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Dynamic Kinetic Cross-Electrophile Arylation of Benzyl Alcohols by Nickel Catalysis

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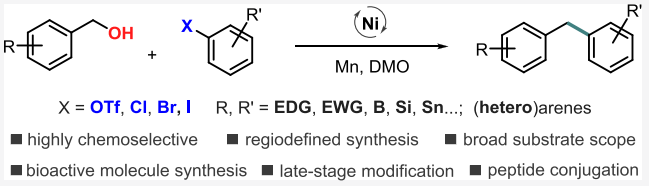
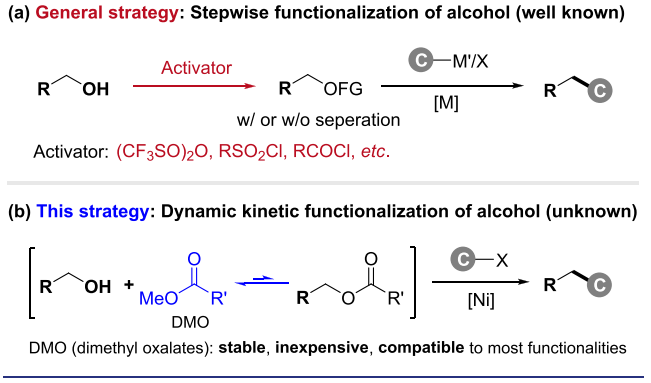
ABSTRACT: Catalytic transformation of alcohols via metal-catalyzed cross-coupling reactions is very important, but it typically relies on a multistep procedure. We here report a dynamic kinetic cross-coupling approach for the direct functionalization of alcohols. The feasibility of this strategy is demonstrated by a nickel-catalyzed cross-electrophile arylation reaction of benzyl alcohols with (hetero)aryl electrophiles. The reaction proceeds with a broad substrate scope of both coupling partners. The electron-rich, electron-poor, and ortho-/meta-/para-substituted (hetero)aryl electrophiles (e.g., Ar−OTf, Ar−I, Ar−Br, and inert Ar−Cl) all coupled well. Most of the functionalities, including aldehyde, ketone, amide, ester, nitrile, sulfone, furan, thiophene, benzothiophene, pyridine, quinolone, Ar−$SiMe_3$, Ar−Bpin, and Ar−$SnBu_3$, were tolerated. The dynamic nature of this method enables the direct arylation of benzylic alcohol in the presence of various nucleophilic groups, including nonactivated primary/secondary/tertiary alcohols, phenols, and free indoles. It thus offers a robust alternative to existing methods for the precise construction of diarylmethanes. The synthetic utility of the method was demonstrated by a concise synthesis of biologically active molecules and by its application to peptide modification and conjugation. Preliminary mechanistic studies revealed that the reaction of in situ formed benzyl oxalates with nickel, possibly via a radical process, is an initial step in the reaction with aryl electrophiles.



1. INTRODUCTION

Alcohols are among the most accessible and versatile organic compounds. Among the various approaches that can be used to transform them into valuable chemicals, the transition-metal-catalyzed cross-coupling based on C−O cleavage has become an essential tool.[1] Studies in this field have led to numerous useful transformations for the couplings of C−O electrophiles with nucleophilic species (e.g., R−MgX, R_2Zn, R−B).[1] There are also several reports describing the coupling of them with electrophiles.[2,3] In general, these processes require multistep operations, albeit a few sequential one-pot protocols were realized (Scheme 1a).[4] Moreover, they rely on highly reactive activators, such as $(CF_3SO)_2O$, RSO_2Cl, and RCOCl, which are sensitive to H_2O and nucleophilic functionalities.[5] Consequently, new coupling technologies for the direct functionalization of alcohols are still desirable and could have a substantial impact on organic synthesis.[6] Herein, we report a dynamic kinetic strategy that offers a straightforward and highly functional-group-tolerant approach to functionalize alcohols (Scheme 1b). The success of this effort hinged on the use of dimethyl oxalate (DMO) as an activator, which is relatively stable, easy to handle, and inexpensive[7] and is compatible with most functionalities. This reagent undergoes equilibrium reaction with alcohols, and the formed alkyl oxalates can participate in coupling reactions while generating.[8] The feasibility of this strategy was demonstrated by the nickel-catalyzed cross-electrophile deoxyarylation reaction of benzyl alcohols with aryl electrophiles.

Scheme 1. Strategies for Functionalization of Alcohols by Cross-Coupling Reactions



Diarylmethanes are ubiquitous structural motifs in a substantial number of pharmaceuticals and functional organic materials.[9] Among the various synthesis methods, described in representative publications,[10−13] the catalytic arylation of

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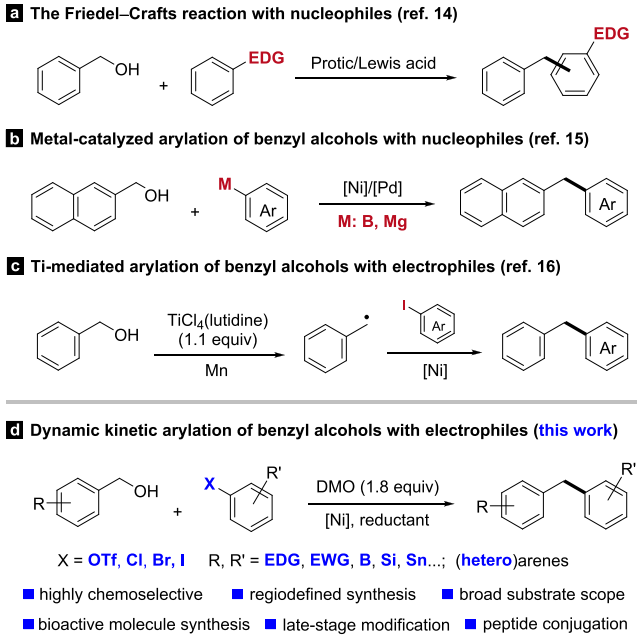
benzyl alcohols is of great interest. To date, approaches to enable this transformation have been restricted to the Friedel–Crafts reactions (Scheme 2a).[14] These methods have

Scheme 2. Synthesis of Diarylmethanes from Benzyl Alcohols



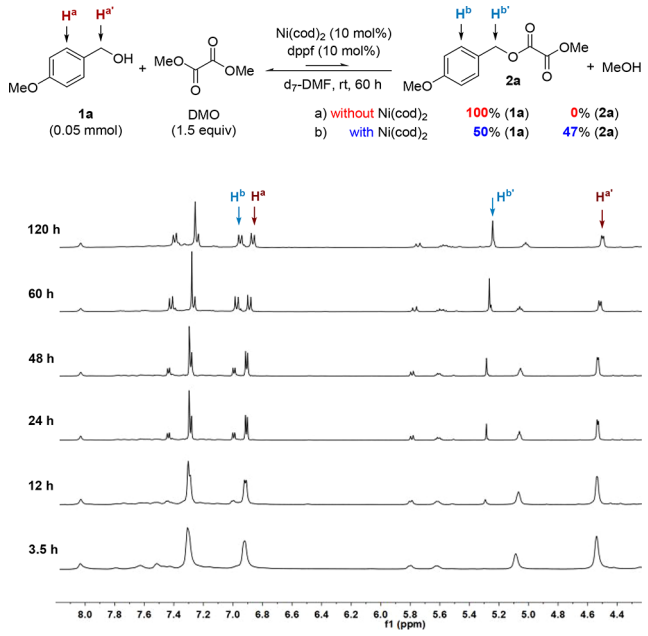
significantly advanced over the past years; however, expanding the scope to electron-poor arenes and achieving regiodefined synthesis remain substantial challenges. The transition-metal-catalyzed cross-couplings can be a powerful alternative, but they remain largely unexplored. There are only a few elegant studies that have achieved the arylation of benzyl alcohols by using Grignard reagents and aryl boroxines (Scheme 2b).[15] One elegant work has documented the cross-electrophile arylation of benzyl alcohols using aryl iodides.[16] In this study, a stoichiometric amount of low-valent titanium complex is required to activate alcohols to benzyl radicals,[17] and both Ar–Cl and Ar–OTf remain ineffective (Scheme 2c). Therefore, new protocols for the regiodefined synthesis of diarylmethanes from a broad range of benzyl alcohols and aryl fragments are still highly desirable. Here, we demonstrate a nickel-catalyzed dynamic kinetic cross-electrophile coupling to fulfill these requirements (Scheme 2d). The reaction is characterized by its mild conditions, broad substrate scope, excellent functional group compatibility, and unique chemoselectivity that is orthogonal to the existing methodologies. These features make our approach generic and applicable for the concise synthesis of biologically active compounds, the late-stage modification of complex molecules, and peptide conjugation. It thus could be considered as a good complementary to the existing methods.[10−16]

2. RESULTS AND DISCUSSION

2.1. Transesterification of Alcohol with DMO. Oxalates have proved to be powerful activating groups for the deoxygenative functionalization of alcohols.[18] Very recently, we and others disclosed that alkyl methyl oxalates are ideal coupling partners for catalytic alkylation reactions.[8] However, some of these reagents are moisture-sensitive and often suffer problems due to hydrolysis when exposed to silica gel chromatography.[19] Moreover, their synthesis requires methyl chlorooxalate, which is highly incompatible with the nucleophilic functionalities. We later wondered if alkyl methyl oxalates could be generated by transesterification between alcohols and unreactive DMO[20] and undergo in situ cross-coupling reactions.

With these considerations in mind, we investigated the possibility of the transesterification between benzyl alcohol **1a** (1.0 equiv) and DMO (1.5 equiv) in DMF-d_7. Our initial studies revealed that the reaction did not occur with the reagents themselves, or by Lewis acid catalysis (Scheme 3,

Scheme 3. Transesterification of 1a with DMO



condition a). Further studies revealed that the transesterification proceeded slowly in the presence of a nickel catalyst at room temperature, resulting in **2a** (yield 47%) after 60 h (Scheme 3, condition b). After this time, the ratio of **1a**/**2a** remained unchanged because of the facile transesterification between **2a** and methanol (Scheme S3 in the Supporting Information). Both Ni(0) and ligand were required for the process. The activation of oxalate **2a** via benzyl C–O cleavage was not observed at room temperature. The use of conventional esters (e.g., CH_3CO_2Et, $PhCO_2Me$, $PhCO_2{}^tBu$, $PhCO_2Ph$), instead of DMO, did not afford any transesterification products (Table S1).

2.2. Reaction Optimization. With these findings in hand, we then explored the cross-electrophile reaction of alcohol **1a** with triflate **3a** using a nickel catalyst (Table 1). After screening of a range of reaction conditions, we found that the combination of Ni(dppf)Cl_2 (10 mol %), dppf (10 mol %), phen (2 mol %), DMO (1.8 equiv), and Mn (3.0 equiv) in DMF at 80 °C gave the best result, affording **4a** in 79% isolated yield (entry 1). The reaction without additional dppf had a significantly decreased yield (entry 2). The presence of a nitrogen ligand usually has positive effects on the yield (entries 1, 3–8). The inferior results were obtained when other nickel sources were used (entries 9–11). The reaction with Zn as a reductant is highly ineffective (entry 12). In the absence of

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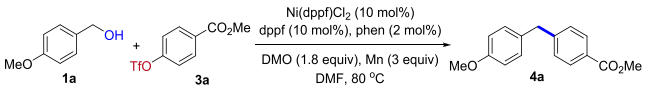
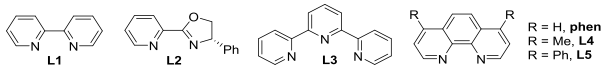
Table 1. Optimization of Reaction Conditions[a]



entry	variation from standard conditions	4a (%)[b]
1	none	82 (79)[c]
2	without dppf (10 mol %)	56
3	without phen (2 mol %)	60
4	**L1** instead of phen	72
5	**L2** instead of phen	68
6	**L3** instead of phen	50
7	**L4** instead of phen	72
8	**L5** instead of phen	68
9[d]	$Ni(cod)_2$ instead of $Ni(dppf)Cl_2$	69
10[e]	$Ni(dppe)Cl_2$ instead of $Ni(dppf)Cl_2$	63
11[f]	$Ni(PPh_3)_2Cl_2$ instead of $Ni(dppf)Cl_2$	71
12	Zn instead of Mn	15
13	no Ni or Mn	0
14	no DMO	0



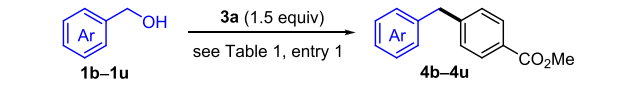
[a]Conditions A: $Ni(dppf)Cl_2$ (10 mol %), dppf (10 mol %), phen (2 mol %), DMO (1.8 equiv), and Mn (3.0 equiv) in DMF at 80 °C for 30 h. [b]**1a** (0.2 mmol) and **3a** (0.3 mmol) were used; the yields were determined by GC analysis with dodecane as internal standard. [c]Isolated yield. [d]dppf (20 mol %) was used. [e]dppe (10 mol %) was used instead of dppf. [f]PPh_3 (20 mol %) was used instead of dppf.

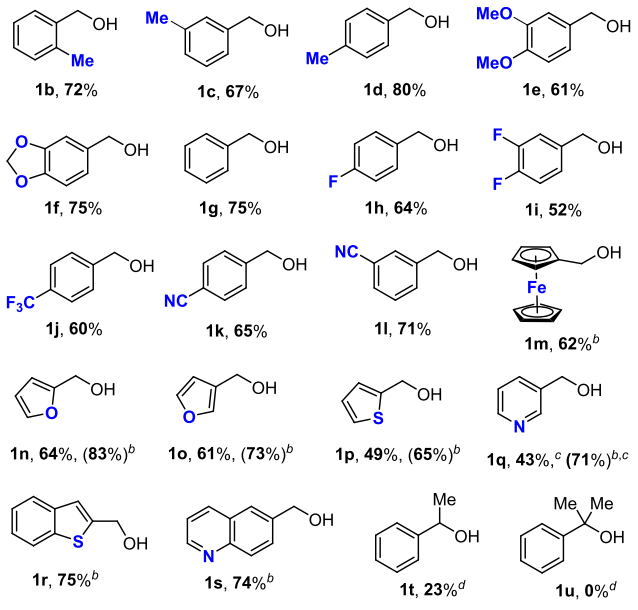
nickel catalyst, reductant, or DMO, no reaction was observed and the alcohol remained intact (entries 13 and 14).

2.3. Scope of the Reaction. The substrate scope of benzyl alcohols is demonstrated in Table 2. Benzyl alcohols, including unsubstituted (**1g**), electron-rich (**1b**–**1f**), and electron-poor (**1h**–**1l**) compounds, were coupled well to afford diarylmethanes in good yields. Substitution around the aromatic ring was tolerated (**1b**–**1d**). Functional groups such as aryl ethers (**1e**, **1f**), fluorides (**1h**, **1i**), trifluoromethyl group (**1j**), and nitriles (**1k**, **1l**) were compatible with the reaction conditions. The reaction of ferrocene-derived alcohol afforded the desired product in good yield (**1m**). The reactions of heterobenzylic alcohols, including furan (**1n**, **1o**), thiophene (**1p**), pyridine (**1q**), benzothiophene (**1r**), and quinolone (**1s**), afforded heteroaryl-containing diarylmethanes in good yields. The use of Lewis acid, $AlCl_3$ (10 mol %), improved the yields of desired products (e.g., **1n**–**1q**). Our studies revealed that $AlCl_3$ could slow down the transesterification of alcohols to form oxalates, and it also had a positive effect on the coupling of oxalates with aryl triflates (see below). The role of pyridine is currently unclear. We assume it may act as a ligand as realized in Gong's work.[21] At present, the reactions of secondary and tertiary alcohols were much less effective (**1t** and **1u**).

A wide range of aryl triflates reacted with **1a** to afford the coupling products with good to high yields (Table 3). Substituents at the para- (**3b**, **3c**, **3h**–**3j**), meta- (**3d**), and ortho-positions (**3e**, **3f**) were tolerated. The reaction with a sterically hindered substrate was effective (**3e**). Both electron-rich (**3b**–**3g**) and electron-poor (**3h**, **3j**) aryl triflates reacted efficiently. Functional groups such as ketone (**3h**), aryl fluoride (**3j**), free indole (**3k**), and alcohol (**3l**) were tolerated. *N*-Benzyl morpholine is an important motif found in various pharmaceuticals.[22] This moiety could be installed by coupling with benzyl alcohol (**3m**).

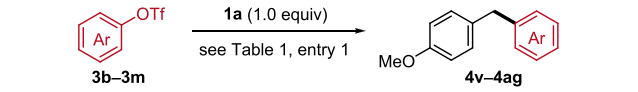
Table 2. Scope of Benzyl Alcohols[a]

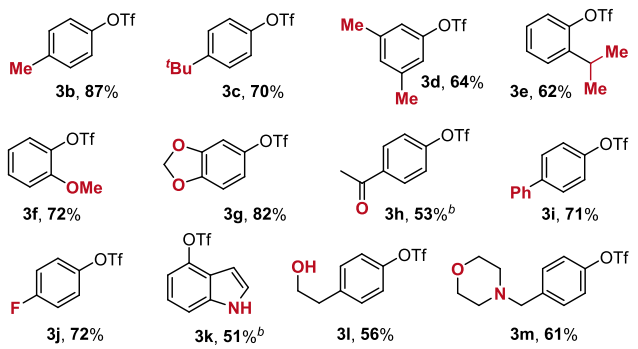




[a]**1b**–**1u** (0.2 mmol) and **3a** (0.3 mmol) were used; isolated yield. [b]Conditions B: $NiBr_2$(diglyme) (10 mol %), dppf (10 mol %), phen (10 mol %), pyridine (10 mol %), $AlCl_3$ (10 mol %), DMO (1.8 equiv), and Mn (3.0 equiv) in DMF at 80 °C for 30 h. [c]The reaction was performed at 100 °C. [d]4-(MeO)PhOTf (0.3 mmol) was used.

Table 3. Scope of Aryl Triflates[a]





[a]**1a** (0.2 mmol) and **3b**–**3m** (0.3 mmol) were used; the reaction time was 30 h; isolated yield. [b]Conditions B in Table 2.

Aryl chlorides are among the most attractive aryl electrophiles because of their low cost and the wide diversity of available compounds. While their application in cross-couplings has received ongoing attention over the past decades,[23] the cross-electrophile reaction using aryl chlorides remains largely unexplored.[24] We then studied the reactions of **1a** with aryl chlorides to investigate the potential of our method for the utilization of these promising, but challenging, substrates (Table 4). Electron-neutral (**5a**), electron-rich (**5b**, **5c**, **5g**), and electron-poor (**5d**–**5f**) aryl chlorides all coupled

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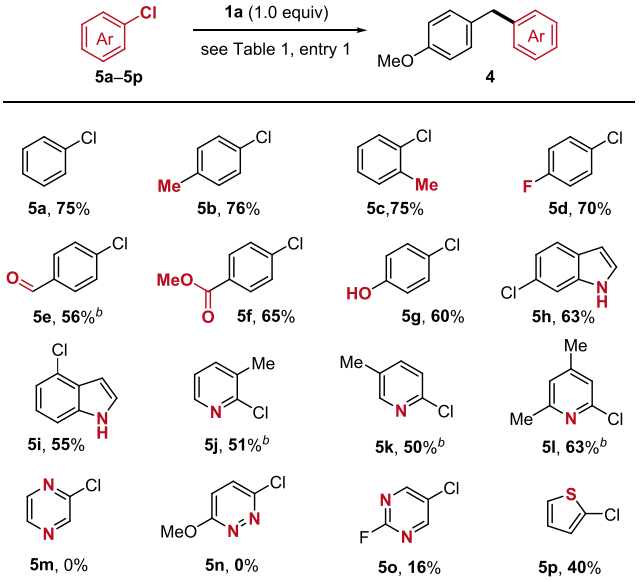
Table 4. Reactions of Aryl Chlorides 5 with Alcohol 1a[a]



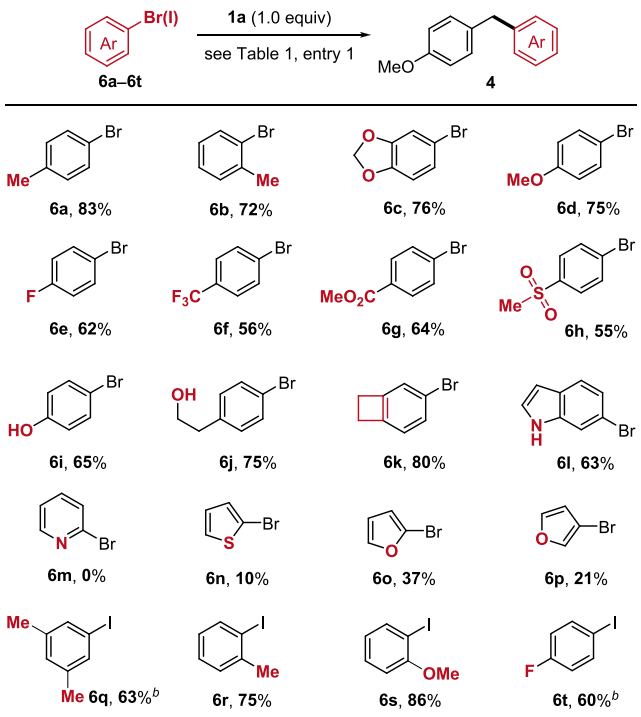
[a]**1a** (0.2 mmol) and **5a–5p** (0.3 mmol) were used; the reaction time was 30 h; isolated yield. [b]$AlCl_3$ (10 mol %) was added.

well, resulting in the diarylmethanes with moderate to good yields. While the pinacol coupling of aldehydes by reductive nickel catalysis was reported,[25] aryl chloride **5e** was selectively functionalized under our conditions. The presence of an aryl ester was tolerated (**5f**). Nucleophilic aryl species were selectively functionalized, thus enabling the nucleophilic functionalities such as phenol (**5g**) and indoles (**5h**, **5i**) to be available for additional transformation. The reactions with substituted 2-chloro-pyridines were effective (**5j–5l**). The reactions of pyrazine, pyridazine, and pyrimidine chlorides afforded no or low yield of desired products (**5m–5o**). A moderate yield of coupling product was obtained when 2-chlorothiophene was used (**5p**).

In general, the cross-electrophile reaction requires the coupling partners to be orthogonally paired in reactivity. However, our method proved to be less sensitive to the reactivity of aryl halides. Besides inert aryl chlorides, reactive substrates such as aryl bromides and iodides coupled efficiently with benzyl alcohol **1a** (Table 5). Both electron-rich (**6a–6d**, **6q–6s**) and electron-poor (**6e–6h**, **6t**) aryl halides were tolerated. The reaction is highly selective for the functionalization of aryl halides, leaving a number of functionalities intact, e.g., aryl ether (**6c**, **6d**, **6s**), aryl fluoride (**6e**, **6t**), trifluoromethyl group (**6f**), ester (**6g**), sulfone (**6h**), phenol (**6i**), alcohol (**6j**), strained four-membered ring (**6k**), and free indole (**6l**). 2-Bromopyridines and 2-bromothiophene gave no or low yield of coupling product (**6m** and **6n**), albeit their chloride substrates coupled well (Table 4, **5j–5l**, **5p**). The use of furanyl bromides gave synthetic useful yields of desired products (**6o** and **6p**).

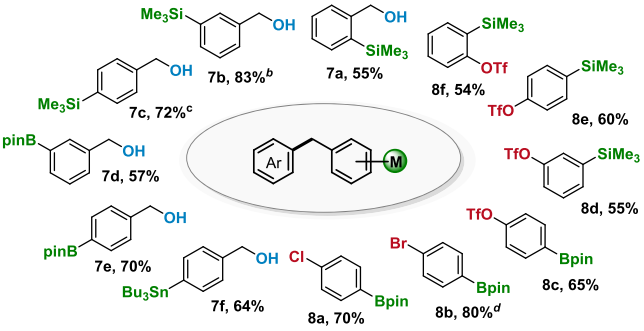
Aryl organometallic reagents have found broad application in cross-couplings, including the Hiyama reaction (Ar–Si), the Suzuki–Miyaura reaction (Ar–B), and the Stille reaction (Ar–Sn).[1] Our method has demonstrated a unique selectivity that is orthogonal to the conventional cross-couplings, thus enabling Ar–M to be available for further functionalization (Scheme 4). For example, the reaction is highly selective for the arylation of alcohols, leaving Ar–$SiMe_3$ (**7a–7c**), Ar–Bpin (**7d**, **7e**), and

Table 5. Reactions of Aryl Bromides and Iodides with Alcohol 1a[a]



[a]**1a** (0.2 mmol) and **6a–6t** (0.3 mmol) were used; the reaction time was 30 h; isolated yield. [b]The reaction was performed at 70 °C.

Scheme 4. Synthesis of Metal-Substituted Diarylmethanes[a]



[a]Standard conditions, **3a** (0.3 mmol) was used for reactions with alcohols **7a–7f** (0.2 mmol), **1a** (0.2 mmol) was used for reactions with aryl electrophiles **8a–8f** (0.3 mmol); isolated yield. [b]5 Å MS (30 mg) was added. [c]3 Å MS (30 mg) was added. [d]Concentration is 0.4 M.

Ar–$SnBu_3$ (**7f**) intact. Metallo groups at the ortho- (**7a**), meta- (**7b**, **7d**), and para-positions (**7c**, **7e**, **7f**) were tolerated. Similar results were obtained when boron-substituted (**8a–8c**) and silyl-substituted (**8d–8f**) aryl electrophiles were employed.

The conventional coupling reactions generally require the additional step for preactivation of alcohols (Scheme 1a). When polynucleophilic alcohols are employed, this process not only needs multiple protection/deprotection operations but also suffers from the selectivity challenge. By contrast, the dynamic kinetic strategy is based on the equilibrium reaction. It allows for the direct arylation of the benzylic alcohol in the presence of other nucleophilic groups (Table 6). For example, the reactions were highly selective for the arylation of benzylic alcohols over nonactivated primary and secondary alcohols,

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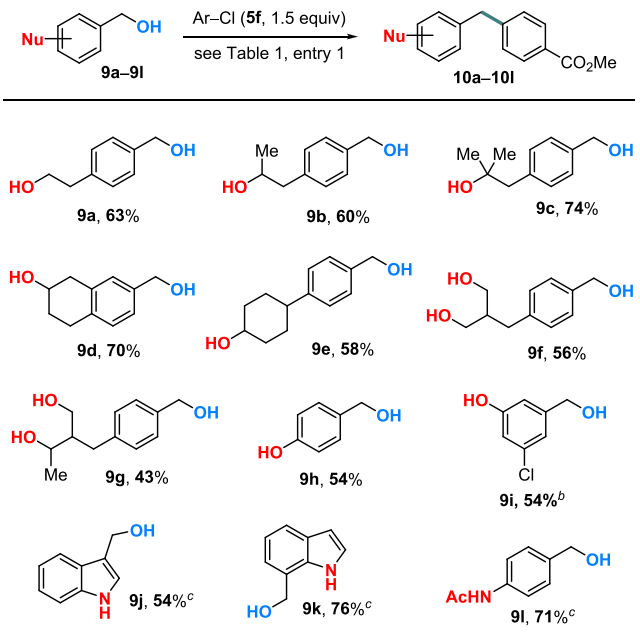
Table 6. Direct Arylation of Benzylic Alcohols of Polynucleophilic Substrates[a]



[a]**9a–9l** (0.2 mmol) and **5f** (0.3 mmol) were used; DMO (0.3 mmol) was used for **9a–9g**; isolated yield. [b]ArBr **6d** (0.3 mmol) was used. [c]Conditions B in Table 2 and ArOTf **3a** (0.3 mmol) were used.

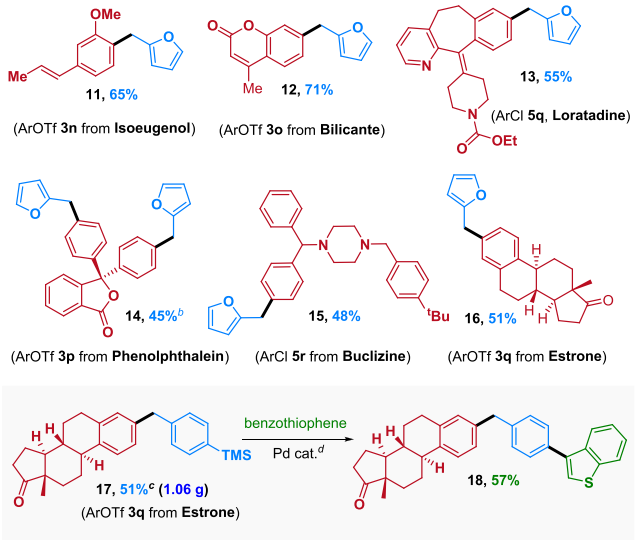
although they all underwent the transesterification with DMO (**9a**, **9b**, **9d–9g**). Only a trace of R–Oxa was detected at the end of the reactions, where the R–O moiety derived from non-benzylic alcohols. The high selectivity was also realized when the tertiary alcohol substrate **9c** was employed. Both cyclic/acyclic alcohols (**9a–9e**) and polyalcohols (**9f** and **9g**) were tolerated. The presence of phenol (**9h** and **9i**), indole (**9j** and **9k**), and amide (**9l**) groups was tolerated, and they did not result in the oxalate protection.

2.4. Synthetic Application. Heteroaryl-containing diarylmethanes are ubiquitous substructures found in various biologically active molecules.[26] Potentially, the construction of these structural units in complex molecules could be achieved by the coupling of complex aryl electrophiles with heterobenzylic species.[12,13] However, the task will be very challenging when electron-rich heterobenzylic substrates are employed. First, as noted by Zhang et al.,[27] the stability and reactivity issues associated with electron-rich heterobenzylic halides would restrict their application on the cross-couplings. Second, the synthesis of their organometallic reagents is very difficult.[28] Therefore, to our knowledge, there has been no report on the coupling of electrophiles with 2-furan/3-pyridine methyl species. Herein, we demonstrate that the dynamic kinetic method offers a practical solution to address this problem, which allows for reactive benzylic oxalate to participate in the coupling while generating in situ. It thus established a method capable of incorporation of a 2-furan methyl group into biologically active molecules (Scheme 5), of concise synthesis of pharmaceutical compounds (Scheme 6), and of peptide modification and conjugation (Scheme 7), which are challenging issues for the literature methods.[10−16]

The phenol and chloroarene are frequently found in biologically active compounds. Our method provides an approach to transfer them into diarylmethanes (Scheme 5). For example, aryl triflates derived from isoeugenol (**11**), bilicante (**12**), phenolphthalein (**14**), and estrone (**16**) could be selectively functionalized to 2-benzylfuran compounds under our conditions. Loratadine (**13**) and buclizine (**15**) were coupled with 2-furanmethanol efficiently. The use of a metallosubstrate enables multistep modification. For example, the reaction of estrone-derived aryl triflate with 4-silyl-benzyl alcohol afforded **17** in 51% yield (1.06 g), which could further react with benzothiophene to afford compound **18**.

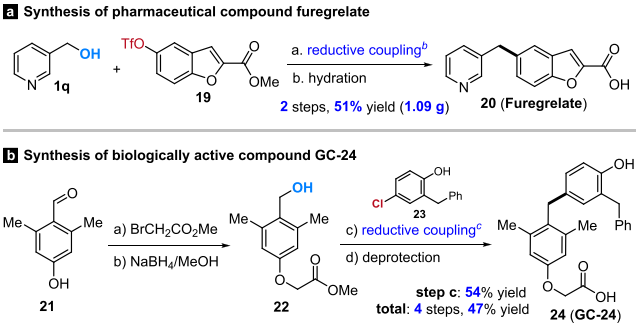
The utility of this method was further demonstrated by a concise synthesis of pharmaceutical and biologically active compounds. Furegrelate is a potent inhibitor of thromboxane synthase.[29] With reductive cross-coupling, furegrelate was accessed in two steps from alcohol **1q** and triflate **19** with a 51% yield on a gram scale (Scheme 6a). Our attempt to produce this compound by some reported coupling methods

Scheme 5. Modification of Biologically Active Compounds[a]



[a]Conditions B in Table 2; aryl electrophiles (0.2 mmol) and alcohol **1n** (0.4 mmol); 4,4′-dimethyl-2,2′-bipyridine (10 mol %) was used instead of phen; isolated yields. [b]Aryl electrophiles (0.1 mmol) and alcohol **1n** (0.4 mmol) were used. [c]Conditions A in Table 1; ArOTf **3q** (5 mmol), alcohol **7c** (7.5 mmol), and 3 Å MS (200 mg) were used; the reaction time was 40 h. [d]See the Supporting Information for reaction conditions.

Scheme 6. Concise Synthesis of Pharmaceutical and Biologically Active Compounds[a]



[a]See the Supporting Information for detailed reaction conditions and procedures. [b]Conditions B in Table 2; Alcohol **1q** (16 mmol) and **19** (8 mmol) were used; the reaction time was 40 h. [c]Alcohol **22** (0.2 mmol), **23** (0.4 mmol), $NiCl_2$(dppf) (20 mol %), 4,5-diazafluoren-9-one (20 mol %), DMO (2.0 equiv), Mn (4.0 equiv) were used.

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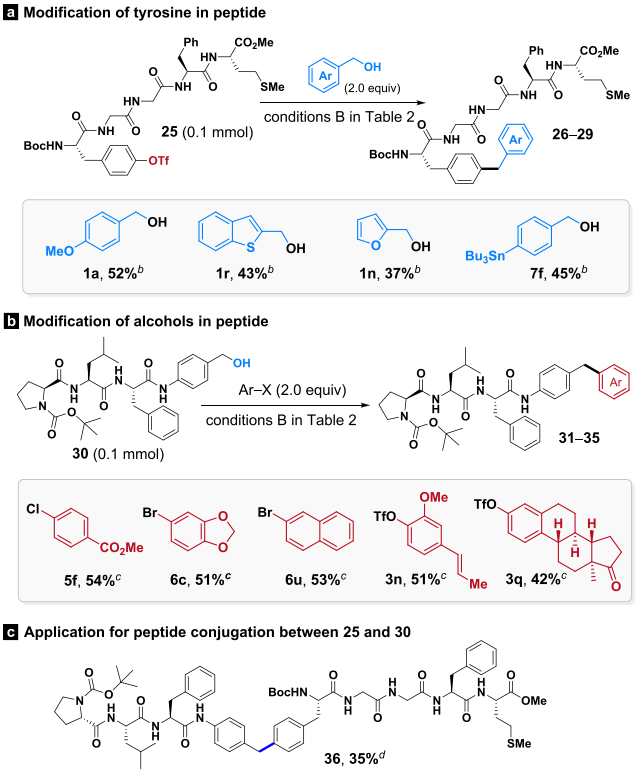
Scheme 7. Application in Peptide Modification and Conjugation[a]



[a]Conditions B in Table 2; the reaction time was 40 h; isolated yield. [b]**25** (0.1 mmol) and **1a**, **1r**, **1n**, **7f** (0.2 mmol) were used. [c]**30** (0.1 mmol) and **5f**, **6c**, **6u**, **3n**, **3q** (0.2 mmol) were used. [d]**25** (0.1 mmol) and **30** (0.1 mmol) were used; the reaction time was 45 h.

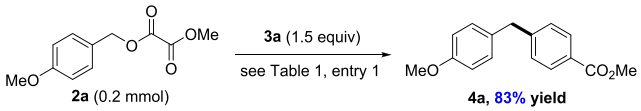
was unsuccessful (Scheme S1). GC-24, an agonist for the human thyroid hormone receptor, is a potential agent for the treatment of obesity and arteriosclerosis.[30] The presently most concise approach to produce this compound relies on a 10-step synthesis.[11d] With our method, the synthesis of GC-24 was accomplished in four steps, with the cross-electrophile coupling as the key step (Scheme 6b).

The late-stage modification of peptides has emerged as a significant task of current interest.[31] Tyrosine is a natural amino acid found in almost all proteins. Although significant progress has been made in the catalytic diversification of tyrosine in peptides, the modification via Csp^2–Csp^3 bond formation remains a challenge.[32] Meanwhile, unlike the conventional cross-couplings, the cross-electrophile reaction for peptide modification has seldom been investigated.[33]

We recently reported a reductive nickel catalysis for the installation of an alkyl group at tyrosine in peptides.[3h] However, the reactions with benzylic substrates were unsuccessful. We demonstrate here that the dynamic kinetic method can be an alternative approach for this purpose. For instance, the peptide met-enkephalin (Tyr-Gly-Gly-Phe-Met) **25** has important biological activity, and its structural diversification is very important.[34] With our method, the benzyl group could be selectively installed at the tyrosine position. Various benzyl alcohols, including aryl (**1a**), heteroaryl (**1r**, **1n**), and metalloaryl (**7f**) compounds, were tolerated (Scheme 7a). No racemization at the stereogenic centers of the product was observed.[35] On the other hand, peptide **30** could be selectively arylated with aryl chloride (**5f**), bromide (**6c**, **6u**), and triflate (**3n**, **3q**), and the biologically active compounds (**3n**, **3q**) could be attached (Scheme 7b). Moreover, this method has shown the potential application of peptide conjugation. For example, met-enkephalin **25** and peptide **30** were selectively conjugated under the reductive conditions, affording peptide **36** in a useful yield (Scheme 7c).

2.5. Mechanistic Investigation. In the absence of DMO, the reaction of alcohol **1a** with **3a** did not afford any desired product, and alcohol **1a** was recovered quantitatively (Table 1, entry 14). The transesterification of **1a** with DMO proceeded smoothly under nickel catalysis (Scheme 3). Moreover, under the standard conditions without DMO, the reaction of oxalate **2a** with triflate **3a** afforded coupling product **4a** in 83% yield (Scheme 8). These results suggest a pathway that may involve the formation of benzyl oxalate.

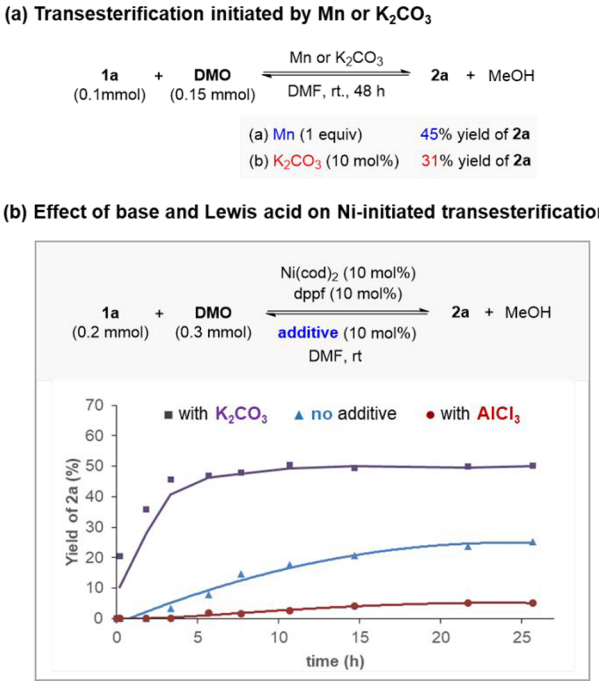
Scheme 8. Reaction of Oxalate 2a with 3a[a]



[a]Conditions A in Table 1, but DMO was not used.

2.5.1. Transesterification. Utley and co-workers have found that the transesterification of alcohol and oxalate could be catalyzed by in situ electrogenerated base.[36] To reveal whether a similar process was involved in our catalytic system, several control experiments were performed. In addition to Ni(0), the transesterification of alcohol **1a** and DMO proceeded well either in the presence of Mn (1.0 equiv) or of K_2CO_3 (10 mol %), affording **2a** in 45% and 31% yield, respectively (Scheme 9a). Moreover, monitoring of the progress of the reaction clearly showed that the transesterification was significantly accelerated by adding K_2CO_3 (10 mol %), but it was strongly

Scheme 9. Experimental Insight into the Transesterification Process



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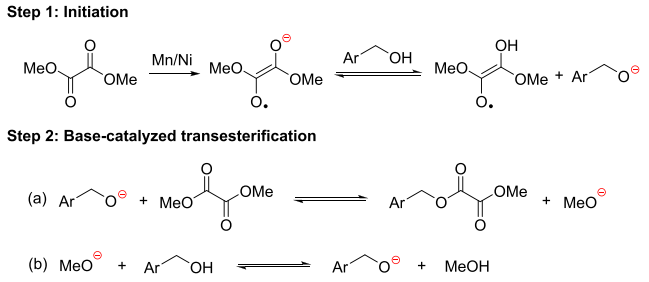
inhibited by the use of $AlCl_3$ (10 mol %) (Scheme 9b). These results suggest the transesterification process is likely to be catalyzed by base generating in situ.

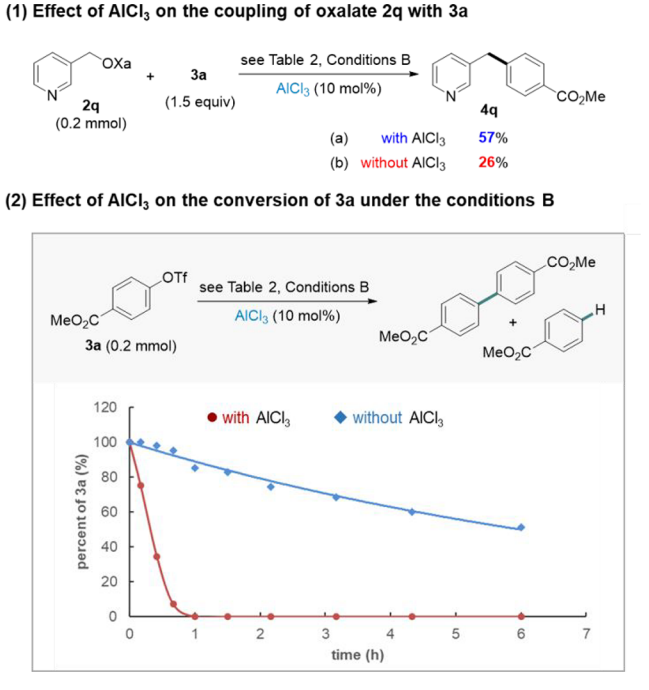
On the basis of the above results, a plausible pathway for the transesterification process is outlined in Scheme 10, which is analogous to the proposal for electrocatalysis.[36] Initiation step: In the presence of reducing reagent, DMO undergoes a single-electron reduction with Mn/Ni(0) to afford radical anion intermediate. The following proton exchange process gives alcohol anions. Base-catalyzed transesterification: the proposed pathway is shown in step 2, which involves alkaline transesterification and benzyl alcohol anion regeneration processes.

Scheme 10. Proposed Transesterification Mechanism



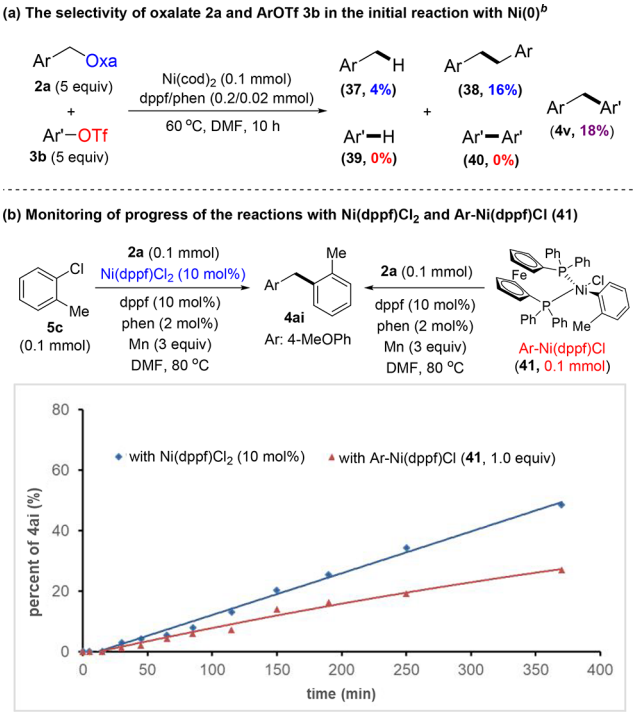
2.5.2. Role of $AlCl_3$. When heterobenzylic alcohols were employed, the addition of $AlCl_3$ (10 mol %) improved the yields of desired products (e.g., **1n**−**1q** in Table 2). The results in Scheme 9b show that $AlCl_3$ could slow down the transesterification of alcohols to form oxalates. The control experiments in Scheme 11, part 1, reveal that it has a positive effect on the coupling of oxalate **2q** with triflate **3a**, improving the yield of the cross-product **4q**. This might be due to it enhancing the reactivity of aryl triflate (Scheme 11, part 2). Taken together, because heterobenzylic oxalate is more reactive, $AlCl_3$ both lowering the concentration of oxalates and enhancing the reactivity of aryl triflates may help to improve the selectivity for the cross-product.[37]

Scheme 11. Effect of $AlCl_3$



2.5.3. Nickel-Catalyzed Cross-Coupling of Aryl Electrophiles with Benzyl Oxalates. Both benzyl oxalate and aryl electrophile will react with Ni(0) to give benzyl−Ni^{II}(L)X and Ar−Ni^{II}(L)X intermediates. To determine which intermediate is formed first, we studied the relative reactivity of oxalate **2a** and aryl triflate **3b** with Ni(0) (Scheme 12a).[38] We found that 3 times more **2a** than **3b** was consumed when 5 equiv of them was subjected to Ni(0) for 10 h. Meanwhile, dimer **38** from oxalate was a major component, but no byproduct from aryl triflate was observed. These results are consistent with a pathway in which benzyl oxalate might react with nickel first.

Scheme 12. Experiments to Reveal if Benzyl Oxalate or Aryl Electrophile Reacts with Nickel First



[a]The yields were determined by GC analysis with dodecane as internal standard. [b]Yield with respect to the amount of Ni(0).

To further confirm this assumption, complex Ar−Ni^{II}(dppf)Cl **41** was synthesized from the reaction of Ni(cod)$_2$/dppf with Ar−Cl. We would expect that, if the reaction begins with Ar−Cl, the initial rate of reaction with Ar−Ni^{II}(dppf)Cl **41** (1.0 equiv) would be faster than that of the reaction catalyzed by Ni(dppf)Cl_2 (10 mol %).[6g] However, the result in Scheme 12b is opposite to what we expected. This result further confirms that the reaction of benzyl oxalate with nickel is an initial step in the reaction with aryl electrophiles.

Most of oxalate **2a** was converted to dimer **38** under the standard conditions without DMO (Scheme 13, part 1, condition a). To determine whether benzyl oxalate was activated via a radical process, several experiments were conducted. (1) Hantzsch ester (HE) is a hydrogen atom donor capable of trapping carbon radicals, and it has been widely applied for detecting radical intermediates.[39] In the presence of HE (1 equiv), the formation of dimer **38** was inhibited,

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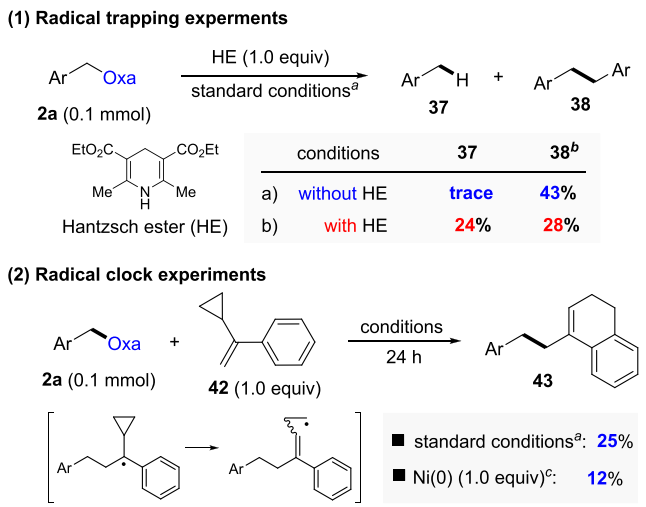
Scheme 13. Radical Trapping and Radical Clock Experiments

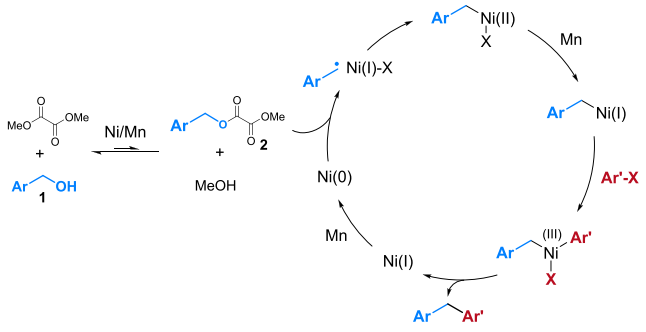


[a]Standard conditions in Table 1, but DMO was not used. [b]The theoretical yield is 50%. [c]$Ni(cod)_2$ (1.0 equiv), dppf (1.0 equiv), phen (20 mol %) were used.

whereas a significant increase in benzyl−H **37** was observed (Scheme 13, part 1, condition b). (2) α-Cyclopropylstyrene **42** is a well-known radical clock substrate probe.[40] The reaction of **2a** with α-cyclopropylstyrene **42** afforded the ring-expanded product **43** either under the standard conditions or in the presence of [$Ni(cod)_2$/dppf/phen] (Scheme 13, part 2). These results suggest that the benzyl oxalates might be activated by a nickel catalyst via a radical process.

On the basis of the above results and literature reports,[41] we tentatively propose a catalytic cycle as shown in Scheme 14.

Scheme 14. Proposed Reaction Mechanism



The nickel/manganese-catalyzed transesterification of alcohol with DMO affords benzyl oxalate **2**. The reaction of oxalate **2** with Ni(0), possibly via a radical process,[42] followed by reduction with Mn, would afford benzyl−Ni(I). The oxidative addition of benzyl−Ni(I) intermediate with aryl electrophiles, followed by reductive elimination, would afford the desired product.[43]

3. CONCLUSION

In summary, we have reported the first dynamic kinetic cross-electrophile reaction that enables the deoxyarylation of benzyl alcohols with aryl electrophiles. This protocol is distinguished by its broad substrate scope, excellent functional group compatibility, and the unique chemoselectivity that is orthogonal to the conventional cross-couplings. These features make our approach a very robust and powerful alternative to the existing methods for the regiodefined synthesis of biarylmethanes, which occur widely in pharmaceuticals and functional organic materials. The synthetic utility of this method was demonstrated by the modification of biologically active compounds, by concise synthesis of pharmaceuticals, and by its applications in peptide modification and conjugation. The success of this process is dependent on the finding of in situ activation of alcohols with DMO, which can be merged with the cross-coupling protocol. This work has established a new framework for deoxygenative functionalization of alcohols via the cross-coupling method. We thus anticipate our assay to be a starting point for more useful discoveries in these promising fields. Further expansion of the scope of the dynamic kinetic cross-electrophile reaction are ongoing in our laboratory.[44]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12462.

General information, experimental procedures, new compound characterization, spectroscopic data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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