Electrochemically driven Nickel-Catalyzed Enantioselective Reductive Conjugate (Hetero)Arylation of Enones

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Abstract

Herein, we report an electrochemical nickel-catalyzed enantioselective reductive conjugate (hetero)arylation of enones in an undivided cell with low-cost electrodes in the absence of external reductants and supporting electrolytes. Aryl bromides/iodides/triflates or vinyl bromides were employed as electrophilic reagents for the efficient preparation of more than 50 valuable β-arylated ketones in a simple manner (up to 97% yield, 97% ee). With the advantages of electrochemistry, excellent functional group tolerance and late-stage modification of complex natural products and pharmaceuticals made the established protocol greener and more economic. Mechanism investigation suggest that a Ni^{I}/Ni^{III} cycle is involved in this electro-reductive reaction rather than metal reductant driven Ni^{0}/Ni^{II} cycle. Overall, the efficient electrochemical activation and turnover of the nickel catalyst avoid the drawbacks posed by the employment of stoichiometric amount of sensitive metal powder reductants.

Introduction

Enantiopure β-arylated ketone, a structure motif frequently found in natural products, materials, pharmaceuticals (Fig. 1a), or agrochemicals, can normally be prepared by rhodium catalyzed asymmetric conjugate addition of Michael acceptors with aryl nucleophiles such as organocuprate or boron reagents which ultimately come from the corresponding readily available aryl halides.[1-8] Nickel catalysis has become a growing and empowering area of research over the past decade, providing new reactivity modes towards organic synthesis and have revolutionized synthetic strategies in pharmaceuticals and materials.[9-13] As early as the 1980s, Ronchi, Lebedev, Sustmann and Condon have reported zinc- or electrochemical-promoted nickel-catalyzed reductive conjugate addition of activated olefins with organic halides, respectively.[14-17] However, only Michael acceptors without β-substitution provide the corresponding products in high yields in those reports. In 2013, Weix and co-workers revealed a nickel-catalyzed reductive addition of aryl halides to enones *via* allylnickel species for the preparation of β-arylated ketone, which required the use of stoichiometric amount of trialkylsilyl chlorides and manganese powder (Fig. 1b).[18,19] Recently, Zhou and co-workers reported a metal

reductant driven Ni-catalyzed enantioselective reductive conjugate arylation of activated olefins and imines in the presence of super-stoichiometric manganese powder (Fig. 1c).[20,21] Despite the significant achievement of these preeminent work, there are still improving space as they rely on the use of super-stoichiometric sensitive, flammable and hazardous metal reductant, glove box and require more than one day to complete the transformation due to the slow turnover-limiting reduction of the Ni catalyst by metal reductant,[22,23] which somehow limit their practical application.

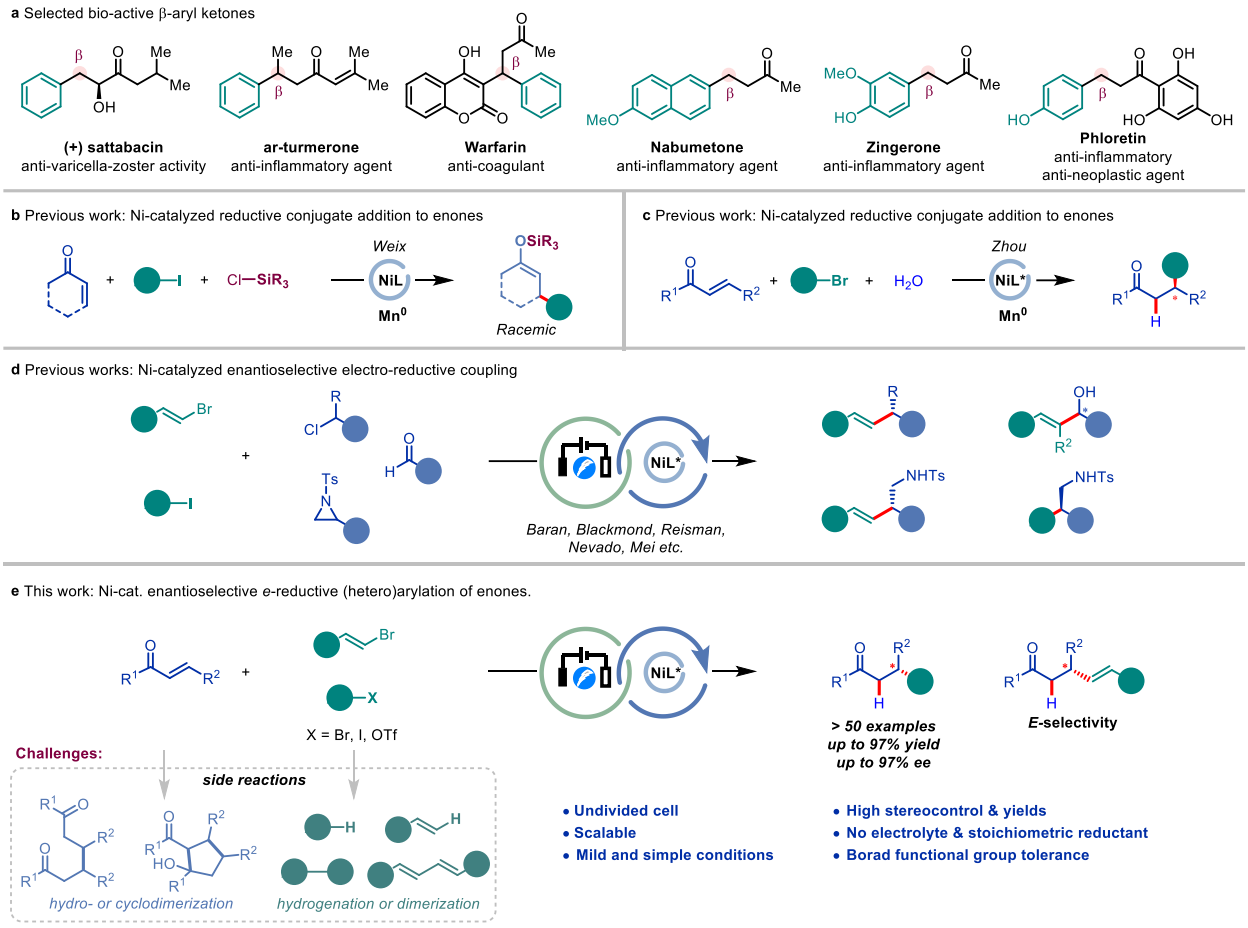


Fig. 1 | **a** Selected bio-active β-aryl ketones. **b-c** Previous reports of Ni-catalyzed reductive conjugate addition to enones. **d** Electrochemical enantioselective reductive cross-couplings. **e** This work and challenges.

Electrosynthesis, employing readily available electrical current as a sustainable and inherently safe redox reagent, achieving extreme oxidation or reduction capacity easily by varying the current or voltage, is recognized as a powerful and scalable methodology for organic synthesis.[24-48] With the renaissance of electrosynthesis, the asymmetric electrocatalysis involving anodic oxidation has made significant progress in recent years.[49-67] However, there are few research focus on the asymmetric electrochemical reductive reactions

(Fig. 1d).[68-75] In 1997, Durandetti and coworkers described the first example of asymmetric electro-reductive coupling (ERC) between α-chloro esters and aryl halides by using chiral auxiliaries.[68] In 2019, Reisman and coworkers reported a Ni/Box catalyzed enantioselective ERC of vinyl bromides and benzyl chlorides.[69] In 2020, Mei and coworkers developed a Ni/Pyrox catalyzed ERC of aryl bromides for the synthesis of biaryl atropisomers.[70] In 2021, Baran and coworkers described a Ni/Cr co-catalyzed electro-Nozaki-Hiyama-Kishi (*e*-NHK) coupling reaction for the synthesis of chiral alcohols.[71] In 2022, Cheng and coworkers developed a Pd-catalyzed asymmetric allylic 4-pyridinylation ERC reaction.[72] Mei and coworkers also reported a paired electrolysis-enabled nickel-catalyzed enantioselective ERC of aryl bromides and α-chloro esters.[73] Recently, Nevado group and Mei group demonstrated the nickel catalyzed enantioselective ERC of aziridines with vinyl bromides and aryl iodides, respectively.[74.75] These excellent studies lay the foundation of electrochemical nickel catalyzed enantioselective reductive coupling.

With our continued interest in developing novel electrosynthetic methodologies,[76-83] we envision the possibility of using powerful and scalable electrosynthesis to achieve the enantioselective reductive addition of aryl halides to enones (Fig. 1e). Notable features of this strategy include: a) using a simple undivided cell with readily available and low-cost stainless steel electrodes; b) avoiding the use of electrolyte and external base; c) mild and efficient electro-reductive conditions with good functional group compatibility and shorter reaction time compare to metal reductant; d) the adjustable reductive potential by replacing the stoichiometric reductant with electricity and enable the fast turnover of chiral nickel catalysts; e) scalable synthesis and late-stage modification of bio-relevant molecules. The successful conduction of this strategy relies on addressing the following significant challenges: First, the inhibition of side reactions such as the reductive hydro- or cyclodimerization of enones and the reductive hydrogenation or dimerization of aryl bromides during electrolysis.[70,84,85] Second, the perfect match of nickel catalyst and chiral ligand to achieve the wide substrate scopes, excellent catalysis effect and high enantioselectivities.[17,86-88]

Results and Discussion

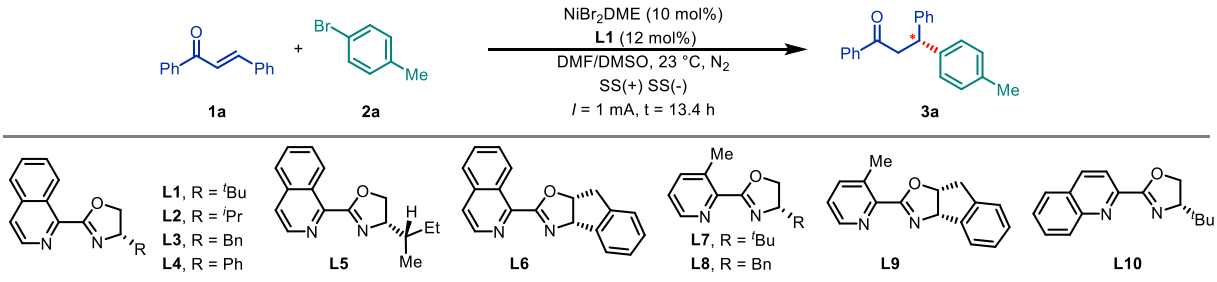
Reaction optimization

Initially, (*E*)-chalcone (**1a**) and 4-bromotoluene (**2a**) were selected as model substrates to identify the suitable reaction conditions. After extensive screening of conditions, electrolysis of a solution of **1a**, **2a**, $NiBr_2$DME, chiral isoquinox ligand **L1** in an undivided cell equipped with 304 stainless steel electrodes as anode and cathode under nitrogen atmosphere, afforded **3a** in 93% yield and 92% ee with 74% faraday efficiency (Table 1, entry 1). Other isoquinox ligand **L2-L6** with different side-arm group such as isopropyl, benzyl, phenyl, *sec*-butyl and

indanyl led to moderate yields (43-53%) and slightly lower stereoselectivity (68-85% ee), which indicated the *tert*-butyl group might be the best side-arm group (Table 1, entry 2). Other 3-methyl-pyridine ligands **L7-L9** gave slightly lower yield (54-66%) and enantioselectivities (60-82% ee) of **3a** (Table 1, entries 3-4).

The use of quinolinox ligand **L10** improved the stereoselectivity of **3a** to 94% along with 72% yield which is much higher than the result (23% yield, 90% ee) reported by Zhou with Mn as reductant (Table 1, entry 5). It may be that manganese powder is difficult to promote the turnover of **L10** coordinated nickel catalysts, while electro-protocol can easily promote this process by adjusting the reductive potential. Other chiral bisoxazoline and phenol-oxazoline ligands are not effective (see Supplementary Information). A slight decrease in the stereoselectivity or yield was observed when the reaction was performed under 1.5 mA for 9 h (98%, 86% ee) or 0.5 mA 26.8 h (90%, 92% ee) (Table 1, entries 6-7). In addition, only 45-50% yield of **3a** was obtained with DMF, DMAc, MeCN or DMSO as single solvent (Table 1, entry 8). It's not surprising that this ERC reaction does not occur in the air atmosphere (Table 1, entry 9). Trace amount of product **3a** was obtained when Zn and Ni foam was used in place of SS anode and cathode, respectively (Table 1, entry 10). Interestingly, when 4-iodotoluene was used to replace 4-bromotoluene, the reaction equipped with Zn anode and Ni foam cathode under 10 mA afford the desired product **3a** in 75% yield and 92% ee in 2 hours (Table 1, entry 11). While using iron electrode as anode, the reaction affords the similar yield and ee compared to SS anode (Table 1, entry 12). Considering the iron electrodes are prone to corrosion, the stainless steel electrodes are employed as anode in this protocol. To our delight, the desired product **3a** was efficiently synthesised (86%, 92% ee) after 6.7 hours of electrolysis when the reaction was carried out at 0.1 mmol scale (Table 1, entry 13). Those results further demonstrate the efficiency of electrochemical reduction compared to metal reductant (24 h).

Table 1 | *Optimization of the reaction conditions.*[a]



Entry	Variation from standard conditions	Yield(%)[b]	ee (%)[c]
1	none	93	92
2	**L2-L6** instead of **L1**	43-53	68-85

3	**L7** instead of **L1**	66	82
4	**L8-L9** instead of **L1**	54-55	60-70
5	**L10** instead of **L1**	72	94
6	*I* = 1.5 mA, 9 h	98	86
7	*I* = 0.5 mA, 26.8 h	90	92
8	DMF, DMAc, MeCN or DMSO as solvent	25-50	91-92
9	air	nr	--
10	Zn(+) Ni foam (-)	trace	--
11	Zn(+) Ni foam (-) with *p*-Tol-I, *I* = 10 mA, t = 2 h	75	92
12	Fe(+) Ni foam (-)	92	92
13	0.1 mmol scale, t = 6.7 h	86	92

[a] Reaction conditions. **1a** (0.2 mmol), **2a** (1.5 equiv.), $NiBr_2DME$ (10 mol%), Ligand (12 mol%), DMF/DMSO (1 mL/1 mL), N_2, under 1 mA constant current in an undivided cell at 23 °C for 13.4 h (Q = 2.5 F/mol, E_{cell} = 1-2 V) with 304 stainless steel as electrodes. [b] Isolated yield. [c] Enantioselectivities were determined by chiral HPLC analysis. SS, stainless steel. nr, no reaction.

Evaluation of substrate scopes

Having established the optimized reaction conditions, we sought to examine the generality of this transformation (Fig. 2). First, the scope of aryl bromide was explored with (*E*)-chalcone **1a** as Michael acceptor. The aryl bromides bearing both electron-donating groups (EDGs, methyl, methoxyl) or electron-withdrawing groups (EWGs, ester, acetyl) all gave the corresponding products **3a**-**3d** in good to excellent yields and ees. 2-Bromonaphthalene also afforded the desired product **3e** in 95% yield and 90% ee. The quinox ligand **L10** was chosen as chiral ligand when (*E*)-enone (**1b**) was employed as Michael acceptor. Considerable improvement of product yields and ees were achieved by the use of quinox ligand **L10** under our electro-conditions compare to Zhou's report. A wide range of aryl bromides bearing both EDGs (methyl **3f**, methylthio **3g**, phenyl **3h**, acetamide **3n**) and EWGs substituents (ester **3i**, acetyl **3j, 3o**, trifluoromethyl **3k**, cyno **3l** and sulfonamide **3m** etc.) reacted smoothly to afford the desired products in 73–97% yields and 91-96% ees. The absolute stereochemistry of compound **3m** was unambiguously confirmed by X-ray diffraction analysis, and the configuration of all other products was assigned by analogy. Notably, aryl iodides, aryl triflates can be employed as electrophilic reagents and provided the desired products (**3n**, **3j**). The *meta*-substituted aryl bromide also gives excellent yield and ee (**3o**). While *ortho*-substituted hindered aryl bromides afford the corresponding

products in lower *ees* than *meta*- or *para*-substituted aryl bromides (See Supplementary Information, Figure S6). Aryl bromides with dihydroisobenzofuran, fluorenyl and naphthyl motif all gave the corresponding products excellent yields and ees (**3p**, **3q**, **3r**). The naphthyl bromide with methoxyl group also gave the corresponding product **3s** in 85% yield and 94% ee with the addition of lithium bromide. It is noteworthy that the reactions with nitrogen-containing heterocyclic bromides as substrates all resulted in the satisfied yields and ees (**3t, 3u**). In addition, the yield and ees of β-arylated ketones synthesized by employing **L10** as ligand were compared with Zhou's method. Generally, the electro-reduction protocol affords higher ee (**3g**, **3j, 3k, 3l, 3r**) with similar yield compare to metal reductant when the aryl bromides containing methylthio, acetyl, trifluoromethyl, cyan, and naphthyl group.

The scope of enones with different substituents on the carbonyl and alkene sides were then investigated. The aryl ketones bearing chloro (**4a**), fluoro (**4b**) or methoxy group (**4r**), the naphthyl (**4c**) or pyridinyl (**4d**) ketones all reacted well and gave the corresponding products in good to excellent yields and ees. Compared to Zhou's relatively limited enone substrates with only Ph or ^{i}Pr on the alkene, we demonstrated that a wide range of enones with various aryl (**4e-4g**) or alkyl substitutes (**4h-4q**) reacted well under the optimum conditions. For example, ethyl (**4h**), phenylethyl (**4i**), protected amine (**4j**), nonyl (**4k**), cyclopropyl (**4m**), cyclohexyl (**4n**) and *N*-Boc piperidyl (**4o**) were all tolerated and gave the corresponding products in excellent yields and ees. However, the enantioselectivity of product **4l** was decreased significantly when there is bulky group on the alkene side. A mixture of roughly 1:1 diastereoisomers (**4p** and **4q)** were obtained in good yields with good stereocontrol. Racemic products were produced in inferior yield when the cyclic enones were employed as coupling partners (See Supplementary Information, Figure S6). In addition, the alkyl ketone substrate also reacted well and afforded the desired product in good yield and ee (**4s**). Futhermore, we also demonstrated that *β*-aryl vinyl bromide can be employed as electrophilic reagent to give the desired product **4t** in moderate to good yields and ees with either isoquinox **L1** or quinolinox **L10** as ligand, respectively.

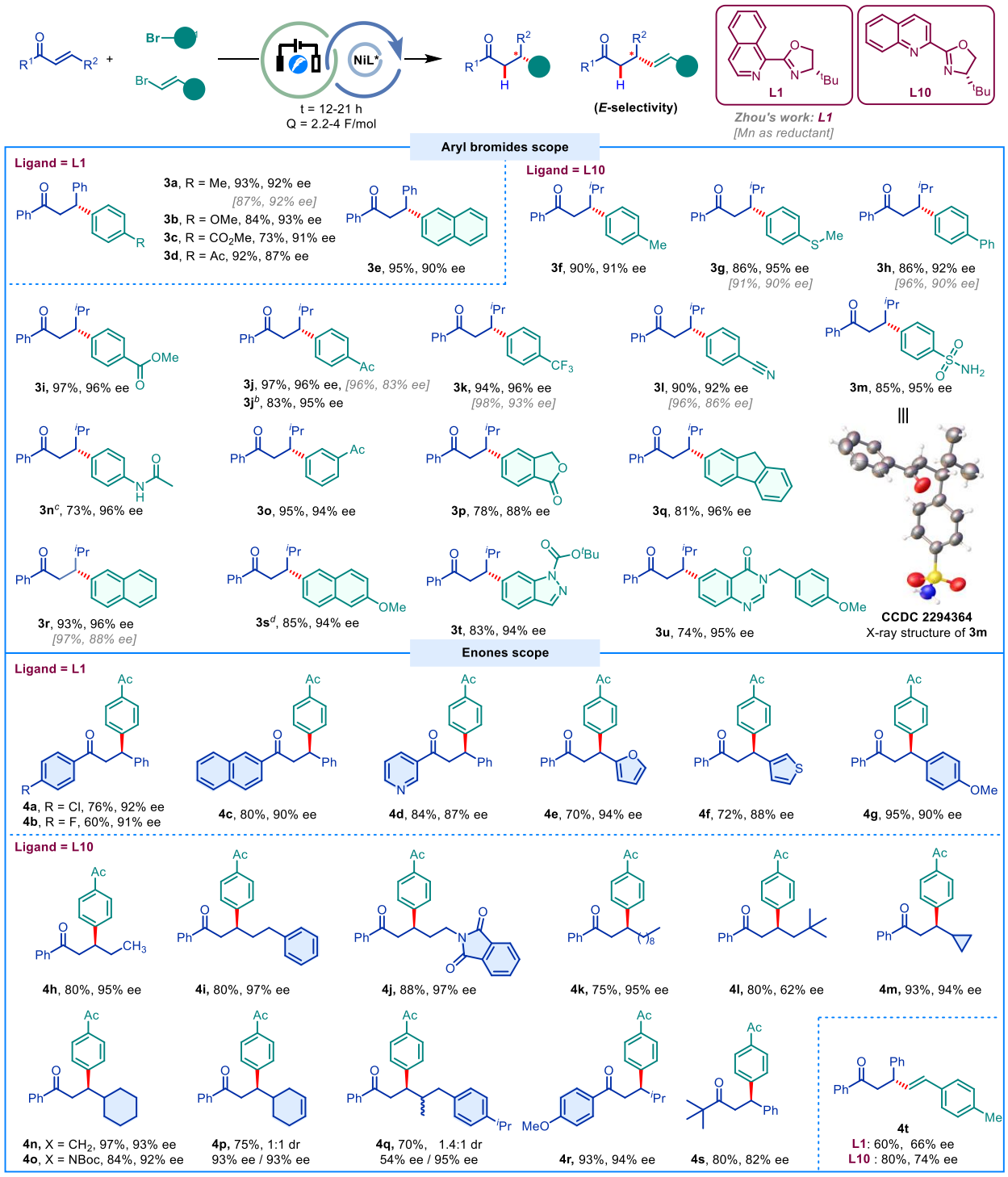


Fig. 2 | Substrate scope of Nickel-catalyzed enantioselective e-reductive conjugate arylation and heteroarylation of enones. [a]Conditions: **1** (0.2 mmol), **2** (1.5 equiv), $NiBr_2DME$ (10 mol%), Ligand (12 mol%), DMF/DMSO (1 mL/1 mL), N_2, 23 °C, SS(+)/SS(-), *I* = 1 mA, E_{cell} = 1-2 V, Q = 2.2-4 F/mol, t = 12-21 h. [b]Aryl triflate was used. [c]Aryl iodide was used. [d]LiBr (1 eq.) was added. All reported yields are isolated yields.

Enantioselectivities were determined by chiral HPLC analysis.

Synthetic applications

To demonstrate the synthetic utility of this asymmetric ERC reaction, we set out to apply this protocol to more structurally complex reaction partners featuring motifs commonly found in natural products and pharmaceutically active molecules (Fig. 3). Complex substrates bearing preexisted stereocenters were also compatible without loss of existing stereochemical property. Diacetone-D-glucose, tocopherol and estrone derivatives were tolerated well, furnishing the corresponding chiral products in 80%, 85%, 65% yields with 97%, 94%, 97% de, respectively (**5a**-**5c**). Trimetazidine and quipazine derived bromides reacted with enone **1b** to give the desired products in 97%, 86% yield with 95%, 96% ee, respectively (**5d**, **5e**). Olaparib and Gefitinib derivatives were also applied in the reaction delivering adducts **5f** and **5g** in 89%, 52% yield and 90%, 90% ee, respectively. The biological evaluation of the above synthesized complex active compounds is being carried out in our laboratory.

To verify the robustness of this electrochemistry, gram-scale reactions were conducted and the corresponding highly functionalized and privileged products **3m** (sulfonamide) and **4u** (*N*-Boc piperidine with quinazolinone) were readily obtained in good yields and excellent ees which could be further transformed into biologically active molecules (Fig. 3).[89-92] For example, the sulfonamide **3m** could be transformed into anti-diabetic sulfonylurea derivative **3m-urea** in 98% yield and 98% ee, which demonstrated the scalability of this powerful protocol for the synthesis of bioactive compounds.

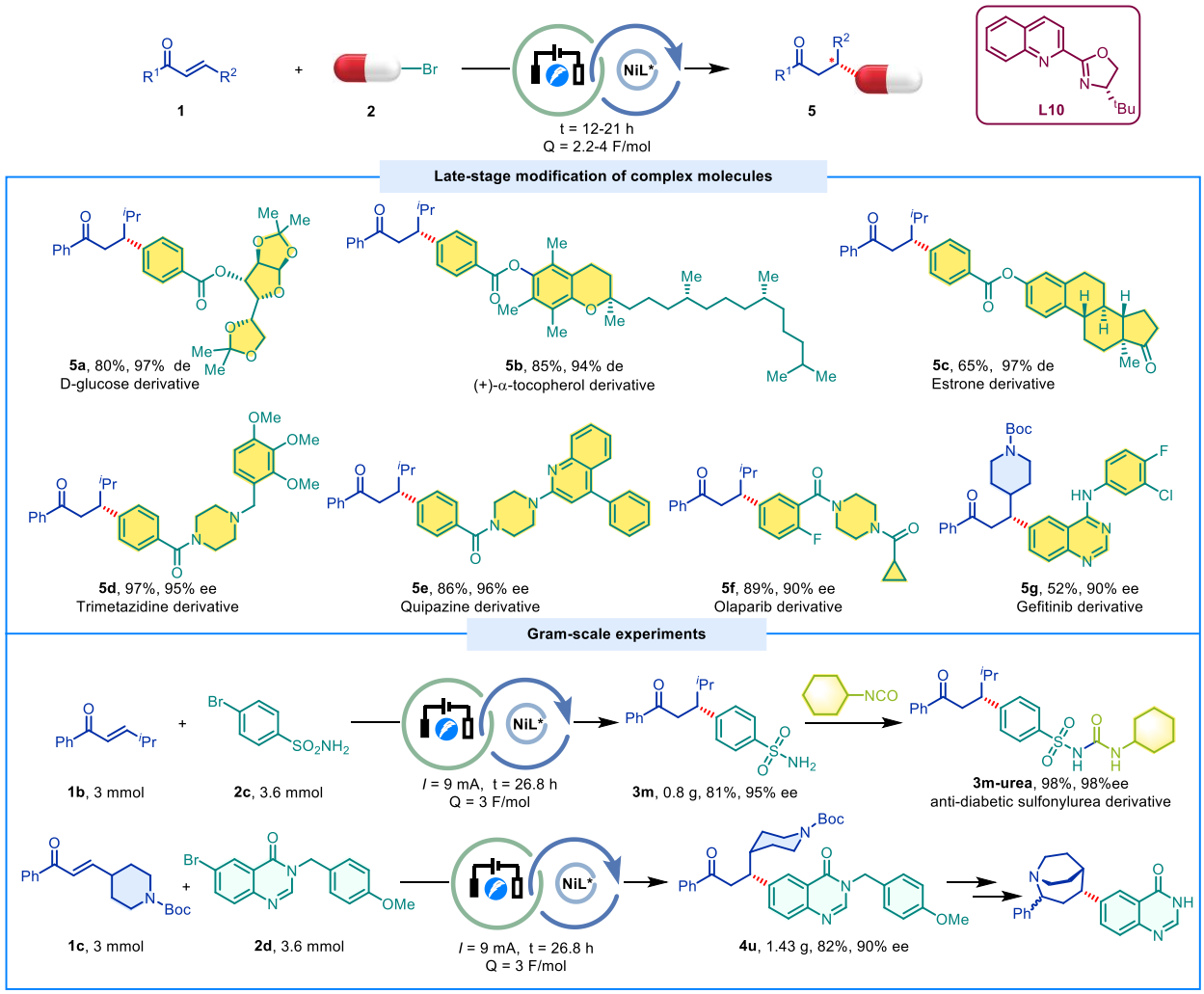


Fig. 3 | Synthetic Applications.

Mechanism investigation

To elucidate the mechanism of this nickel-catalyzed asymmetric ERC reaction, additional experiments were conducted, the results of which are summarized in Fig 4. According to literature reports,[93-95] the competitive experiments with different electronic 4-substituted bromobenzenes were conducted (Fig. 4a). The results show that electron-deficient aryl bromide reacts much faster than the electron-rich one. To identify the proton source the related control experiments were conducted (see Supplementary Information, Table S4). The yield of product **3j** decreased significantly when the reaction was conducted in anhydrous solvents. In contrast, **3j** was obtained in good yields by adding 1.5-3.0 equivalents of water into the reaction which suggest that the trace amount of water is beneficial to the reaction. Furthermore, the undeuterated product **3j** was obtained by ^{1}H-NMR when DMSO-d_6 was used as solvent which indicates the proton is not from the organic solvent (see

Supplementary Information). However, the deuterated product **3j**-*d* was obtained when 2 equivalent of D_2O was added which indicates the proton is from the water. The result is consistent with Zhou's report (Figure 4b).

When two equivalents of a radical scavenger, such as butylated hydroxytoluene (BHT) or bis(pinacolato)diboron (B_2Pin_2) were added, the desired product **3j** was formed in good yield and ee, which indicated radical mechanism might not be involved in this reaction (Figure 4c). And a slight decreased yield was observed when two equivalents of chlorotrimethylsilane (TMSCl) was added, which suggest the reaction might proceed via elementary insertion of arylnickel species rather than allylnickel species (Figure 4c).[18] To clarify whether the migration insertion mediated by $[Ni]^{II}$ species in the reaction, we were prepared arylnickel^{II} complex **6** [96-99] and subjected it to stoichiometric reactions with 2 equiv of enone **1b** (Figure 4d). Not surprisingly, trace desired product rac-**3k** was detected in the absence of electricity. In comparison, rac-**3k** was produced in 80% yield with the current at 10 mA after 2 h, indicating that electro-reduction was essential for aryl transfer. In addition, the crucial role of electricity in this transformation has been proven through on/off experiments (Figure 4e). Finally, the reaction proceeded more efficiently under electrochemical conditions, including Zn (table 1, entry 11) and SS anode, than manganese powder enabled nickel catalyzed protocol, which further demonstrates the relative efficacy of electrochemistry (Figure 4f).

To gain insights into the reaction mechanism, a series of cyclic voltammetric (CV) analyses were conducted (Figure 4g-h). The enone **1b** exhibits a reversible reductive peak at −1.60 V vs. $Ag/AgNO_3$ in DMSO (line b, blue line). And 4-bromotoluene **2a** exhibits an unreversible reductive peak at −2.82 V vs. $Ag/AgNO_3$ (line c, green line). The mixture of $NiBr_2$•DME and **L10** in a ratio of 1:1 exhibits two quasi-reversible reductive peaks at −1.79 V and −2.18 V vs. $Ag/AgNO_3$, which may be attributed to the reductive potential of $[Ni]^{II}/[Ni]^{I}$ and $[Ni]^{I}/[Ni]^{0}$, respectively (line d, red line). Those results were similar to Mei's report.[70] Significant increase current in the reduction peak of $[Ni]^{II}/[Ni]^{I}$ was observed (E_p = −1.86 V, −81 μA vs E_p = −1.79 V, −47 μA) by the addition of **2a** into the mixture of $NiBr_2$•DME and **L10** (line e, purple line) which indicates the oxidative addition of **2a** to $[Ni]^{I}$ species by generating aryl-$[Ni]^{III}$ species. During the reaction process, the voltage of the reaction is maintained below 2 V. These results demonstrate that the $[Ni]^{I}/[Ni]^{III}$ cycle with fast activation of the electrophile by a $[Ni]^{I}$ species was operated in this electro-reductive reaction rather than metal reductant driven $[Ni]^{0}/[Ni]^{II}$ cycle,[20] which is consistent with Reisman's report.[95]

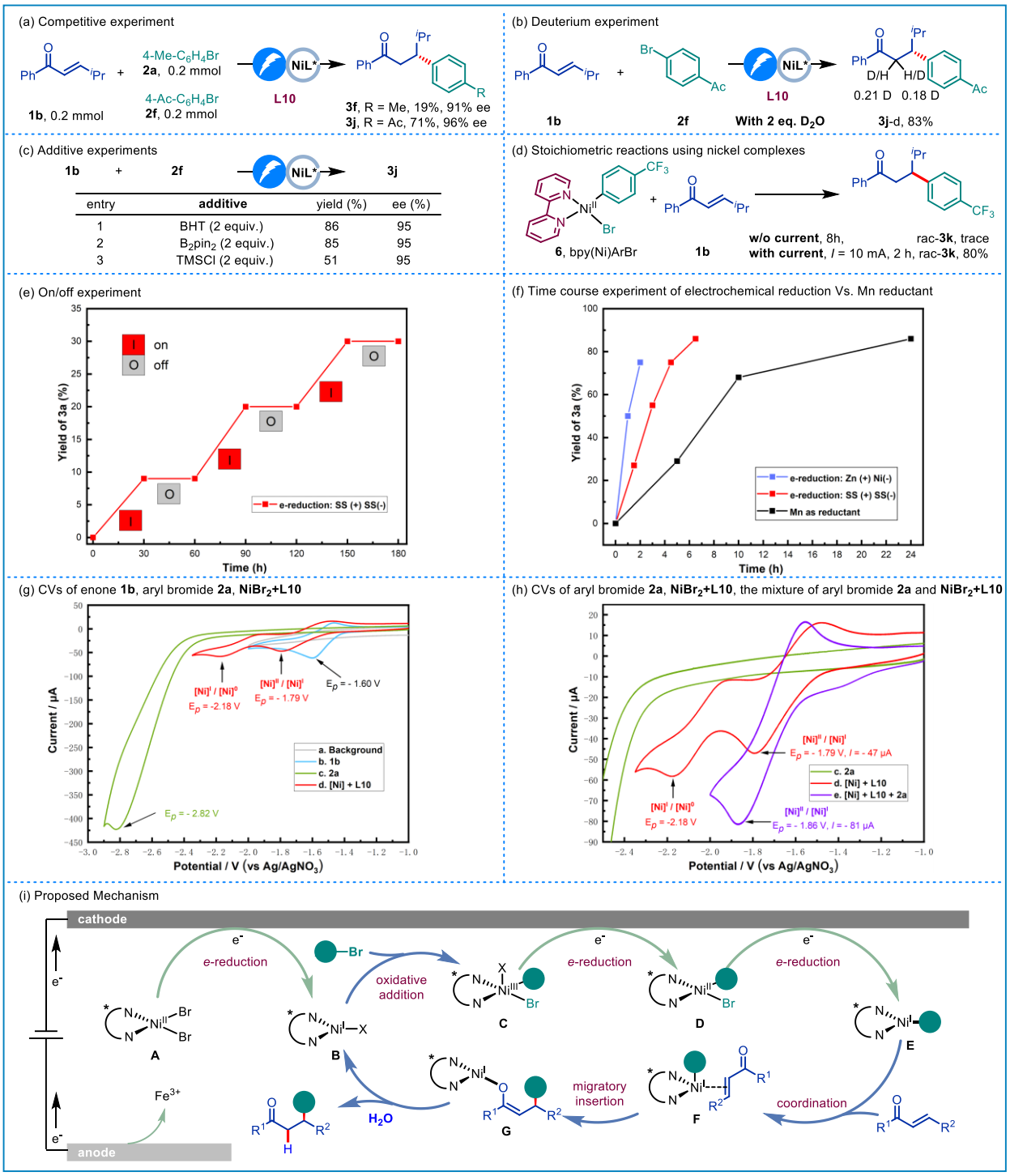


Fig. 4 | Mechanistic Investigation and Proposed Mechanism.

Based on these studies and previous reports,[20,21,86-88,93-99] a plausible mechanism for the Ni-catalyzed ERC reaction is presented in Figure 4i. Upon cathodic reduction of the $[Ni]^{II}$ precatalyst **A**, the resulting $[Ni]^{I}$ species

B rapidly reacts with aryl bromide to give $[Ni]^{III}$ species **C**, which can be reduced to furnish resting state $[Ni]^{II}$ species **D**. The active $[Ni]^{I}$ species **E** could be formed after another cathodic reduction from species **D**, which coordinate with enones to give π-complex **F**. After migratory insertion and the resulting nickel *O*-enolate **G** could be hydrolysed by water to release the final product and $[Ni]^{I}$ species **B** to complete the catalytic process.

Conclusion

In summary, we have developed an electrochemical Ni-catalyzed enantioselective reductive conjugate arylation of enones with readily available and low-cost stainless steel electrodes. The aryl bromides, iodides or triflates, and vinyl bromides could be employed as electrophilic reagents for the efficient synthesis of valuable β-arylated ketones in good to excellent yields and enantioselectivities under mild conditions in a simple manner. This scalable protocol was further applied for the late-stage modification of bio-relevant compounds. The success of this reaction relies on the perfect match of electrochemistry with chiral nickel catalysts which avoid the drawbacks by employing the external sensitive metal reductants. Mechanistic studies and CVs illustrated a possible Ni^{I}/Ni^{III} cycle is involved in this transformation. Overall, we envisioned this established protocol with green and economic properties would be potentially applicable in organic synthesis and drug discovery.

Experimental Methods

A 10 mL Schlenk tube with a stir bar was charged with $NiBr_2$(DME) (6.2 mg, 0.02 mmol, 10 mol%), (S)-4-(*tert*-butyl)-2-(isoquinolin-1-yl)-4,5-dihydrooxazole **L1** (6.1 mg, 0.024 mmol, 12 mol%) or (*S*)-4-(*tert*-butyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole **L10** (6.1 mg, 0.024 mmol, 12 mol%), enone (0.2 mmol), aryl halide (0.3 mmol), DMF (1 mL) and DMSO (1 mL). The tube was sealed with rubber septum which equipped with stainless steel electrodes (1.5 cm x 1 cm, about 1 cm immersion depth in solution, S = 1 cm^2) as anode and cathode and stirred for 10-20 min at room temperature. It was then evacuated, and backfilled with nitrogen for three cycles. The reaction mixture was electrolyzed under a constant current of 1 mA (J = 1 mA / cm^2， E_{cell} = 1~2 V) until the complete consumption of the starting material as judged by TLC or LC-MS of an aliquot (12~21 h, 2.2~4 F/mol). After the reaction, the electrodes were taken out and rinsed with EtOAc. Aqueous sat. EDTA was then added; the resulting mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography to furnish the desired products. The enantioselectivity of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Supporting Information

Supporting Information is available and includes the general procedures for electrochemical nickel-catalyzed enantioselective reductive conjugate (hetero)arylation of enones, additional optimization results, electrochemistry analyses, crystal structures, characteristic data, and spectra of new compounds.

Conflict of Interest

The authors declare no competing interest.

Acknowledgments

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