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Nickel-Catalyzed Enantioselective Reductive Conjugate Arylation and Heteroarylation via an Elementary Mechanism of 1,4-Addition

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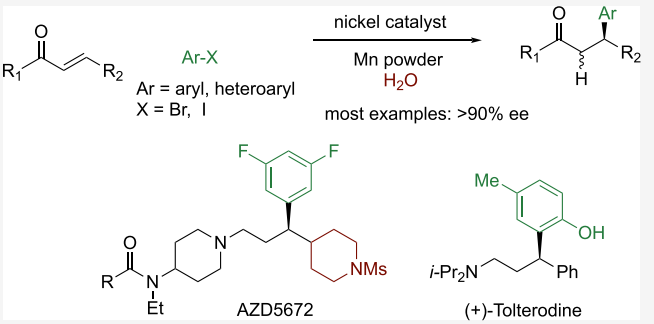
ABSTRACT: A nickel complex of isoquinox promoted enantioselective conjugate arylation and heteroarylation of enones using aryl and heteroaryl halides directly. The reaction was successfully applied to stereoselective syntheses of *ar*-turmerone, chiral fragments of (+)-tolterodine and AZD5672. Mechanistically, experiments and calculations supported that an arylnickel(I) complex inserted to enones via an elementary 1,4-addition.



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INTRODUCTION

Metal-catalyzed asymmetric conjugate arylation of Michael acceptors constitutes an important family of C-C bond-forming reactions, which have been widely used in total synthesis of natural products and medicines. In the past, chiral copper catalysts have dominated in asymmetric conjugate addition of arylmetal reagents, for example, Li, Mg, Al, Zn, and so on (see Figure 1a).[1] For conjugate addition of aryl-nonmetal reagents, especially air-stable arylborons, however, stereoselective examples catalyzed by copper still remain limited.[2,3] In comparison, 4d transition metals Rh[4] and Pd[5] have met great success in promoting conjugate addition of both organoboron reagents (Figure 1b). In particular, the rhodium-catalyzed Hayashi−Miyaura reaction has become the state-of-the-art in asymmetric metal catalysis in terms of excellent levels of stereocontrol and substrate diversity, for example, including both cyclic and acyclic acceptors. It has been utilized in the preparation of multiple chiral pharmaceuticals on kilogram scales.[6]

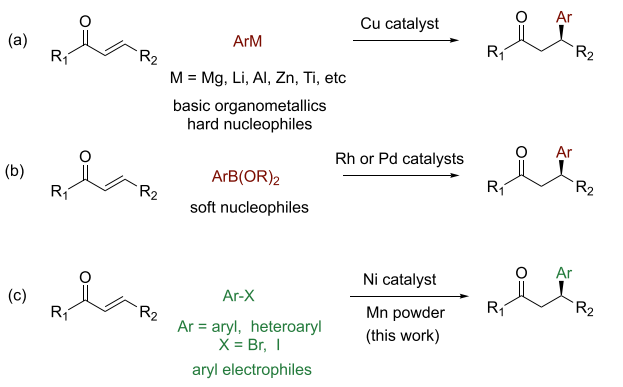

Figure 1. Examples of metal-catalyzed enantioselective conjugate addition: (a) Cu-catalyzed addition of reactive arylmetal reagents; (b) Rh- and Pd-catalyzed addition of arylboron reagents; (c) Ni-catalyzed reductive addition of aryl halides.

Aryl halides are electrophilic reagents. Direct use of aryl halides certainly has practical benefits. This major family of carbon electrophiles are readily available and benchtop-stable. In comparison, some organometallic reagents (e.g., Grignard reagents) are incompatible with relatively acidic groups and also are less tolerant of polar groups (e.g., aldehydes and ketones), especially when room temperature or heating is applied. This also avoids preparation of arylboron reagents. Regioselective preparation of some arylboron reagents uses arylmetal reagents (e.g., those of Mg and Li) or aryl halides as a starting material. Additionally, transmetalation of some arylborons requires strong bases under catalytic conditions.

In 2013, Weix and co-workers first disclosed nickel-catalyzed reductive addition of aryl halides to enones, in the presence of trialkylsilyl chlorides and manganese powder.[7] The reaction proceeded via η^3 − 1-siloxyallylnickel species and subsequent coupling with aryl halides, rather than elementary insertion of arylnickel species. However, achieving an intermolecular

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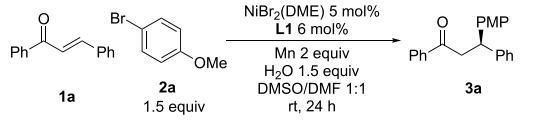
reductive arylation has proved to be challenging.[8] Herein, we report such an enantioselective variant under very mild conditions (Figure 1c). It should be pointed out that organometallic reagents (M = Mn or Zn) are not directly involved in the C−C bond formation herein.[9]

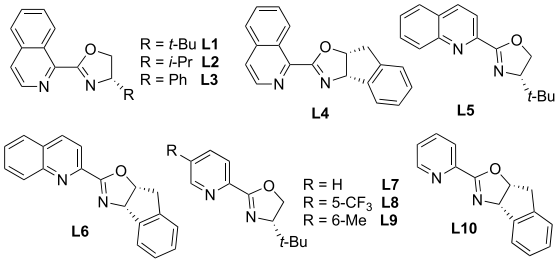
CONDITION OPTIMIZATION

Initially, we examined a model reaction between 4-bromoanisole **2a** and (*E*)-chalcone **1a** to identify suitable nickel catalysts and conditions. After many trials, we established an efficient protocol using a precatalyst of $NiBr_2$(DME) and isoquinox **L1**, manganese powder, and 1.5 equiv of H_2O in a 1:1 mixed solvent of dry DMSO and DMF. Thus, desired product **3a** was generated in 86% yield and 92% enantiomeric excess (ee) after 24 h at rt (Table 1, entry 1).

Table 1. Condition Optimization of Asymmetric Reductive Arylation of (*E*)-Chalcone (Calibrated GC Yields on 0.1 mmol Scale in 0.3 mL of Solvents)



Entry	Conditions	Conv of **1a** (%)	Yield of **3a** (%)	Ee (%)
1	**L1**	96	86	92
2	**L2**	64	49	79
3	**L3**	52	39	80
4	**L4**	45	41	87
5	**L5**	43	23	90
6	**L6**	32	18	94
7	**L7**	19	10	86
8	**L8**	21	18	77
9	**L9**	10	6	89
10	**L10**	18	12	82
11	[Ni] 2.5 mol%	52	48	92
12	DMF solvent	44	36	93
13	DMSO solvent	75	41	91
14	without H_2O	94	7	64
15	H_2O 3 equiv	82	69	92
16	50 °C	81	19	87



With regard to isoquinox ligands,[4k,10] changing the sidearm from the *tert*-butyl group to isopropyl, phenyl, and indanyl (**L2**−**L4**) led to moderate yields (41−49%) and slightly lower stereoselectivity (79−87% ees), as shown in entries 2−4. Among other dinitrogen chelators, quinox **L5**−**L6** and pyrox **L7**−**L10** resulted in very low yields of **3a** (6−23%), albeit in good-to-excellent ees (entries 5−10).

The additive of water proved essential. Without water, **3a** was produced in only 7% yield and 64% ee. Most chalcone **1a** was thus sidetracked to form trimeric side products (via sequential nickel(0)-catalyzed reductive coupling of enones, conjugate addition to a third chalcone, aldol cyclization to form cyclopentanols, and final dehydration)[11] (entry 11). Addition of 3 equiv of H_2O led to lower yield of the product (entry 12). Additionally, a mixed solvent of 1:1 DMSO/DMF was optimal; only ∼40% yield was obtained in pure DMF or DMSO in comparison (entries 13 and 14). In DMF, only 44% enone was consumed after 24 h; a significant amount of side product, arene was detected after 24 h. The enone conversion was 75% in DMSO, along with a significant amount of the trimeric side products. In 1:1 DMF/DMSO, the excess of aryl bromide remained after 24 h, along with small amounts (<5%) of anisole and biaryl (for details, see the Supporting Information).

SUBSTRATE SCOPE

With the optimized conditions in hand, we first examined the scope of (hetero)aryl bromides with (*E*)-enone **1b** (Scheme 1). A wide range of aryl bromides bearing both electron-donating (**3b**−**g**, **3m**) and electron-withdrawing substituents (**3h**−**l**, **3p**) reacted smoothly to afford desired products in 80−93% ees. Notably, aryl bromides carrying aldehyde, ketone, and nitrile groups gave slightly lower ees. Importantly, the condition was also compatible with benzyl alcohol (**3m**), aniline (**3t**), aryl boronic acid, and aryl Bpin (**3n**−**o**), but not phenol. The reaction also worked well with 2-bromoanisole (**3q**), but hindered aryl bromides possessing *o*-*i*Pr and *o*-vinyl groups provided only 67% ee and 70% ee (**3r**−**s**). To our delight, many heteroaryl bromides proved to be suitable electrophiles, including derivatives of benzofuran (**3w**), benzothiophene (**3x**), indole (**3y**), thiophene (**3z**), quinoline (**3aa**−**ac**), pyridine (**3ad**−**ah**), and pyridone (**3ai**); parent 3-pyridyl bromide also provided adduct **3ae** in 80% ee. Some bromides of electron-rich heteroarenes, thiophene, benzothiophene, and indole, reacted rather sluggishly; 1 equiv of LiI was added to ameliorate this problem. In terms of reactivity and selectivity, electron-neutral and electron-rich aryl halides (Br and I) provided similar isolated yields and ees, but some electron-deficient aryl iodides gave slightly better ees than bromides (**3j**, **3l**). Hindered *o*-iodocumene, however, afforded product **3r** in poor yield, along with significant biaryl formation.

Next, we examined the scope of α,β-enones, using 4-tolyl bromide (4-tolyl iodide was used in some sluggish reactions) (Scheme 2a). Conjugate arylation to parent (*E*)-chalcone furnished β,β'-diaryl ketone **4a** in 87% yield and 92% ee. On β-aryl rings of chalcones, both electron-donating and -withdrawing substituents can be present such as phenoxy (**4c**), ester (**4d**), methoxy (**4e**), phenyl (**4f**), diphenylamino (**4g**), methylthio (**4h**), fluorine (**4j**), and trifluoromethyl groups (**4k**). Notably, the presence of an *ortho*-anisyl group at the β-position slightly decreased the stereoselectivity (86% ee for **4i**), while an *o*-tolyl group reduced the value to 57% ee. Moreover, β-aryl rings of chalcones can be substituted with heteroaryl rings, for example, thiophene, furan, pyridine, and quinoline (**4m**−**q**). For some substrates above, especially chalcones having β-electron-deficient aryl groups and heteroaryl rings, switching from aryl bromides to iodides significantly improved chemical yields and minimized the trimeric side products formation. Notably, a 2,4-dienone led to exclusive β-arylation in 91% ee (**4r**). Moreover, β-positions of (*E*)-enones can have isopropyl, methyl (**4s**), *n*-hexyl (**4t**), other alkyl chains carrying ester and phthalimide groups (**4u**−**v**), and an *N*-benzylpiperidyl group (**4w**). Finally, arylation of (*E*)-2-benzylidenetetralone and its 4-oxa derivative generated products **4t** and **4y** as 1:1 mixtures of diastereomers, with both isomers formed in 91 and 90% ee, respectively. We also attempted arylation of α-

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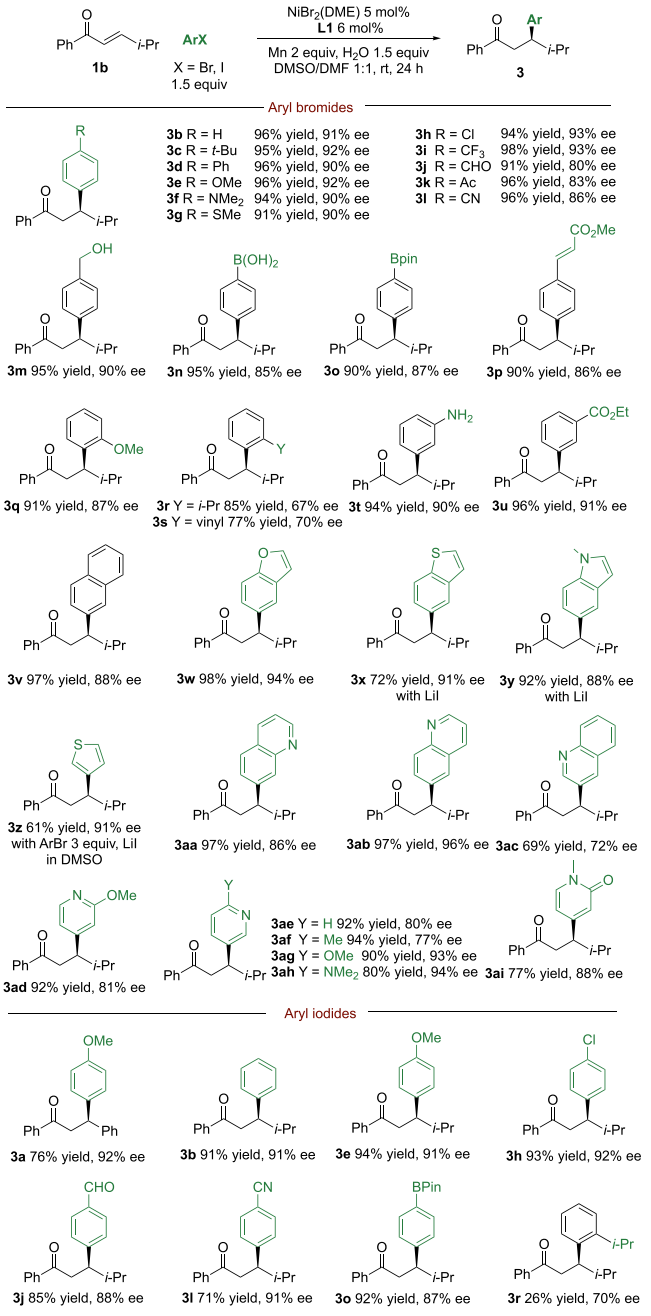
Scheme 1. Substrate Scope of (Hetero)aryl Bromides and Iodides in Asymmetric Conjugate Arylation (Isolated Yields on 0.1 mmol Scale in 0.3 mL of Solvents)



methylchalcone using 4-tolyl bromide, which resulted in low conversion and low yield, along with a significant amount of biaryl.

As shown in Scheme 2b, enones can have different α'-aryl groups containing *ortho*-groups (**5a**) and electron-donating and -withdrawing groups (**5b**–**f**). On the α'-position, aryl rings can be replaced by heteroaryls including furan, thiophene, benzothiophene, thiazole, and 2-methoxypyridine (**5i**–**n**). Again, some reactions using heteroaryl iodides proceeded more efficiently than the corresponding bromides (**5l** and **m**). (*S*)-(+)-*ar*-turmerone **5o** is a key component of turmeric essential oil. Recent studies found that it possessed promising neuroprotective properties.[12] Without modification of the conditions, regioselective tolylation of dialkenyl ketone **1o** proceeded exclusively at the less-substituted alkene to give (*S*)-*ar*-turmerone **5o** in 93% ee (Scheme 2c).

In the reaction of isopropyl styryl ketone with 4-tolyl bromide, only 36% conversion was observed after 24 h, giving product **5p** in 27% yield and 54% ee. To our gratification, switching from isoquinox **L1** to quinox **L6** and employing 4-tolyl iodide significantly improved the result, giving **5p** in 72% yield and 93% ee (Scheme 2d). Similarly, the new procedure also enabled stereoselective arylation of enones bearing other α'-alkyl groups such as *t*Bu and *i*Bu (**5q** and **r**).

SYNTHETIC APPLICATION

To demonstrate synthetic utility, we have applied the new reaction in formal syntheses of (+)-tolterodine,[13] a blockbuster drug for the treatment of urinary incontinence (Figure 2). Thus, 4′-methoxychalcone was arylated with 2-iodo-4-methylanisole, and subsequent Baeyer–Villiger oxidation yielded ester **6a**, a synthetic precursor to (+)-tolterodine, in 70% yield with 87% ee in two-steps. Similarly, the two-step sequence was applied to conjugate arylation using 3,5-difluorophenyl bromide to provide **6b** in 86% yield and 96% ee. The latter is a key intermediate en route to AZD5672,[14] a drug candidate for the treatment of rheumatoid arthritis.

MECHANISTIC STUDIES

We have carried out some experiments to probe the reaction mechanism (Figure 3): (a) conjugate 4-tolylation of enone **1m** in the presence of D_2O resulted in products **4m**–*d* with deuterium at both α positions in nearly 1:1 ratio. A nondeuterated sample of **4m**, when added to a live catalytic arylation of enone **1a**, 4-anisyl bromide, and 1.5 equiv D_2O, no deuteration was detected in recovered **4m**. Thus, after 1,4-addition, an *O*-bound nickel enolate undergoes a non-stereoselective protonation (Figure 3a); the resulting hydroxonickel(I) complex is directly reduced to Mn powder or it is converted to a bromide complex, which was then reduced. (b) In catalytic tolylation of chalcone **1a** (*Z*/*E* 10:1) (Figure 3b), the (*E*)-isomer was depleted after 2 h, after which the *Z*/*E* ratio was maintained at 99.8:0.2 in both reactions. The kinetics showed that 4-tolyl iodide reacted much faster than the bromide; for instance, the reaction of ArI reached >90% conversion of the enone after 10 h, while only 40% conversion was seen in that of ArBr. Importantly, in both reactions of 4-tolyl bromide and iodide, product **4a** was formed in identical 92% ee. We reasoned that in situ formed MnX_2 catalyzed slow *Z*/*E* isomerization of (*Z*)-**1a** to form (*E*)-**1a** in low concentrations, the latter being the reactive substrate for catalytic arylation. (c) Catalytic arylation of cyclic enones, for example, 2-cyclopentenone and 2-cyclohexanone, led to ∼50% conversion of enones, and *racemic* products **4z** and **4z**′ were produced in poor yields, along with a significant amount of biaryl (Figure 3c).

To gain insights of the reaction mechanism, we prepared arylnickel^{II} complex (bipy)Ni(*Ar*)Br **7** (Ar = *o*-*i*PrC_6H_4)[15] and subjected it to stoichiometric reactions with 3 equiv of enone **1b** (Figure 4a). With Mn powder, *rac*-**3r** was produced in 60% yield after 8 h, along with 5% cumene and 2% biaryl. In comparison, almost no *rac*-**3r** (3%) was detected without Mn, indicating that Mn reduction was essential for aryl transfer. Several additional observations were made: (1) prestirring of the nickel complex of bipy **7** with 2 equiv of isoquinox **L1** at rt. for 2 h caused little change to the outcome of the arylation

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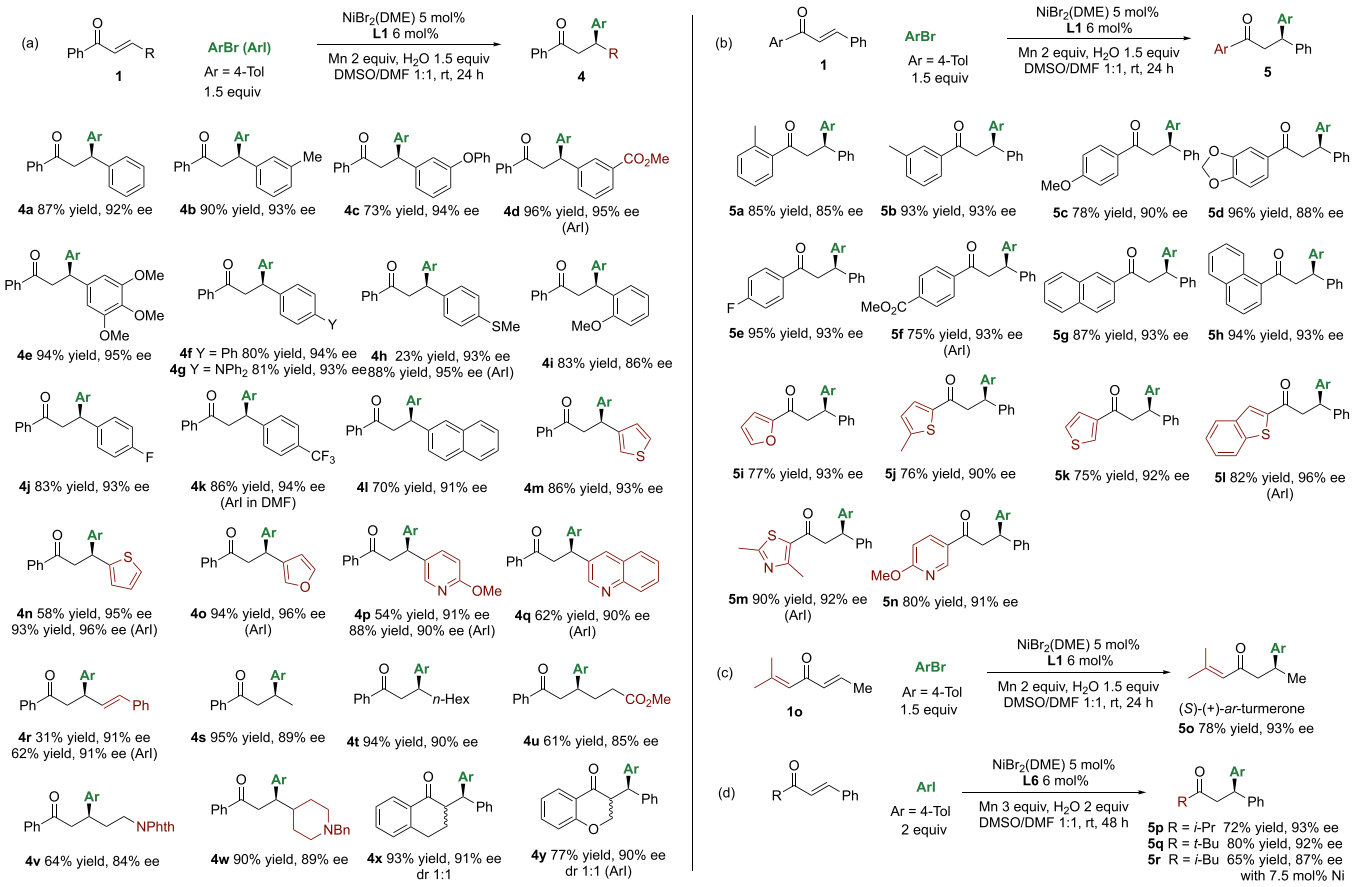
Scheme 2. Asymmetric Conjugate (Hetero)arylation of Enones with Structural Variations: (a) (Hetero)aryl, Alkenyl, and Alkyl Groups at the β-Position; (b) (Hetero)aryl, (c) Alkenyl, and (d) Alkyl Groups at the α'-Position (Isolated Yields on 0.1 mmol Scale in 0.3 mL of Solvents)



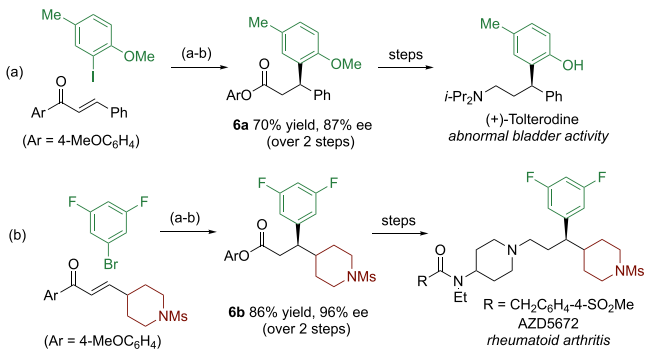
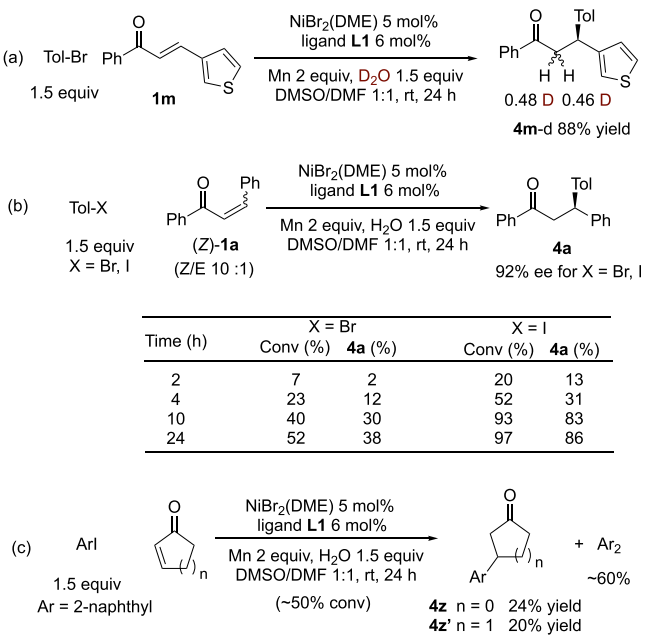


Figure 2. Formal syntheses of (a) (+)-tolterodine and (b) AZD5672 (isolated yields on 0.1 mmol scale in 0.3 mL of solvents for catalytic arylation): (a) enone (1 equiv), ArX (1.5 equiv), 5 mol % $NiBr_2$(DME), 6 mol % **L1**, Mn powder (2 equiv), H_2O (1.5 equiv), 1:1 DMSO/DMF, rt., 24 h; (b) $TsOH{\cdot}H_2O$ (0.2 equiv), *m*CPBA (3 equiv), DCM, 35 °C, 36 h.

(66% yield; 4% ee), indicating that ligand exchange on the nickel complex was slow at rt. (2) When 30 mol % $MnBr_2$ and 36 mol % ligand **L1** were added to the stoichiometric arylation of complex **7**, it gave *racemic* **3r** in 55% yield, suggesting that complex (**L1**)$MnBr_2$ did not participate in the stereoselective aryl transfer to enones.

We also prepared isoquinox complex (**L1**)Ni^{II}(*o*-*i*-PrC_6H_4)Br **8** as a 1:1 cis/trans isomer. The large *o*-*i*-Pr group is essential to preventing decomposition via biaryl formation. A stoichio-



Time (h)	X = Br Conv (%)	X = Br **4a** (%)	X = I Conv (%)	X = I **4a** (%)
2	7	2	20	13
4	23	12	52	31
10	40	30	93	83
24	52	38	97	86

Figure 3. Mechanistic studies using different enones in catalytic arylations (0.1 mmol scale in 0.3 mL of solvents): (a) arylation of enone **1 m** using D_2O; (b) catalytic arylation of chalcone (cis/trans 10:1) using 4-tolyl halides; (c) catalytic arylation using 2-cyclopentenone and 2-cyclohexenone.

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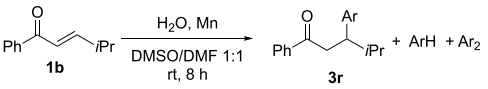
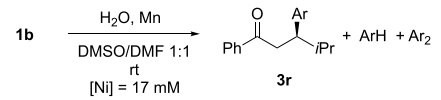
(a) (bipy)Ni(Ar)Br **7**
Ar = *o*-*i*-PrC$_6$H$_4$



Mn	Conv of **1b** (%)	**3r** (%)	ArH (%)	Ar_2 (%)
+	69	60	5	2
-	9	3	6	6

(b) (**L1**)Ni(Ar)Br **8**
Ar = *o*-*i*-PrPh
(cis/trans ~1:1)



Mn	Time	Conv of **1b** (%)	**3r** (%)	ArH (%)	Ar_2 (%)
+	10 min	18	8	13	9
+	20 min	32	20	20	15
+	30 min	44	29	23	16
+	1 h	60	31 (69% ee)	24	16
-	10 min	14	1	8	4
-	20 min	26	4	11	9
-	30 min	36	7	14	11
-	1 h	48	13	17	13
-	2 h	56	20	22	13
-	5 h	62	26	27	13
-	10 h	76	27 (72% ee)	27	13

Figure 4. Stoichiometric reactions using nickel complexes. (a) Arylation of enone **1b** (0.15 mmol) with complex **7** (0.05 mmol), water (0.08 mmol), and Mn (0.25 mmol) in 1:1 DMSO/DMF (0.3 mL) (full conversion of **1b** is 300%). (b) Arylation of enone **1b** (0.5 mmol) under conditions similar to catalytic reactions (5 mol % nickel): complex **8** (0.025 mmol), water (0.75 mmol), and Mn (1.0 mmol) in 1:1 DMSO/DMF (1.5 mL).

metric reaction of complex **8**, enone **1b**, and Mn powder (see Figure 4b), under conditions similar to catalytic arylations ([Ni] = 17 mM), gave **3r** in ~30% yield (69% ee) after 30 min. However, the arylation without Mn was much slower, providing **3r** in ~30% yield (72% ee) after 5 h. As a side note, the stoichiometric arylation at a high nickel concentration (170 mM) gave the product in 40% ee, suggesting that a bimetallic complex of nickel (possibly with a bridging bromide ligand) may exist at high nickel concentrations and lead to a less stereoselective pathway. When the catalytic reaction of *o*-*i*PrC$_6$H$_4$Br and enone **1b** was conducted with 50 mol % nickel ([Ni] = 170 mM), the selectivity of **3r** also dropped to ~40% ee (see the Supporting Information).

Mn reduction of complex **8** (with a maximal absorbance at 520 nm) was monitored by UV-ultra red spectroscopy (see Figure 5). Clearly, a putative complex (**L1**)Ni^{I}(*o*-*i*PrC$_6$H$_4$) **9** (540 nm) was produced quickly within 2−10 min, which eventually transformed to a solvated complex of (**L1**)Ni^0 (550 nm). The latter was identified in comparison with (**L1**)-Ni^0(cod). Organic byproducts were identified to be mainly cumene and a small amount of biaryl. Reduction with zinc dust was faster than Mn reduction and showed a similar kinetic profile.

Surprisingly, we found that complex **8** itself *slowly* decomposed in 1:1 DMSO/DMF with a half-life of ~1 h to give complex **9** and biaryl (as the main organic byproduct). The reaction probably proceeds via a sequence of aryl exchange, diaryl reductive elimination, and bromine abstraction by(*L*)Ni^0 from complex **8** to form complex **9**, as depicted in eqs 1 and 2 (see the Supporting Information). This explains

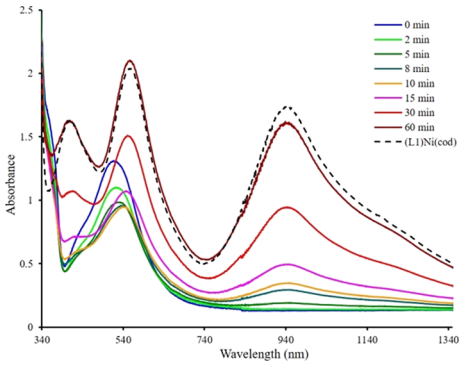
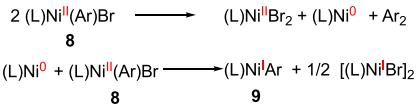
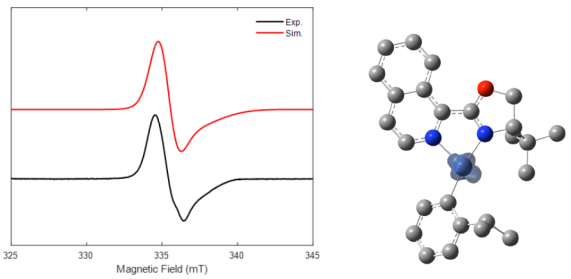


Figure 5. Kinetics of Mn reduction of (**L1**)Ni(*o*-*i*PrC$_6$H$_4$)Br **8** as monitored by UV-ultra red spectroscopy.

slow formation of product **3r** from complex **8** even in the absence of Mn (see Figure 4b).



Next, we conducted electron paramagnetic resonance (EPR) analysis to detect elusive complex **9** via in situ zinc reduction of complex **8** in 1:1 DMSO/DMF (Figure 6a). $MnBr_2$ produced



(a) (b)

Figure 6. Characterization of (**L1**)Ni^{I}(*o*-*i*PrC$_6$H$_4$) **9**. (a) X-band EPR spectrum of complex **9** collected in frozen 1:1 DMSO/DMF at 173 K (microwave frequency 9.422 GHz, power 0.6325 mW, modulation amplitude 2 G, and modulation frequency 1 mT/100 kHz) and a simulated spectrum (parameters used for simulation: g = 1.981, 1.996, 1.996). Hyperfine couplings from nitrogen atoms were unresolved. (b) DFT-computed (M06L/6-31G*) spin density plot of complex **9**.

in the Mn reduction interfered with the EPR signal. The EPR spectrum of complex **9** acquired at 173 K displayed anisotropy (g = 1.981, 1.996, 1.996) expected for a nickel-centered radical, rather than an organic radical delocalized in the isoquinox ligand. Density functional theory (DFT) calculations confirmed that the majority of the spin density resided on nickel (Figure 6b).[16]

DFT CALCULATIONS

We have conducted DFT calculations on elementary addition of putative species (**L1**)Ni^{I}(Ph) **9** to enone **1b** to understand the origin of its enantioselectivity. Geometry optimization calculations were performed at the M06L, SMD(DMF)/Def2-TZVP level of theory, using the SDD effective core potential basis set for Ni and 6-31G(d,p) basis set for other atoms. The alkene-bound complex is 6.6 kcal mol^{-1} lower in Gibbs free energy than any ketone-bound structure. Assuming that these ground-state structures are quickly interconverting, we chose

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the alkene complex as a reference point to compare relative energies of transition states in Figure 7. Among four transition

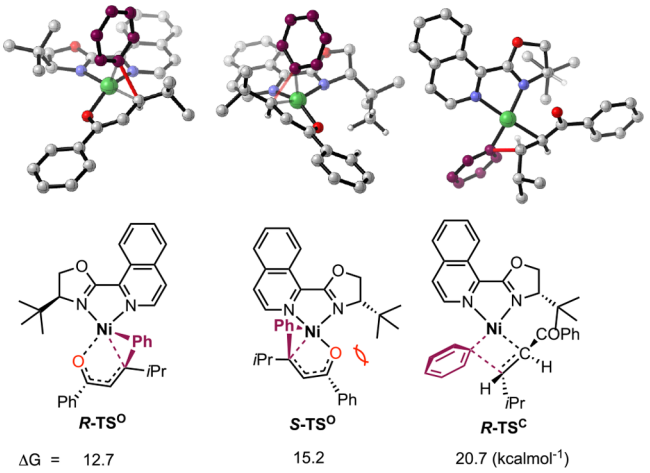

Figure 7. Calculated transition states and relative free energies for elementary 1,4-addition and 1,2-addition of (**L1**)Ni^{I}(Ph) **9** to enone **1b**. The migrating phenyl ring is highlighted in crimson in the ball-and-stick representation and the nascent C-C bond is marked in crimson; nickel, oxygen, and nitrogen atoms are marked in green, red, and blue, respectively.

states for 1,4-addition that we have identified, two lowest-energy ones **R-TS^{O}** and **S-TS^{O}** are shown, along with a transition state for 1,2-addition of the ketone **R-TS^{C}**.

Structures **R-TS^{O}** and **S-TS^{O}** are six-membered cyclic transition states for 1,4-addition,[3] each possessing a migrating phenyl group above the coordination plane; they have Gibbs free energies of 12.7 and 15.2 kcal mol^{-1}, respectively (note: the barrier from a ketone-bound structure to **R-TS^{O}** is 6.1 kcal mol^{-1}). We conclude that **S-TS^{O}** is destabilized to alleviate close contact between the α'-Ph group of enone **1b** and *t*-butyl group of **L1** (both pointing downward). The energy gap of two TSs is 2.5 kcal mol^{-1}, which is expected for a reaction giving 91% ee. In comparison, structure **R-TS^{C}** for classical 1,2-addition across the olefin has a much higher energy of 20.7 kcal mol^{-1}. As a side note, simple 1,2-addition of the ketone has an inhibitory barrier of ∼30 kcal mol^{-1}.

The cyclic transition states of 1,4-addition are instrumental to understanding some key experimental observations: (a) Enone (*Z*)-**1a** having a cis-β-substituent encountered difficulties in aryl addition owing to steric interactions. (b) The reacting enones must have *s*-cisoid conformers during aryl transfer, so cyclic 2-enones, being locked in *s-transoid* conformers, failed to produce enantioenriched adducts under the catalytic conditions (e.g., formation of racemic **4z** and **4z**′ in low yields via another pathway in Figure 3c). (c) Large *ortho* groups on migrating aryl groups have a detrimental effect on the stereoselectivity; for example, aryl halides with *o*-*i*Pr and *o*−vinyl groups provided products **3r-s** in moderate 70% ee. (d) For tolylation of an enone containing an α'-*i*Pr group leading to product **5p**, the energy gap of two cyclic TSs on Ni/isoquinox **L1** was calculated to be 1.2 kcal mol^{-1}, consistent with observed 54% ee; switching to quinox **L6** boosted the selectivity to 93% ee. DFT calculations revealed that the large indanyl ring of **L6** raised the energy of the disfavored **S-TS^{O}** in order to avoid close contact with the *i*Pr group, which consequently increased the energy gap of two diastereomeric TSs to 2.8 kcal mol^{-1} (see the Supporting Information for details of DFT calculations). (e) We have calculated three 1,4-addition pathways of enone **1b** using complexes (**L1**)Ni^{I}(Ar), (**L1**)Ni^{II}(Ar)$^{+}$, and (**L1**)Ni^{II}(*Ar*)Br (Ar = *o*-*i*PrPh) leading to the major (*R*)-isomer. The barriers were 10.4, 21.3, and 32.9 kcal mol^{-1} respectively, which is consistent with fast arylation by neutral arylnickel^{I} (for details, see the Supporting Information of DFT calculations). The high barrier for cationic d^{8} arylnickel^{II} complexes of bipy-type ligands originates from a tendency to assume square-planar geometry (i.e., ground-state stabilization).[16a]

DISCUSSION

Putting all the information together, we constructed a catalytic cycle for the reductive arylation of enones (Figure 8). After

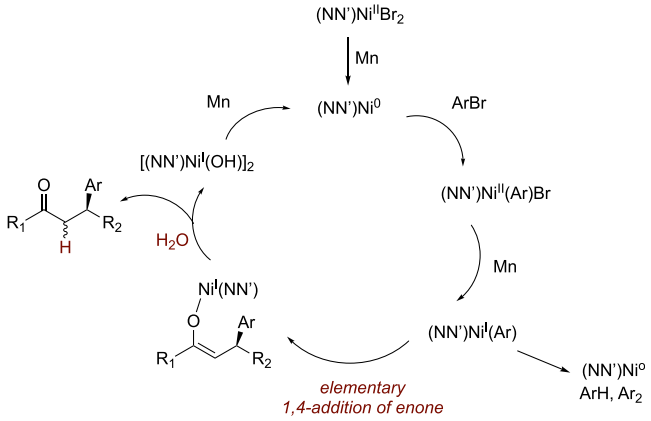

Figure 8. Proposed catalytic cycle.

oxidative addition of ArBr, (**L1**)Ni^{II}(*Ar*)Br was reduced by Mn powder to (**L1**)Ni^{I}(Ar). The latter underwent fast 1,4-addition to enones, and the resulting nickel *O*-enolate was hydrolyzed by water to release the final product. Finally, Mn reduction of either (**L1**)Ni^{I}(OH) (or its dimer) or (**L1**)Ni^{I}(Br) (or its dimer) completed the catalytic process.

Why do 3d late transition metals nickel and copper[17,3,16] participate in rare elementary 1,4-addition of α,β-unsaturated carbonyls? Nickel and copper have relatively smaller covalent radii (1.24 and 1.32 pm),[18] and they are more oxophilic (electronegativity 1.9) than 4d congeners rhodium and palladium. In addition, the 3d orbitals in the first transition series are contracted because of their poor ability to shielding nuclear charges. Thus, 3d orbitals of mid-to-late groups do not mix very effectively with bound ligands. Consequently, the aryl complexes of nickel and copper can participate in facile 1,4-addition via six-membered cyclic TSs (typically <10 kcal mol^{-1}), provided that Michael acceptors can assume the *s*-cisoid conformation. Direct M-O bonding stabilizes the nascent enolate structures which is a key feature of the cyclic TS. In comparison, putative 1,2-addition at α,β-positions of enones on nickel and copper has high barriers (>20 kcal mol^{-1}). In contrast, 4d metals palladium and rhodium have larger covalent radii (1.39 and 1.42 pm), and they are more carbophilic (electronegativity 2.2). They have more diffused and extended 4d orbitals with relatively low energies to effectively interact with frontier molecular orbitals of alkenes (including those of enones). Therefore, aryl complexes of Pd and Rh exhibit a high propensity toward classical 1,2-addition of olefinic moieties of enones.[19] The 1,4-addition also differs from classical Cu^{I}/Cu^{III} shuttling which operates in conjugate

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addition of high nucleophilic diorganocuprates and copper-catalyzed conjugate addition of organometallic reagents of Li, Mg, Zn, Al, and so on.[20] A bimetallic complex $(L)_2CuR{\bullet}MgBr_2$ was proposed to undergo reversible oxidative addition at the β carbon of a Michael acceptor with the newly formed enolate intimately stabilized by the bridging $MgBr_2$ preceding rate-limiting C-C reductive elimination.

CONCLUSIONS

In summary, we report a nickel-catalyzed enantioselective reductive (hetero)arylation of α,β-unsaturated ketones. The new reaction has several attributes: very mild conditions, excellent tolerance of polar groups and heterocycles, broad scope of (hetero)aryl halides, broad scope of enones, and excellent stereoselectivity across the board (>90% ee). Mechanistically, both experiments and DFT calculations supported that arylnickel(I) species inserted to enones via a cyclic transition state of 1,4-addition.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c05678.

Experimental procedures and compound characterization (PDF)

NMR spectra (PDF)

DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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