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Intermolecular Alkene Difunctionalization via Gold Catalyzed Oxyarylation

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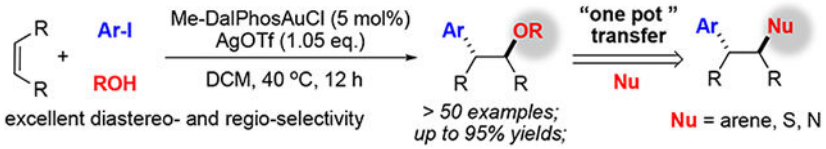
Abstract

The gold-catalyzed intermolecular oxyarylation of alkene is reported. This work employed the oxidative addition of aryl iodide to Me-DalphosAu$^+$ for the formation of Au(III)-Ar intermediate. The better binding ability of alkene over O nucleophiles ensured the success of intermolecular oxyarylation, giving desired products with broad substrate scope and high efficiency (>50 examples with up to 95% yield). “One-pot” converting of methoxy group into other nucleophiles allowed achieving alkene difunctionalization with C-N, C-S, and C-C bonds construction under mild conditions.

Graphical Abstract



Keywords

gold redox catalysis; alkenes; oxidative addition; oxyarylation; hemilabile (P,N) ligand

Homogeneous gold catalysis has witnessed tremendous development over the past two decades.[1] Comparing to Au(I), Au(III) complexes are stronger π-acids to promote reactions of less reactivity substrates, such as alkenes and internal alkynes.[2] Also, with a high oxidative potential, facile reductive elimination on Au(III) enables challenging bonds formation.[3] Therefore, the gold redox catalysis possesses an inherent capability to promote new transformations with high efficiency.[4] Among those reported examples, direct oxidation of Au(I)-Ar using strong oxidants, photocatalytic activation of diazonium, and ligand enabled gold(I) oxidative addition to aryl halide have received considerable attention as an easy access to active Au(III)-Ar intermediates, which is feasible for further arylation (Scheme 1A).[5] One route is to react with nucleophiles to give coupling products through reductive elimination. Both carbon (electron rich arene and terminal alkyne) and

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Conflict of interest

The authors declare no conflict of interest.

heteroatom nucleophiles have been reported as feasible coupling partner.[6] Additionally, the better π-acid properties of gold cations ensure stronger C-C unsaturated bond coordination. [7] As shown in Scheme 1A, nucleophilic addition to Au^{III} activated alkene **B**, followed by reductive elimination, could reach 1,2-difunctionalization of the alkene in high efficiency with excellent regio- (Markovnikov addition) and diastereoselectivity (trans-addition). [8] However, an intramolecular fashion is dominated to avoid unrenderable reaction pathways, including cross-coupling and protodeauration. Very few examples have been reported via an intermolecular "three-component" reaction. The only successful example is gold-catalyzed intermolecular alkene oxyarylation. The pioneering studies by Toste and Russell have demonstrated the feasible approach of using strong oxidants, such as Selectfluor or hypervalent iodine.[9] Recently, one elegant example by Glorius showed the feasibility of photoactivation of the aryl diazonium salt approach (Scheme 1B).[10] However, one common limitation of these transformations is that the electron-deficient aryl precursor is necessary to be compatible with more reactive electrophilic oxidants in the system. In the presence of EDG-modified aryl precursor, almost no product was observed. In some cases, a large excess amount of nucleophile is required (MeOH as solvent). Therefore, developing new intermolecular alkene difunctionalization methods bearing a broader substrate scope is highly desired. Herein, we report a first example of intermolecular oxyarylation of alkene through ArI directed oxidative addition of Au(I), bearing a broad substrate scope and good functional group tolerance (Scheme 1C).

Over the past decade, our group has focused on developing new synthetic methods using homogenous gold catalysis.[11] Recently, we reported a series of transformations on base promoted diazonium activation for gold redox catalysis.[12] Compared with the photo-activation conditions, this base activation approach is much more robust with no need of strict degassing. With the interest in achieving the combination of gold π-acid and redox catalysis under intermolecular fashion, we have explored reactions between alkene, diazonium and nucleophiles under various reaction conditions. As shown in Figure 1A, our initial attempt to achieve the desired transformation was less successful after a systematic screening. As a result, we are seeking using a stable Au(III) intermediate to achieve this transformation.

In 2017, Bourissou and co-workers first reported the application of hemilabile (P,N) ligand (Me-DalPhos) to facilitate ArI oxidative addition and stabilize the Au^{III} intermediate formed *in-situ*.[13] Using this strategy, cross coupling with electron rich arenes has been achieved. [14] Later, this method has also been applied in peptide modification through C-S bond construction.[15] In 2019, Patil group further extended this reaction's scope to direct C-N bond coupling.[16] Encouraged by these results, we wondered whether this new [Au^{III}-Ar] forming strategy could be applied to achieve the challenging intermolecular nucleophilic addition. It is important to note here that during our investigations, Patil and Bourissou simultaneously reported the combination of gold oxidation and alkene π-activation via intramolecular nucleophilic addition (C-C by Patil and C-O/C-N by Bourissou).[17] These two seminal works highlighted the great excitement for this gold redox catalysis strategy and implied the potential challenge for the intermolecular reaction. When we conducted the intermolecular reaction among $TsNH_2$, aryl iodide, and simple alkene **1a** under their

reported optimal conditions, the desired amino arylation product **2a** was only obtained in < 8% yields for both cases (Figure 1B).

Analyzing the reaction mixture revealed C-N coupling compound **2b** as the major product under basic conditions. To avoid this competing reaction, we carried out the reactions under neutral or acidic conditions. We were pleased to find the aminoarylation product **2a** in 38% yield with the addition of 5.0 eq. MeOH at 70 °C. However, after carefully monitoring the reaction process (2 h vs 6 h), we found that aryl iodide was completely consumed within two hours with the formation of **4a**, extension of reaction time gave continuous formation of **2a** and the disappearance of **4a**. This result strongly suggested that the amino arylation product **2a** was likely formed from methoxy arylation product **4a** under the reaction conditions. Based on this result, we put our efforts on the condition screening for the oxyarylation. After exploring different reaction factors, an optimal condition was identified with Me-DalPhos-AuCl (5%) in DCM at 40 °C, giving the desired oxyarylation product **4a** in 95% isolated yield. Some alternative conditions are summarized in Table 1.

As shown in Table 1, with the addition of 2.0 eq. alkene **1a**, 1.05 eq. AgOTf, and 3.0 eq. MeOH, the aryl iodide **1a** was completely converted to the desired product **4a** in 95% yield (entry 1). Conducting reaction using $AgSbF_6$ as iodide scavenger led to a lower yield with more elimination product **2d**, likely caused by the increased acidity (entry 2). Similarly, a higher temperate (60 °C) also resulted in the increasing of elimination product (entry 3). The conversion dropped to 20% at room temperature (entry 4). DCB was also the suitable solvent for this transformation (entry 5). Interestingly, when methanol was used as the solvent, slow reaction kinetic was observed, which might due to the competing coordination of OMe with alkene towards Au(III) intermediate (entry 6). Base is not necessary in the reaction (entries 7 and 8). Only 20% conversion was observed when using Mor-DalphosAuCl (entry 9). Finally, we performed the control experiments, showing that Au catalyst, Ag salt and aryl iodide were all necessary for this transformation (entries 10-12). With the optimal condition in hand, we then explored the substrate scopes, and the results are summarized in Table 2.

We first examined the scope of alkenes. In general, monosubstituted terminal alkene substrates worked well in all cases, giving desired products in good to excellent yields (**4a**-**4o**). Substrates containing various functional groups, such as ester (**4e**-**4i**), benzyl ether (**4k**), phthalimide (**4j**), and coumarin (**4o**) were tolerated under this condition. Electron-rich phenyl ether groups (**4l**-**4o**) were also compatible, giving moderate yields. Notably, no aromatic electrophilic addition product was observed under this condition, indicating that OMe is a better nucleophile. For internal alkene substrates, slower reaction kinetics was observed under standard condition (<20% conversion in 24 h). To our delight, cyclic alkenes run smoothly with an increased concentration (0.5 M), affording the desired oxyarylation products in excellent yield and good diastereoselectivity (**4p**-**4r**). As for acyclic internal alkenes, only *cis*-1,2-disubstituted alkene was suitable for this transformation, though with relatively lower conversion (50%) and yield (42%) in 24 h (**4s**). *Trans*-4-octene remained unreactive under the same condition. These results suggested that reducing steric hindrance will be benefit for both alkene coordination and OMe addition.

The reaction scopes of aryl iodide were also investigated. All these substrates were treated at a higher concentration (0.5 M) due to slower reaction kinetics. The presence of both electron-withdrawing/-donating groups on the aromatic ring of aryl iodide did not show influence on the reaction outcome, and the products were formed in good to excellent yields. The ortho-substituted aryl iodides usually required a harsher condition (60 °C) with a decreased yield (**5b**, **5e**, **5n**, **5o**), which might be associated with less feasible oxidative addition under the steric influence. Comparing with Pd, Au cation exhibited a good selectivity, which exclusively underwent oxidative addition into C-I bond (**5o**). This result highlighted an orthogonal reactivity of gold redox catalysis. Menthol ester modified aryl iodide was also explored, giving the corresponding oxy-arylation product in good yield but 1:1 dr selectivity (**5q**). Overall, this approach presented a broader scope than gold redox catalysis using aryl diazonium salt, highlighting the mild condition and synthetic potential for more complex system.

Next we explored the substrate scope of alcohols (Table 3). Both primary and secondary alcohols can serve as suitable nucleophile, generating corresponding products in excellent yields (**6a**-**6c**, **6e**). Water can also work as a nucleophile here, achieving the alcohol product in 90% yield (**6d**). Benzyl alcohol containing Br on aromatic rings was also tolerated (**6f**). Some bio-compatible alcohols, including β-Citronellol (**6g**), Menthol (**6h**), and Prolinol (**6l**) proved successful for this transformation. However, the dr selectivity of corresponding products are all 1:1, indicating no steric control on nucleophilic addition step. Overall, various alcohol derivatives performed well with good functional group tolerability under this optimal condition, making it a practical late-stage functionalization strategy for complex molecule synthesis.

Encouraged by the successful application of alcohol nucleophile, we then turned our attention to other nucleophiles. However, among all tested nucleophiles, only a few cases worked. 4-nitroaniline performed well at a higher concentration (0.5 M), generating the desired product in 75% yield (**6l**). 1,3,5-trimethoxybenzene can also react, giving a decreased yield due to a large amount of C-C bond cross coupling products. Other tested nucleophiles, such as tosyl amine, phenol, and thiophenol failed to yield our desired product (see SI for the detailed nucleophile screening). Inspired by our initial discovery of amino arylation (Figure 1B), we reasoned that OMe could be a good leaving/transformation group, therefore, other nucleophiles may still have their position on this alkene difunctionalization reaction. We then conducted the reaction in a “one-pot” fashion: oxyaryalation of alkene followed by various nucleophiles substitution.

As shown in Figure 2, to our delight, we were able to complete these transformations in good yields (**2a**, **6k**-**6s**). The methoxy group can be transferred to various nucleophiles (N, C, S) with elimination product **2d** as the only byproduct. Interestingly, control experiment revealed that the optimal yield can only be achieved under this “one-pot” fashion, highlighting the unique promotion effect in this reaction system. Notably, the thiophenol product (**6m**-**6p**) was obtained through this reaction protocol, showing the potential application on cysteine modification in the biological system with catalytic amount of gold.

In conclusion, we reported an example of ligand enabled Au(I/III) catalyzed intermolecular alkene oxyarylation reaction with a broad substrate scope and good functional group tolerability. The one-pot nucleophile transfer strategy enabled diversed alkene 1, 2-difunctionalization, which provides a practical synthetic value and offers a valuable mechanistic insight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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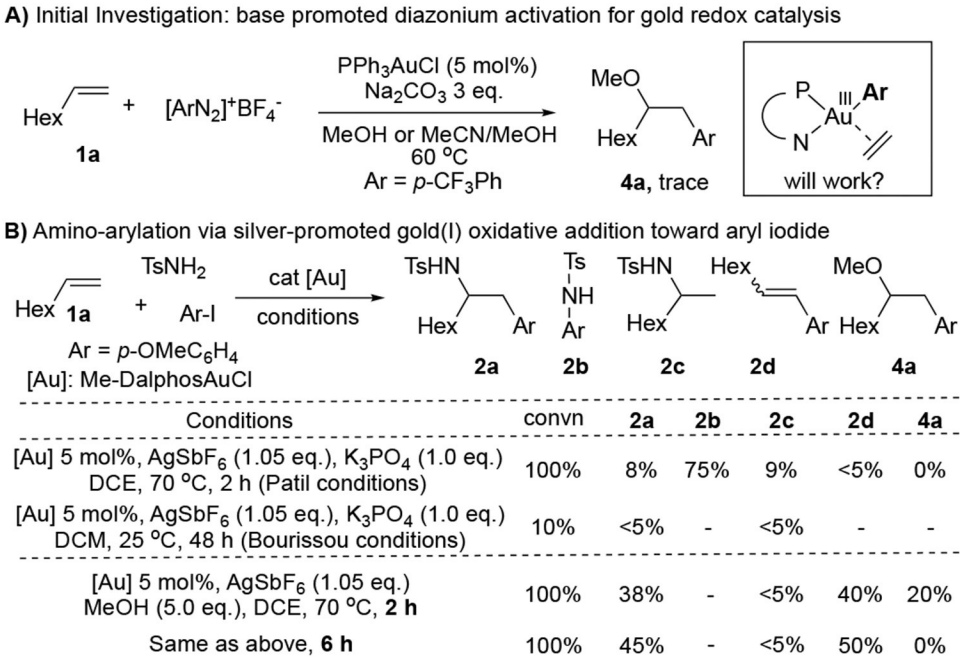


Conditions	convn	2a	2b	2c	2d	4a
[Au] 5 mol%, $AgSbF_6$ (1.05 eq.), K_3PO_4 (1.0 eq.) DCE, 70 °C, 2 h (Patil conditions)	100%	8%	75%	9%	<5%	0%
[Au] 5 mol%, $AgSbF_6$ (1.05 eq.), K_3PO_4 (1.0 eq.) DCM, 25 °C, 48 h (Bourissou conditions)	10%	<5%	-	<5%	-	-
[Au] 5 mol%, $AgSbF_6$ (1.05 eq.) MeOH (5.0 eq.), DCE, 70 °C, **2 h**	100%	38%	-	<5%	40%	20%
Same as above, **6 h**	100%	45%	-	<5%	50%	0%

Figure 1.
Intermolecular difunctionalization of alkene

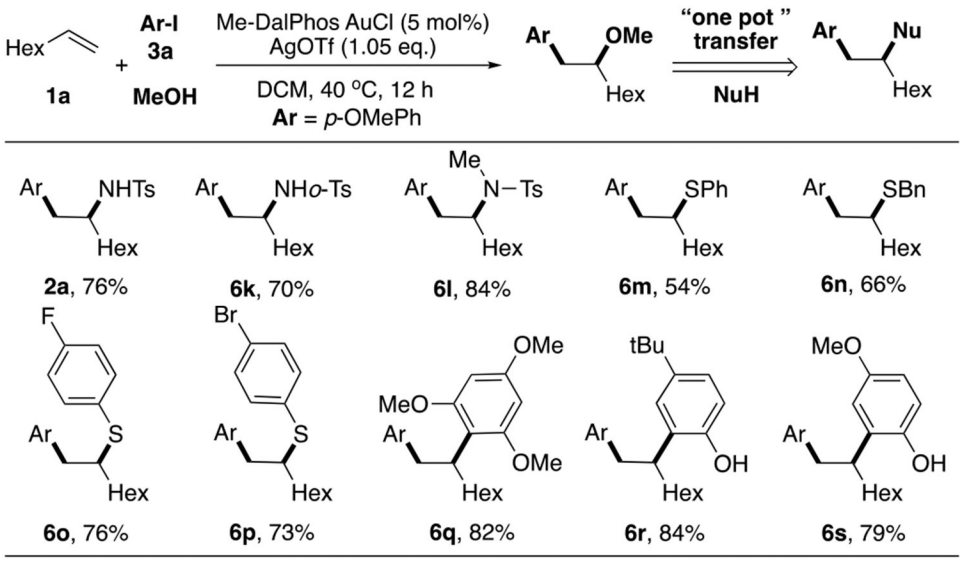
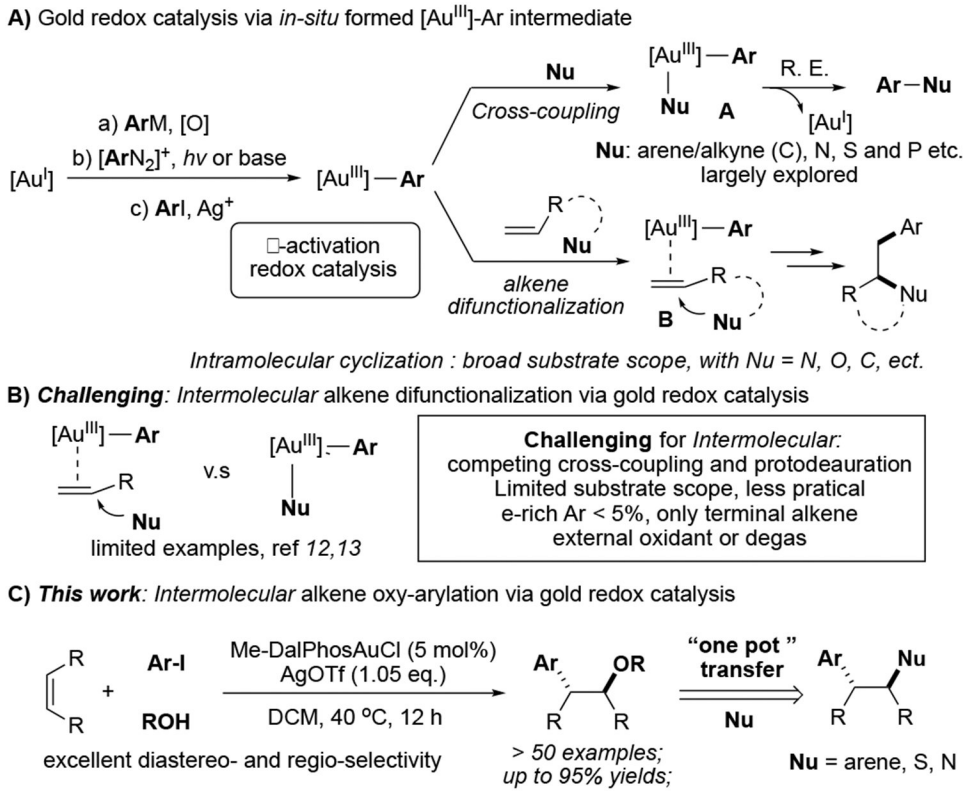


Figure 2.
Synthetic utility of the products.

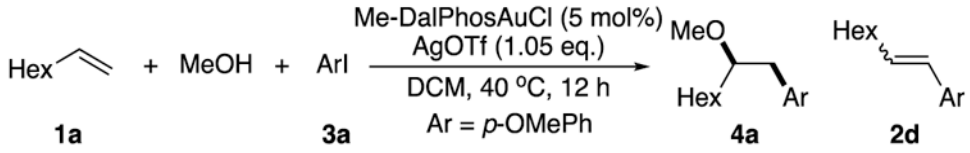


Scheme 1.

Alkene difunctionalization via gold redox catalysis.

Table 1.

Optimization of reaction conditions[a][b]



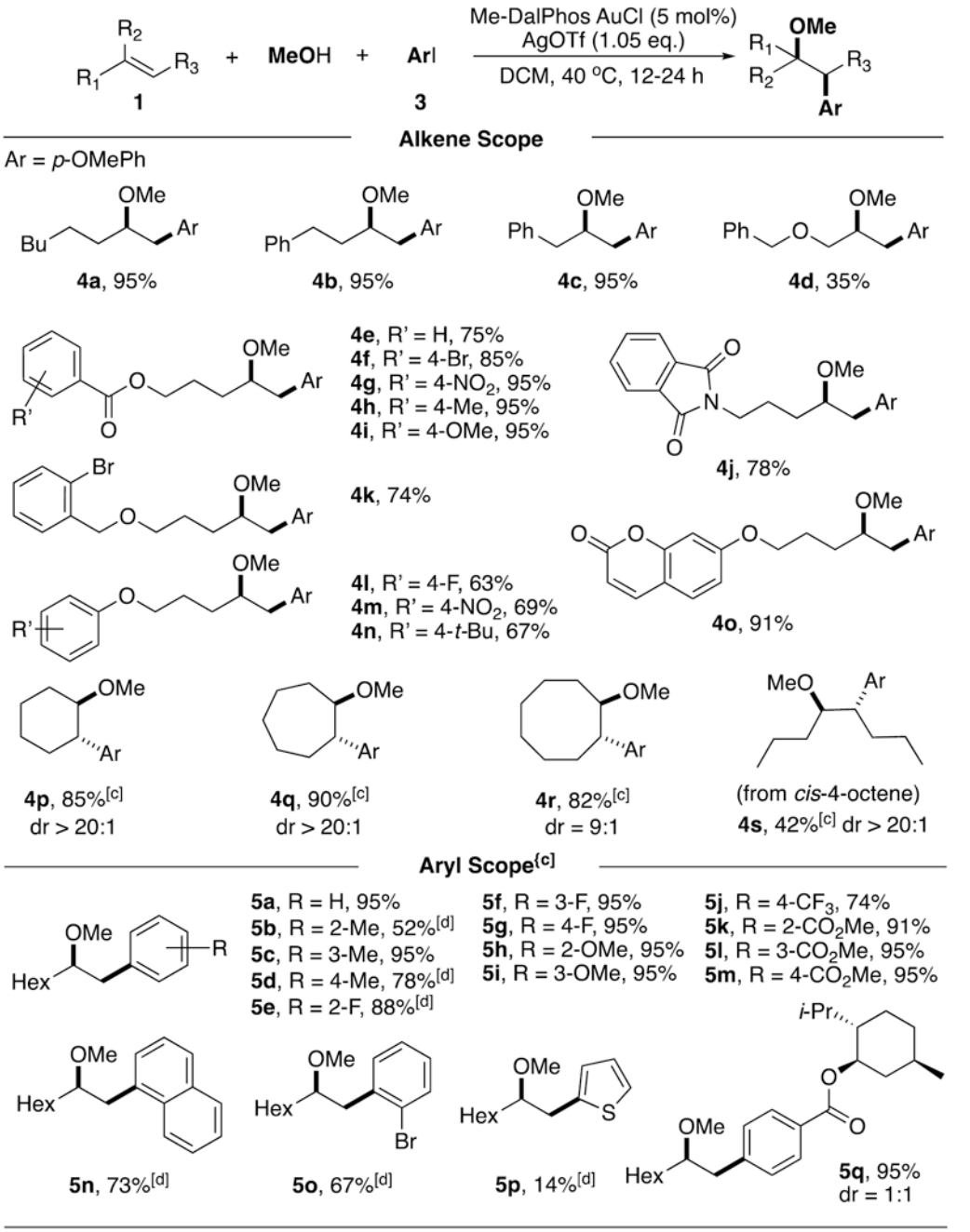
Entry	Variation from "standard conditions"	conv. (3a)	4a	2d
1	none	100%	95% (93%)	<5%
2	$AgSbF_6$	100%	73%	25%
3	60 °C	100%	65%	30%
4	rt	20%	15%	<5%
5	DCB as solvent	100%	89%	10%
6	MeOH as solvent	50%	45%	<5%
7	Add 1 eq. K_3PO_4	100%	87%	10%
8	Add 1 eq. KOAc	<5%	0%	0%
9	Mor-DalphosAuCl 5 mol%	20%	15%	<5%
10	No [Au]	0%	-	-
11	No [Ag]	0%	-	-
12	No ArI	No conversion on **1a**		
13	$dppm(AuBr)_2$ 10 mol%, $ArB(OH)_2$, Selectfluor, MeCN/MeOH, 50 °C	20%		
14	PPh_3AuCl 10 mol%, ArN_2BF_4, [Ir] cat. MeOH, rt, *hv*	0%		

[a]Conditions: **1a** (0.4 mmol), MeOH (0.6 mmol), **3a** (0.2 mmol), Au cat. (0.01 mmol), AgOTf (0.21 mmol), DCM (2 mL), 40 °C, 12 h.

[b]^{1}H NMR yields using 1,3,5-tribromobenzene as an internal standard (isolated yields).

Table 2.

Substrate scope for alkene and aryl iodide [a][b]



[a]Conditions: **1** (0.4 mmol), MeOH (0.6 mmol), **3a** (0.2 mmol), Au cat. (0.01 mmol), AgOTf (0.21 mmol), DCM (2 mL), 40 °C.

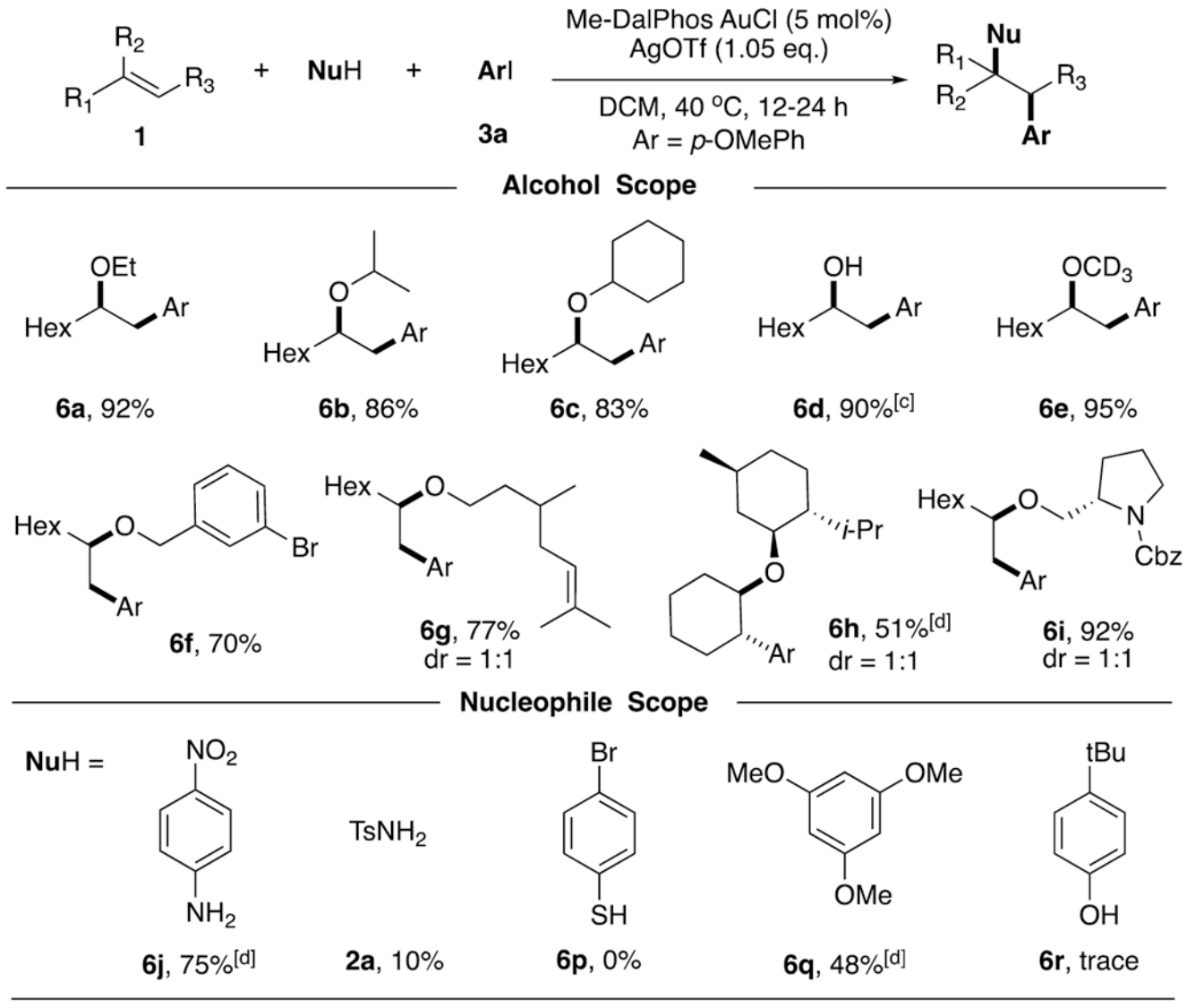
[b]isolated yields.

[c]use DCM:MeOH = 1:1 (0.5 M) as solvent instead.

[d] 60 °C and DCE instead.

Table 3.

Substrate scope for alcohol and nucleophiles. [a][b]



[a]Conditions: **1** (0.4 mmol), NuH (0.6 mmol), **3a** (0.2 mmol), Au cat. (0.01 mmol), AgOTf (0.21 mmol), DCM (2 mL), 40 °C.

[b]isolated yields.

[c]10 eq. of NuH instead.

[d]0.5 M DCM instead.