the method. To demonstrate the synthetic practicability, a large-scale of the methylated drug analogue **67** was prepared as 654 mg.

Scheme 4. Mechanistic Investigations

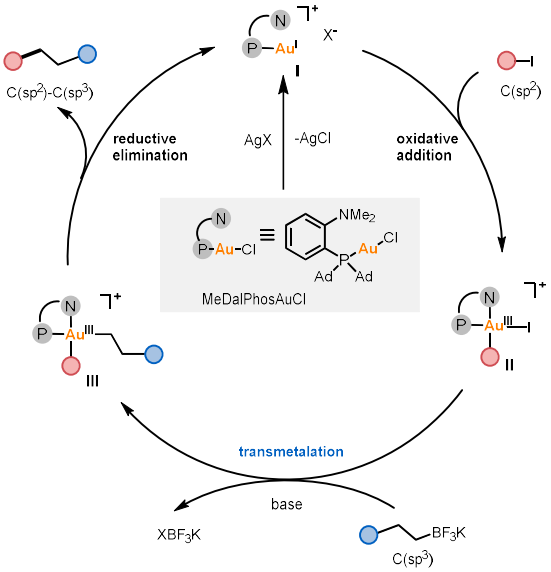


After exploring the reaction scope, we moved our attention toward mechanistic investigations (Scheme 4). Firstly, the Au(III) complex **A** could be formed smoothly from MeDalPhosAuCl and 4-iodoanisole **1a**, which is consistent with Bourissou and Patil's result.[5a,13] When the *in situ* generated Au(III) complex **A** was treated with potassium alkyl trifluoroborates **2a**, the desired product **3** was obtained in a 67% yield (Scheme 4a). While the transmetalation reaction between the MeDalphosAuCl and potassium alkyl trifluoroborates **2a** was difficult to occur (Scheme 4b). In fact, it was found that potassium alkyl trifluoroborate **2a** could not dissolve well in DCE solvent, even in base and heating conditions. Therefore, it was suggested that, in this gold-catalyzed Suzuki reaction, oxidative addition might precede the transmetalation step. Notably, as shown in Table 1, in the absence of base, 35% of desired product **3** still could be obtained, which might be attributed to the strong nucleophilicity and a basic anion of potassium alkyl trifluoroborates. Moreover, the control experiments suggested that the side products **x** and **y**, which were proposed come from the *β*-hydride elimination and metathesis of the proposed intermediate Au(III) **C**, are obtained with the desired C(sp^3)-C(sp^2) cross-coupling product **3** (Scheme 4c). And the substituent group will affect the ratio distribution of the products, the electro-donating group will favor the desired product, whereas electron-poor aryl iodide gives higher side products **x** and **y**. This may be attributed to the electron-deficient intermediate gold(III) aryl complex **C** being less susceptible to 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 5. First, the cationic Au(I) complex **I**, generated after the halide

abstraction by silver salts (AgX), would undergo oxidative addition with iodoarene 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 propagate the catalytic cycle. The reactive transmetalling species, may be involved with 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 5. Plausible Mechanism



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 elementary organometallic step of transmetalation has been realized in the redox catalytic cycle in gold chemistry. The present methodology overcomes the limitations of previously known transition-metal catalyzed coupling reactions of alkyl organometallic reagents, such as the low reactivity of transmetalation and susceptibility to β-hydride elimination. 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 strong synthetic capabilities of this gold-catalyzed Suzuki-Miyaura allow it for late-stage application of complicated biomolecules.

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Notes

The authors declare no competing financial interest.

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