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Au-Catalyzed Intermolecular [2+2] Cycloadditions between Chloroalkynes and Unactivated Alkenes

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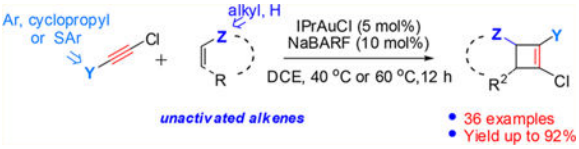
Abstract

The [2+2] cycloaddition is a versatile strategy for the synthesis of strained cyclobutenes of high synthetic value. In this study, two efficient intermolecular [2+2] cycloadditions between two different types of chloroalkynes and unactivated alkene are realized with gold catalysis. Of significance is that the reaction works with challenging monosubstituted unactivated alkenes, which is unprecedented in gold catalysis and scarcely documented in other metal-catalyzed/promoted reactions; moreover, the reaction exhibits excellent regioselectivities, which are much better than those reported in literature. With 1,2-disubstituted unactivated alkenes, the reaction is largely stereospecific. The cyclobutene products can be prepared in nearly gram scale and readily undergo further reactions including various cross-coupling reactions using the C(sp^2)—Cl and/or C(sp^2)—SPh bond, which in turn substantially broaden the scope of accessible cyclobutenes and enhance the synthetic utility of this bimolecular reaction.

Graphical Abstract



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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01813.

Detailed experimental procedures and compound characterization (PDF)

X-ray diffraction data of **6f** (CIF)

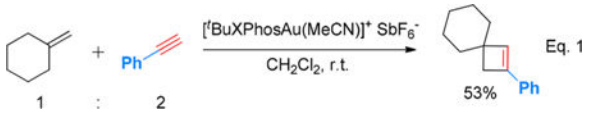
Notes

The authors declare no competing financial interest.

INTRODUCTION

The [2+2] cycloadditions constitute the most straightforward and atom-economical approaches to the construction of cyclobutane and cyclobutene rings,[1] which are versatile and highly valuable strained structures for organic synthesis[1a,2] and embedded as key structural features in various natural products.[3] The synthesis of cyclobutenes, the more strained of the two ring types, via intermolecular cycloadditions between alkynes and alkenes, have been quite extensively documented,[1] and the alkene partners are usually strained norbornene,[4] electron-rich ones including those with 1,1-disubstitutions,[5] or electron-deficient ones.[6] Only a few reported bimolecular scenarios[7] employing unactivated 1,2-disubstituted alkenes are known (Scheme 1A).[7h–m] For seldom reported reactions with more challenging unactivated monosubstituted alkenes,[6e,7h,i] they exhibit low to moderate regioselectivity (Scheme 1A). It is apparent that there is still much a need to discover new intermolecular [2+2] cycloadditions en route to cyclobutenes that would (a) accommodate unactivated alkenes and especially those that are monosubstituted and, at the same time, (b) exhibit excellent regioselectivities.

The reactions between alkynes and alkenes have been extensively studied in intramolecular settings in homogeneous gold catalysis,[8,9] some leading to cyclobutene formations.[7e–g] However, the intermolecular version[5b,7l,m,10] en route to cyclobutenes has only been reported by Echavarren and co-workers, where 1,1-disubstituted or trisubstituted alkenes are almost exclusively employed (e.g., eq 1).[5b,7l,m] With the only exception of cyclooctene,[7l] alkenes with 1,2-dialkyl or monoalkyl substitutions have not be reported as suitable alkene partners and appear to be electronically not activated enough; moreover, the necessity of arylacetylenes[5b,7l,m] and terminal diynes[7l] as alkyne partners in these gold catalysis prevents access to various other types of cyclobutene structures. Herein, we report two versatile gold catalyses employing challenging unactivated alkenes in [2+2] cycloadditions with two types of chloroalkynes (Scheme 1B). These cyclobutene products can be readily further functionalized to achieve formally an unprecedented broad reaction scope. Moreover, in contrast to all the known reactions with monosubstituted alkenes, this chemistry exhibits excellent regioselectivity.



RESULTS AND DISCUSSION

Reactions with (Chloroethynyl)arenes as the Alkyne Partner.

The limited literature precedents of haloalkynes reacting with unactivated alkenes (see Scheme 1A), albeit using different metal catalysts/promoters, inspired us to explore chloroalkynes in their gold-catalyzed [2+2] cycloadditions. At the outset, (chloroethynyl)benzene (**1a**) was chosen as the alkyne partner, and cyclohexene (**2a**, 3 equiv) the unactivated alkene. As shown in Table 1, entry 1, in the presence of IPrAuCl (5 mol %)/NaBARF (10 mol %), the desired intermolecular cycloaddition indeed occurred at ambient temperature, and the cyclobutene product 3a was formed in 54% NMR yield. Gold

catalysts based on other ligands were, however, less effective (entries 2–4). Brief screening of counteranions revealed that SbF_6^- (entry 5) is slightly worse and NTf_2^- (entry 6) much so with regard to the reaction yield. Raising the reaction temperature to 40 °C (entry 7) improved the yield dramatically to 86%, but further to 60 °C led to a decreased efficiency (81% yield). Other chlorinated solvents such as DCM (entry 8) and $CHCl_3$ (entry 9) can also accommodate this reaction, so is trifluorotoluene (entry 10). But DCE remained the most effective. In addition, MeCN (entry 11) and $MeNO_2$ (not shown) resulted no desired reaction. Lowering the Au loading to 2 mol % decreased the yield (entry 12). With cyclohexene as the limited reagent, the yield (70%, entry 13), albeit lower, was still fairly good. On the other hand, lowering the amount of cyclohexene from 3 equiv to only 1.5 equiv led to only slight decrease of reaction yield (entry 14). The excellent efficiency of this cycloaddition is remarkable, especially considering the unactivated nature of the C—C double bond.

With the optimal conditions established in Table 1, entry 7, we then investigated the reaction scope, and the results are depicted in Table 2. The reaction readily tolerates cyclic alkenes of various other ring sizes (entries 1–3), with an isolated 92% yield in the case of cyclopentene (entry 1). To our delight, monosubstituted unactivated alkenes participated the [2+2] cycloaddition smoothly, affording the trisubstituted cyclobutenes in moderate yields (entries 4–7). Of particular importance is that in contrast to the few precedents[6e,7h,i] these reactions mostly exhibited regioisomeric ratios of >20:1 and represent the best regioselectivities to date with these rudimentary alkenes. To probe the reaction stereoselectivity, we subjected *cis*-tetradec-7-ene and *trans*-tetradec-7-ene to the reaction separately (entries 8 and 9). No *trans*-isomer of the cyclobutene product **3i** was detected in the reaction of the former, and a *trans*-**3i**/*cis*-**3i** ratio of 20:1 was observed in the reaction of the latter. These results indicate that the reaction is mostly stereospecific. Cyclic dienes are also examined. With the alkene being in excess, double cycloadditions are minimal. The reaction is efficient with cyclohexa-1,4-diene (entry 10), but moderate with cycloocta-1,5-diene (entry 11). Interestingly, when cyclopentadiene dimer is reacted, the cyclopentene C—C double bond reacts selectively over the strained norbornene **π** bond. This is in contrast to various Co/Ru/Re-catalyzed intermolecular [2+2] cycloadditions using norbornenes as preferred substrates[4a–d] and indicates that the mechanism of this gold catalysis is distinctively different from these precedents. The reaction, however, exhibits little regio-selectivity. The reaction of cycloocta-1,3-diene is high yielding, but to our surprise not regioselective (entry 13). We also examined different chloroalkynes. Tolerated on the benzene ring of **1a** are *p*-Me (entries 14 and 15), *o*-Me (entry 16), *p*-MeO (entry 17), *p*-bromo (entry 18), and *p*-phenyl (entry 19), albeit a low yield in the case of *p*-MeO. In addition, 1-chloroethynylnaphthalene reacted efficiently to afford the cyclobutene **3u** in an excellent 84% yield (entry 20).

Extending the reaction to include chloroalkynes terminated with aliphatic, alkenic, and strongly electron-deficient aryl groups led to no or poor yields of desired products. On the other hand, a cyclopropyl group is allowed (entry 21). In addition, (bromoethynyl)benzene can also undergo the cyclo-addition reaction, albeit less efficient than its chloro counterpart (entry 22). However, the corresponding iodoalkyne led to no product.

A proposed mechanism for this [2+2] cycloaddition is depicted in Scheme 2. It entails an initial gold activation of a chloro(aryl)alkyne in the form of complex **A** or its polarized resonance structure, i.e., vinyl cation **A′**, followed by a nucleophilic attack by an alkene to afford the mesomeric cationic intermediates **B** and **B′**. **B** then undergoes ring enlargement and subsequent E1-type elimination of the gold catalyst to afford the cyclobutene product. While the mechanism follows closely to the previous report by Echavarren,[5b,7l] we believe the terminal chloro group is critical for the unprecedented accommodation of unactivated alkenes as the inductively electron-withdrawing nature of Cl makes the alkyne gold complex **A**/**A′** more polarized toward the vinyl cation mesoisomer **A′** and hence more reactive and capable of reacting with unactivated alkenes. The lower efficiency in the bromoalkyne case (i.e., **3w**) is consistent with Cl being more electron-withdrawing. The excellent regioselectivities observed in **3e–h** and the outstanding stereoselectivities in **3i** and **3j** can be rationalized as follows: (a) the cationic nature of the catalysis, in contrast to other transition metal catalysis,[6e,7h,i] makes the regioselectivity easily controlled with monosubstituted alkene substrates; (b) the rather reactive nature of the secondary cation in **B′** makes its mesomeric isomer, i.e., the cyclopropyl gold carbene **B** a dominant contributor; as such, rotation around the original alkene C—C σ bond via B′ is minimal, so is the stereochemistry scrambling. Such scrambling, however, is extensive in Echavarren's systems[5b] due to the intermediacy of more stable tertiary carbocations.

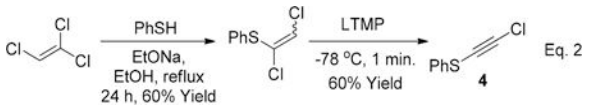
Notably, the requisite of an electron-donating aryl substituent on the C—C triple bond is consistent with significant contribution of the vinyl cation A′ upon the alkyne activation, which is less stabilized when the aryl group is replaced with an alkyl (with the exception of cyclopropyl) or electron-deficient one. On the other hand, electronically activated 1,1-disubstituted or trisubstituted alkenes are poor substrates for this reaction, leading to no or little desired products.

Reactions with Chloroethynyl Phenyl Sulfide as the Alkyne Partner.

To broaden the scope of chloroalkynes, we envisioned that heteroatom-based substituents in place of the aryl group could play a similar role in stabilizing **A′**. Shi[11] recently reported that an alkyl-/arylthiol group serves this purpose in facilitating gold-catalyzed regioselective nucleophilic additions to its tethered C—C triple bond. To this end, we targeted chloroethynyl phenyl sulfide (**4**), which can be synthesized in a reported two-step sequence.[12] We modified the reaction conditions in the dehydrochlorination step by using lithium tetramethylpiperidide (LTMP) as base, which leads to an improved 60% yield (eq 2). Due to its unstable nature in neat form, 4 was stored as a 0.9–1.1 M solution in DCE, which remained unchanged in a freezer at –18 °C for a week.

To our delight, under the standard conditions developed for (chloroethynyl)benzene **1a**, the reaction between **4** and excess dodec-1-ene (3 equiv) indeed afforded the desired cyclobutene product **5a** in a decent 66% yield (Table 3, entry 1). While the reaction efficiency is comparable to that in Table 2, entry 5, we examined various ways to improve the reaction including higher catalyst loadings (e.g., 10 mol %) with little success. We anticipated the reaction scope of this chemistry is more meaningful with the alkene part varied and hence later employed dodec-1-ene as the limiting reagent. With 2 equiv of **4** used,

the reaction yield based on alkene was a lower 60% (entry 2). To our surprise, we noticed that there was ~40% dodec-1-ene unreacted and the yield based on alkene conversion was nearly quantitative. The addition of 5 Å MS led to a slight increase of the yield; on the other hand, increasing the reaction temperature improved the product yield substantially to 78% (entry 4). Tripling of catalyst loading led to an even better yield (entry 5). However, the alkene conversions were still not complete in these cases. We surmised that catalyst poisoning must be caused by decomposition of the sulfide **4**. To alleviate the problem, we injected **4** into the reaction via syringe pump for a period of 2 h. Much to our delight, the reaction proceeded to near completion and become highly efficient, affording **5a** in 92% yield (entry 6). The addition of 5 Å MS again led to some yield increase (entry 7), as did increasing the reaction temperature to 60 °C (entry 8). Finally, the best yield was achieved by running the reaction at 60 °C and slowing the injection (entry 9) to a 4 h period. The isolated yield, under the optimal conditions, was 91%. Comparing this case to Table 2, entry 5, it appears that **4** is a more efficient alkyne partner than **1a** in the [2+2] cycloaddition with unactivated long-chain terminal alkenes.



The reaction scope was then examined, and the results are shown in Table 4. It worked well with cycloheptene (entry 2) and cyclooctene (entry 3), and the reaction yields are similar to those employing **1a** (cf. Table 2, entries 2 and 3). For cyclopentene (entry 1) and 4-methylpent-1-ene (entry 4), the moderate yields are attributable to their volatility and the fact that they are used as limiting reagents. The reaction with (*E*)-tetradec-7-ene is also highly stereoselective and notably more efficient than its counterpart in Table 2, entry 9 (75% vs 52%). Interestingly, unlike Table 2, entry 7, the reaction of 1,7-octadiene could not be stopped selectively at monocycloaddition despite varying its ratios over **4**, and the double cycloaddition product **5g** was formed in 68% yield, which amounts to 82% yield per cycloaddition (entry 6). Much to our delight, this reaction could tolerate inductively deactivating and lone-electron-pair-bearing heteroatom-based functional groups (entries 7–10). For example, terminal alkenes possessing a remote (entry 7) or δ-(entry 8) TIPSO group undergo efficient cycloaddition with 4. The latter case displays much higher yield (i.e., 78%) than its corresponding reaction with 1a (49% yield; see SI for details). A γ-bromo poses no problem, either (entry 9), and a remote ester group apparently does not interfere with the cationic nature of the cycloaddition despite its Lewis basic carbonyl oxygen (entry 10). With an internal alkene (entry 11), no regioselectivity was observed. The reaction with a sterically more demanding 1-vinylcyclohexane also works, albeit with a moderate yield (entry 12). Notably, for entries 6–12, the optimized conditions in Table 3, entry 7, do not permit the full substrate consumption. The addition of 5 Å MS largely solved the problem. It is believed that for these slower reactions the removal of trace water prevented the formation of thioester due to alkyne hydration and the potential subsequent release of catalyst-poisoning thiophenol upon further hydrolysis. Molecular sieves of 3 or 4 Å were not as effective.

These scope studies reveal that **4** can react in general more efficiently with unactivated alkenes than (chloroethynyl)arenes and similarly exhibit excellent regioselectivities on the

monosubstituted alkene part. On the other hand, similar to (chloroethynyl)arenes, **4** does not react with electronically activated alkenes with serviceable yields.

Further Transformations of Cyclobutene Products.

The synthetic utility of the cyclobutene products[4e] was examined by using **3a** and **5a** as illustrative examples. In the case of **3a**, it was first prepared in nearly gram scale without incident (Scheme 3). Under standard hydrogenation conditions, it is fully reduced to bicyclobutane **6a** with excellent diastereoselectivity. Its oxidation by DMDO leads to chlorinated cyclobutanone **6b** via an epoxide intermediate. Couplings of its C(sp^2)—Cl bond with oct-1-yne, phenylboronic acid, β-styrylboronic acid, and the alkylborane generated from 1-octene and 9-BBN were readily accomplished in excellent yields by using the combination of the Pd(II) dimer precatalyst **Pd-1**[13] and XPhos. The two-step sequences of the gold catalysis and these cross-coupling reactions achieve formally [2+2] cycloadditions of a diverse range of arylalkynes with unactivated alkenes, which has not previously been realized. The assigned cyclobutene structure of the cyclo-adducts is confirmed by X-ray diffraction analysis of one of the cross-coupling products, i.e., **6f** (Figure 1).

In the case of **5a**, it was readily oxidized into the corresponding sulfone **7a** in 89% yield (Scheme 4). A chemoselective Suzuki—Miyaura cross-coupling of its C—Cl bond efficiently installed a β-styryl group in **7b** by employing the above **Pd-1**/XPhos system. Likewise, its reaction with phenylboronic acid was equally chemoselective and highly efficient, affording **7c** in nearly quantitative yield. While the phenyl sulfide moiety was an innocent bystander in these Suzuki—Miyaura reactions, it can participate in Ni-catalyzed Kumada cross coupling with methyl Grignard[14] and hence offers a valuable site in the cyclobutene products for further functionalization/derivatization. For example, in a two-step sequence with **7c** as the intermediate, the methylated **7d** was formed in a combined 70% yield. It is noteworthy that a similar Kumada coupling of **3f** would end up with the homologue of **7d** with the opposite regiochemistry. A one-step double Ni-catalyzed Kumada reaction of **5a** afforded the bismethylated cyclobutene **7e** in 57% yield.

CONCLUSION

We have realized two new types of gold-catalyzed intermolecular [2+2] cycloadditions between alkyne and alkene with moderate to excellent yields. (Chloroethynyl)arenes and phenyl chloroethynyl sulfide are demonstrated as effective alkyne partners, with the latter leading to generally more efficient reactions. The salient feature of these reactions is the scope of alkenes, which are all electronically unactivated and hence challenging. They range from various disubstituted alkenes to monosubstituted alkenes. In comparison, prior experiments in gold catalysis have demonstrated only one success with cyclooctene and none with monosubstituted unactivated alkenes. In addition, the reactions with monosubstituted alkenes exhibit excellent regioselectivities, which are markedly better than those reported in the scarce literature precedents promoted/catalyzed by other metals. With 1,2-disubstituted unactivated alkenes, the reactions are largely stereospecific. The cyclobutene products can be prepared in nearly gram scale and readily undergo further transformations, including various cross-coupling reactions involving the C(sp^2)—Cl and/or

the C(sp^2)—SPh bonds, which in turn substantially broaden the scope of accessible cyclobutene products and therefore notably enhance the synthetic utility of these bimolecular reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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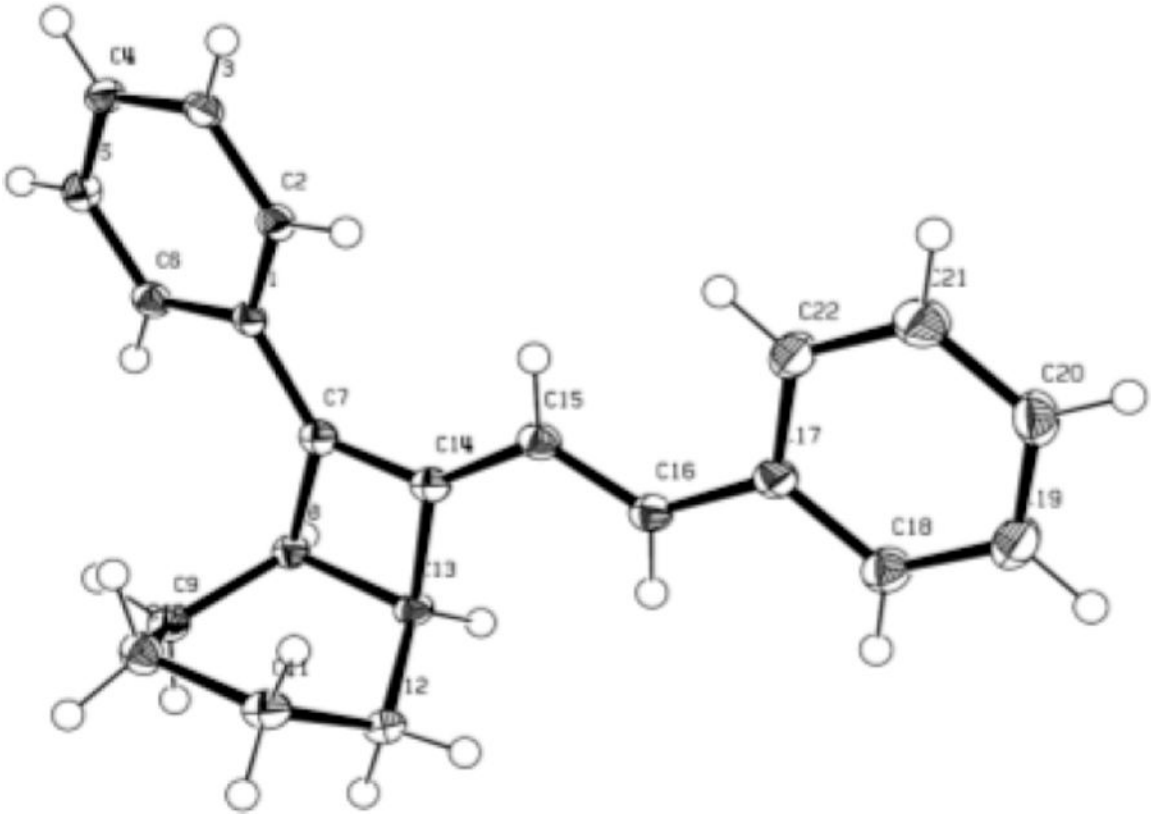
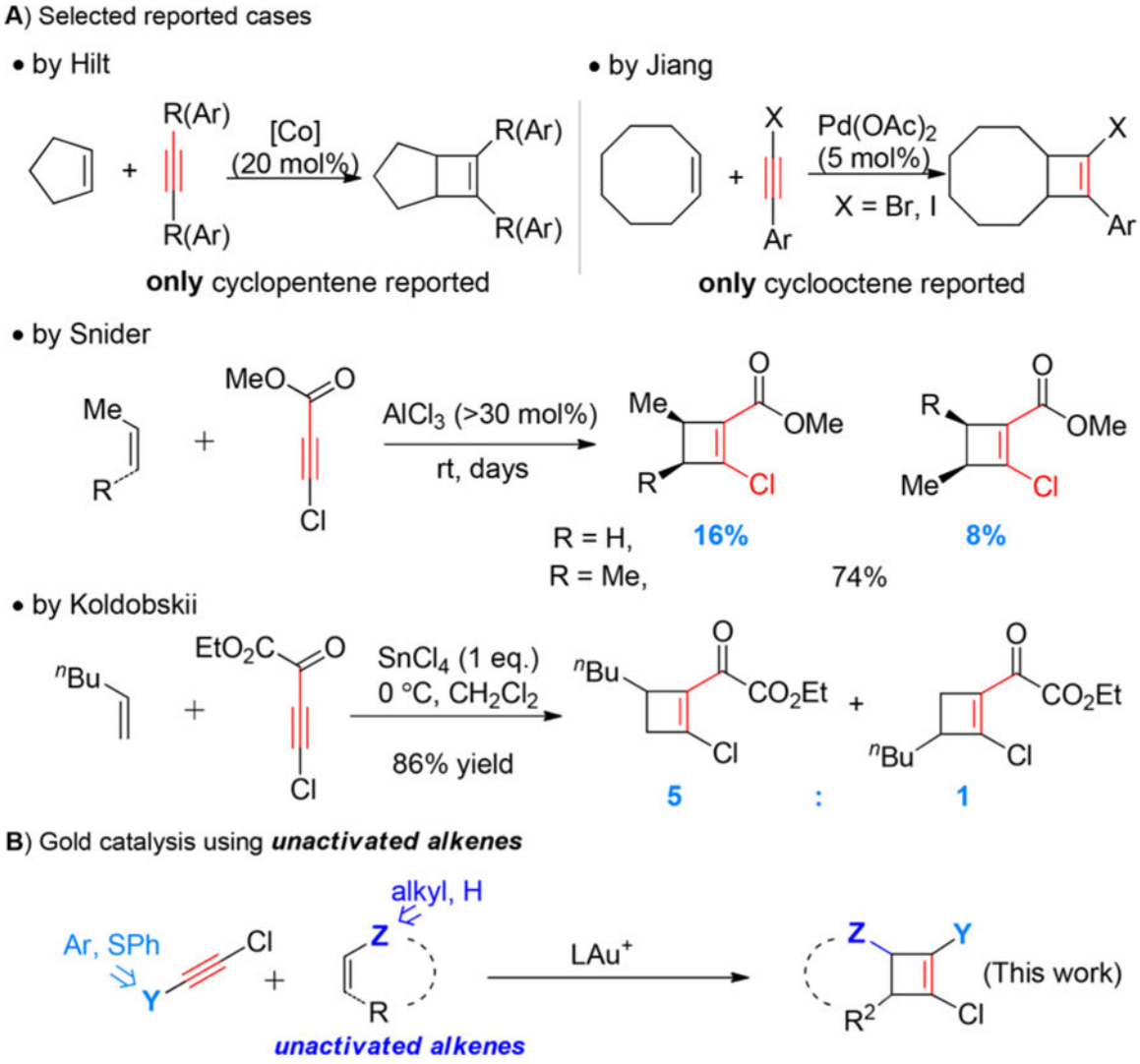
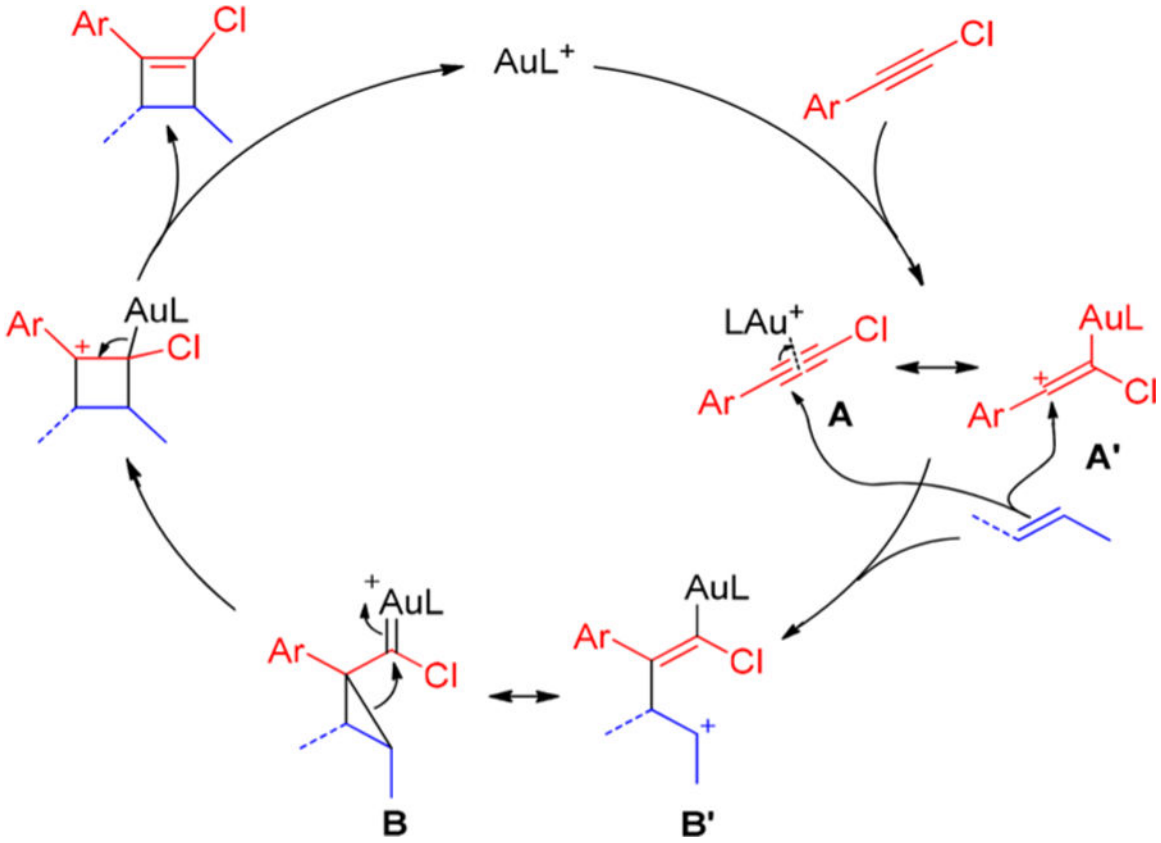


Figure 1.
ORTEP drawing of **6f** with 50% probability ellipsoids.

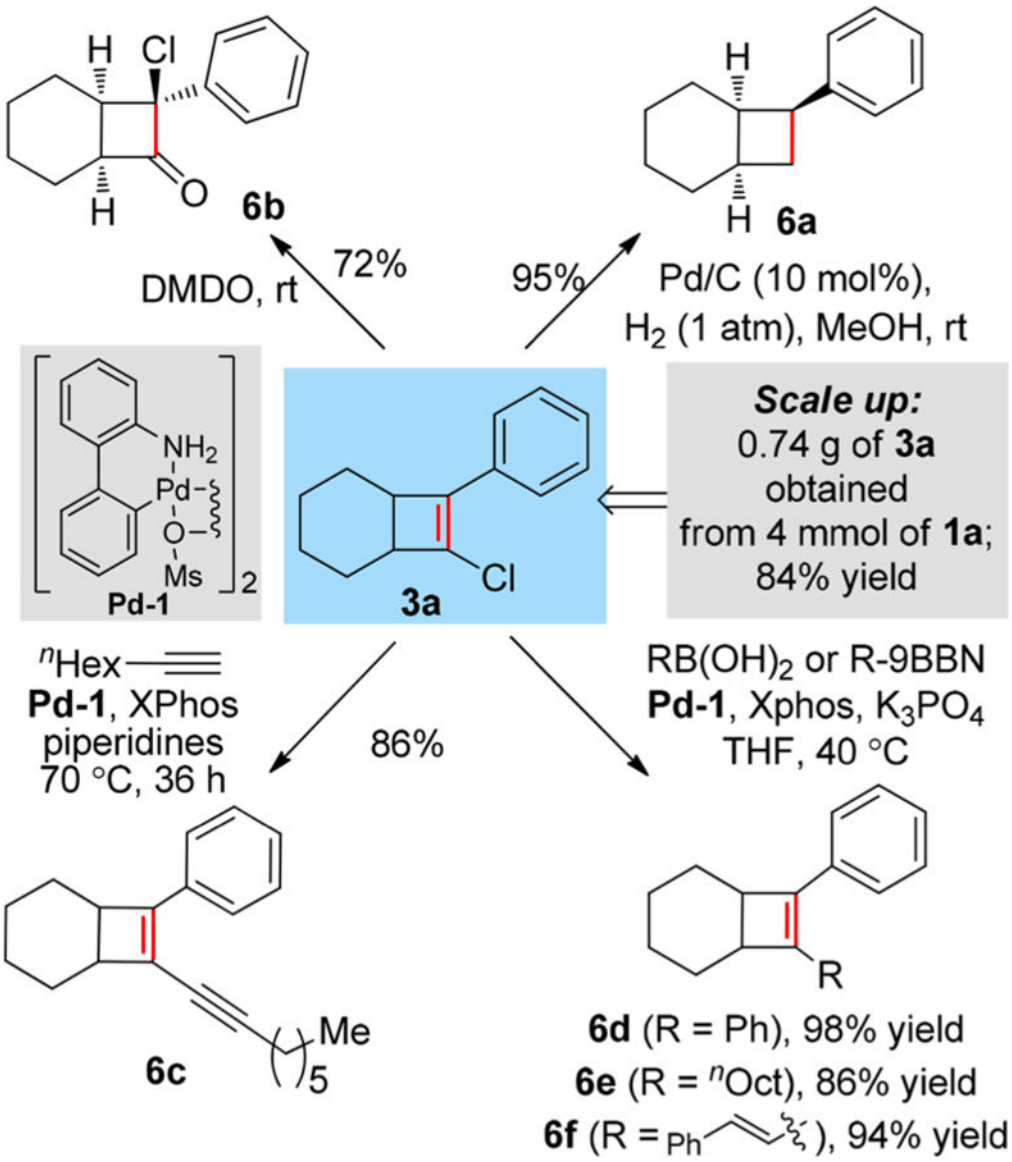


Scheme 1.

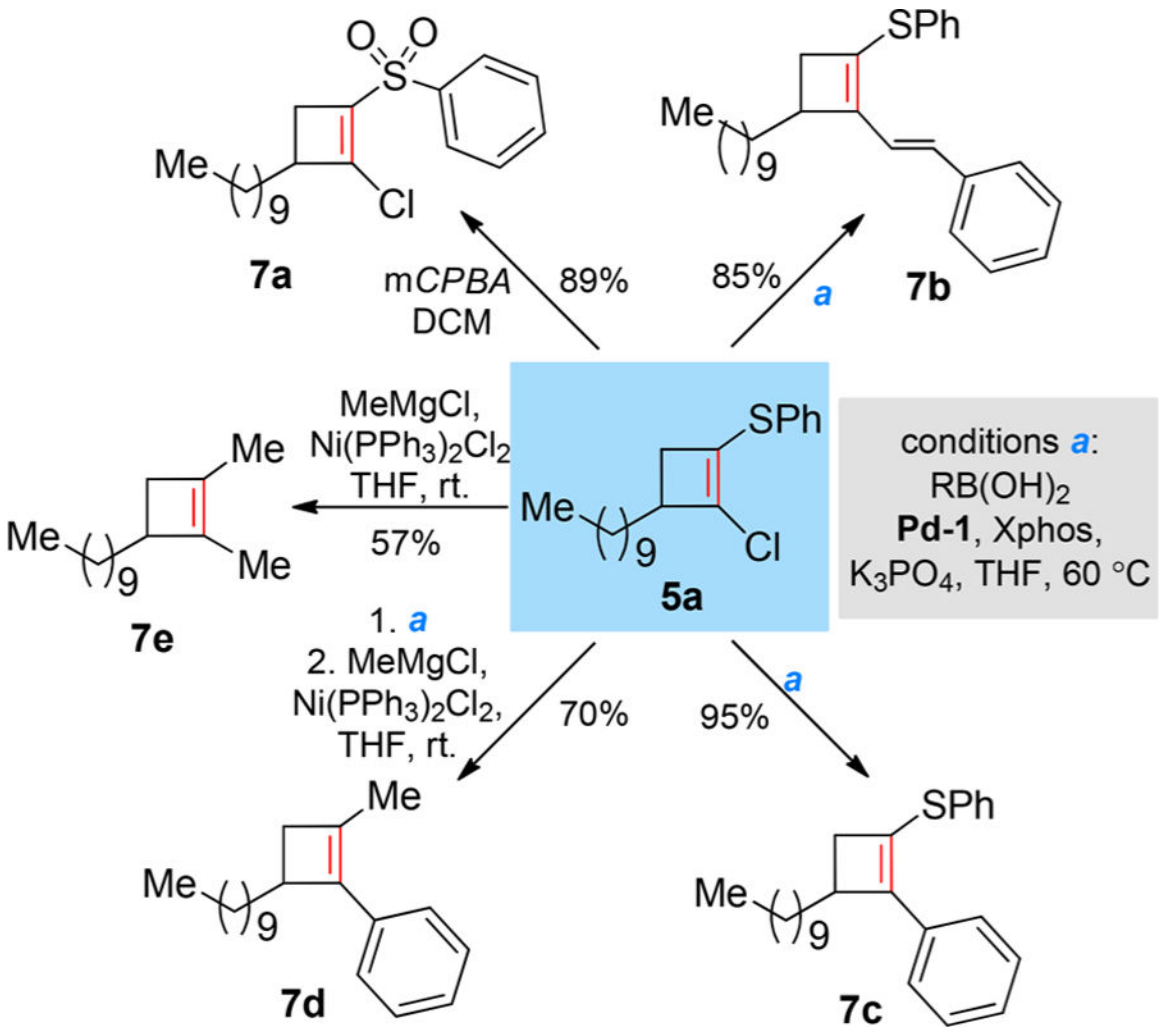
Catalytic Intermolecular [2+2] Cycloadditions of Alkynes with Alkenes



Scheme 2.
Proposed Reaction Mechanism



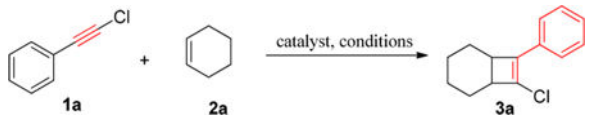
Scheme 3.
Transformations of 3a[a]



Scheme 4.
Transformations of 5a

Table 1.

Optimization of the Reaction Conditions[a]



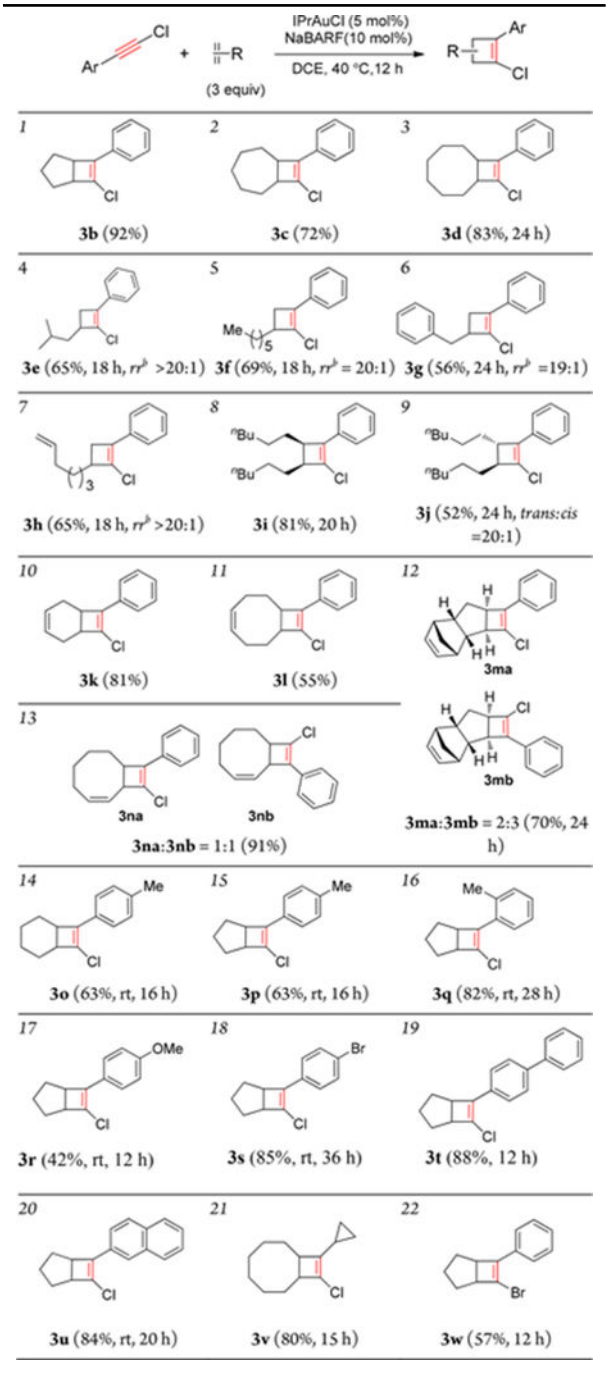
entry	1a:2a	catalyst	conditions	yield (%)
1	1:3	IPrAuCl (5%), NaBARF (10%)	DCE, rt, 12 h	54[b]
2	1:3	JohnPhosAuCl (5%) NaBARF (10%)	DCE, rt, 12 h	22[b]
3	1:3	BrettPhosAuNTf$_2$ (5%)	DCE, rt, 12 h	0[b]
4	1:3	CyJohnPhosAuCl (5%) NaBARF (10%)	DCE, rt, 12 h	13[b]
5	1:3	IPrAuCl (5%), AgSbF$_6$ (10%)	DCE, rt, 12 h	50[b]
6	1:3	IPrAuNTf$_2$ (5%)	DCE, rt, 12 h	30[b]
7	1:3	IPrAuCl (5%), NaBARF (10%)	DCE,12 h40 °C,	86
8	1:3	IPrAuCl (5%), NaBARF (10%)	DCM, 40 °C,12 h	76
9	1:3	IPrAuCl (5%), NaBARF (10%)	CHCl$_3$, 40 °C, 12 h	82
10	1:3	IPrAuCl (5%), NaBARF (10%)	PhCF$_3$, 40 °C, 12 h	80
11	1:3	IPrAuCl (5%), NaBARF (10%)	MeCN, 40 °C, 12 h	0
12	1:3	IPrAuCl (2%), NaBARF (4%)	DCE, 40 °C, 12 h	65
13	3:1	IPrAuCl (5%), NaBARF (10%)	DCE, 40 °C, 16 h	70
14	1:1.5	IPrAuCl (5%), NaBARF (10%)	DCE, 40 °C, 16 h	82

[a] [**1a**] = 0.1 M. Reaction scale is 0.1 mmol. Yield determined by ^{1}H NMR using diethyl phthalate as the internal reference.

[b] Some **1a** remained.

Table 2.

Gold-Catalyzed [2+2] Cycloadditions of (Chloroethynyl)arenes with Alkenes[a]

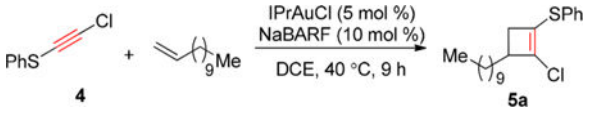


[a]General reaction conditions: chloroalkyne (0.3 mmol), alkene (0.9 mmol), NaBARF (10 mol%), IPrAuCl (5 mol%), DCE (3 mL), 40 °C or ambient temperature for 12–36 h. Isolated yields are reported.

[b]*rr* = regioisomeric ratio. The major isomer is shown.

Table 3.

Optimization of the Reaction between Chloroethynyl Phenyl Sulfide and Dodec-1-ene[a]



4 5a

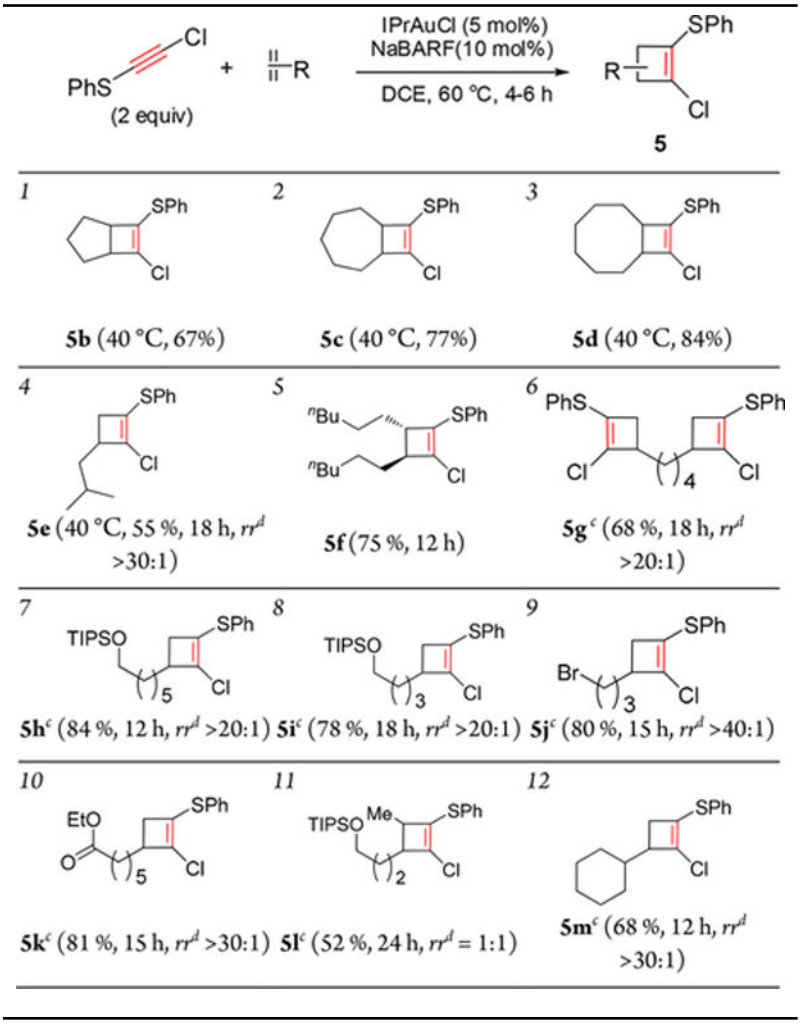
entry	4:alkene	additional conditions variations	conversion (%)	yield (%)
1	1:3	none	100 (4)	66
2	2:1	none	61	60
3	2:1	5 Å MS added	66	66
4	2:1	75 °C instead of 40 °C	78	78
5[b]	2:1	IPrAuCl (15 mol%) /NaBARF (30 mol%) used	88	88
6	2:1	**4** added via syringe pump over 2 h	92	92
7	2:1	**4** added via syringe pump over 2 h and 5 Å MS added	94	94
8	2:1	**4** added via syringe pump over 2 h and at 60 °C	94	94
9	2:1	**4** added via syringe pump over 4 h and at 60 °C	99	98
				(**91**)[b]

[a] Yield and conversion determined by ^{1}H NMR using diethyl phthalate as the internal reference.

[b] 91% isolated yield.

Table 4.

Gold-Catalyzed [2+2] Cycloadditions of (Chloroethynyl) Phenyl Sulfide with Alkenes[a,b]



[a] General reaction conditions: a DCE solution of **4** was syringe-pumped into the heated reaction mixture (60 °C) for 4–6 h. The total reaction time is 9 h.

[b] Isolated yields reported.

[c] 5 Å MS added.

[d] *rr* = regioisomeric ratio. The major isomer is shown.