Nickel-catalyzed asymmetric α-arylation of ketone enolates†

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An atropisomeric dipyridyldiphosphine, P-Phos, can effect highly enantioselective Ni-catalyzed α-arylation of ketone enolates with aryl halides to install an all-carbon quaternary stereogenic center in up to 98% ee and excellent yields.

Optically active α-aryl carbonyl moieties are important structural features of many naturally occurring products, pharmaceutically attractive molecules, synthetically useful intermediates and precursors to emissive polymers.[1] Particularly, direct carbon–carbon bond formation between an arene and the α-carbon adjacent to a carbonyl group remains a formidable challenge in organic synthesis, since enolate nucleophiles and aromatic halides are rare reaction partners. The development of efficient catalytic methods, especially enantioselective catalysis, for accessing these classes of compounds is highly desirable.

Successful metal-mediated coupling of enolates was achieved initially using stoichiometric quantities of nickel complexes. Semmelhack *et al.* reported the nickel-mediated intramolecular arylation of an ester,[2] and Millard and Rathke covered the Ni-mediated intermolecular arylation of Li-enolates.[3]

The catalytic version of Reformasky-type arylation of zinc-enolates was reported by Fauvarque and Jutand within a limited substrate scope.[4] Significant development of this area was achieved by Migita *et al.*, who pioneered the Pd-catalyzed coupling of aryl and vinyl halides with transmetallating zinc- or tin-enolates,[5–7] albeit applicable only to acetates or methyl ketones. Buchwald and Palucki elegantly demonstrated the foremost direct α-arylation of enolate in the absence of transmetallating agent.[8] A number of Pd-complexes with bulky electron-rich ligands have been used successfully for the non-enantioselective intra- and intermolecular version of these processes.[1] Recently, some progress on the reaction of enolates with main group arylating reagents (*e.g.* organobismuth and aryllead) also appeared in the literature.[9]

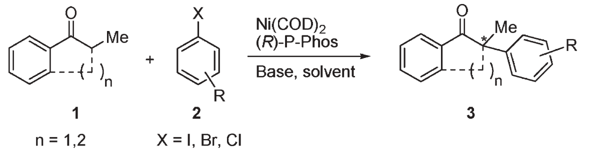
The asymmetric arylation of enolates is an attractive means to prepare optically active carbonyl compounds, which possess an α-quaternary asymmetric center. Buchwald and coworkers achieved the asymmetric α-arylation of ketone enolates in good yield and enantioselectivity by using Pd complex of BINAP[10] or dialkylphosphino-binaphthyl ligands.[11] High catalyst loading (10–20 mol% Pd/12–24 mol% (*S*)-BINAP) was required in this Pd(BINAP)-catalyzed system with moderate substrate scope. We are attracted to some recent reports on the asymmetric Ni-BINAP-catalyzed α-arylation of esters (α-substituted γ-butyrolactones).[12] Herein, we report the first highly enantioselective Ni-catalyzed α-arylation of ketone enolates with aryl halides in the presence of an atropisomeric dipyridyldiphosphine P-Phos[13] as supporting ligand (Scheme 1).

A prototypical reaction of 2-methyl-1-tetralone (**1**) with bromobenzene in the presence of 2 mol% $Ni(COD)_2$ and 2.4 mol% (*R*)-P-Phos was initially examined for optimizing the reaction conditions (Table 1). The α-phenylated product **3a** was obtained in 88% isolated yield and 90% ee with NaHMDS as base. A survey of different solvents and bases revealed that toluene and sodium *tert*-butoxide are a superior combination (Table 1, entry 2). Employing weaker inorganic bases such as K_3PO_4 resulted in lower productivity even with prolonged reaction time. The yield and enantioselectivity decreased in THF at 60 °C; addition of $ZnBr_2$ led to poor reactivity and enantioselectivity. Adding LiOAc would slighly increase the product yield, albeit with a compromised ee value (Table 1, entry 6).

In order to test the effectiveness of the Ni-(*R*)-P-Phos-catalyzed enantioselective arylation reaction, various aryl bromides were examined under these preliminary optimized conditions using **1** as substrate (Table 2). The *meta*- and *para*-substituted aryl bromides showed good yields and moderate-to-excellent enantioselectivities (Table 2, entries 1–7). However, poor reactivity was observed with 2-bromoanisole as reactant (less than 10% yield after 36 h). Excellent enantioselectivity (98% ee) was attained for the reaction with 4-bromobenzonitrile (Table 1, entry 4). To our best knowledge, this is the highest ee value reported so far for this type of Ni-catalyzed transformation. Iodobenzene is also an effective reactant under these reaction conditions at 70 °C, furnishing the coupling product in 97% yield and 92% ee (Table 2, entry 8). Notably, unactivated aryl chloride was found, for the first time, to react with **1** in Ni-catalyzed reaction conditions to yield the coupling product in 91% ee (Table 2, entry 9).

In addition to the 2-methyl-1-tetralone, we have synthesized the propyl analogue **6** for the further investigation of this class of substituted six-membered cyclic ketone. The arylated product **7** was obtained in 76% *ee*. (Scheme 2).

The α-arylation of 2-methyl-1-indanone (**4**) is still problematic with the Pd(BINAP) system, especially with the *para*-substituted



Scheme 1 Ni-P-Phos-catalyzed α-arylation of ketone enolates.

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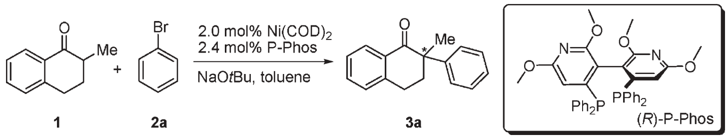
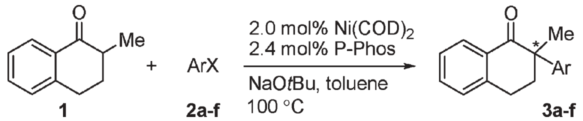
Table 1 Ni-(*R*)-P-Phos-catalyzed asymmetric α-arylation of 2-methyl-1-tetralone under various reaction conditions[a]



Entry	Base	Solvent	Temp. (°C)	Time (h)	% Yield[b]	% ee[c]
1	NaHMDS	toluene	100	24	88	90
2	NaO*t*-Bu	toluene	100	24	85	92
3	K_3PO_4	toluene	100	48	trace	Nd.[d]
4	NaO*t*-Bu	THF	60	24	49	85
5	NaO*t*-Bu/$ZnBr_2$	THF	60	24	30	77
6	NaO*t*-Bu/LiOAc	toluene	100	24	93	71

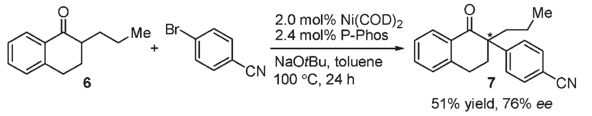
[a] Reaction conditions: $Ni(COD)_2$: (*R*)-P-Phos : 2-methyl-1-tetralone : PhBr : NaO*t*-Bu = 1 : 1.2 : 50 : 150 : 100. [b] Isolated yield. [c] The enantiomer ratios were determined by chiral HPLC (Chiralcel® OB-H column). [d] Not determined.

Table 2 Ni-P-Phos-catalyzed asymmetric α-arylation of 2-methyl-1-tetralone with various aryl halides[a]



Entry	ArX	3	% Yield[b]	% ee[c]
1	PhBr	**3a**	85	92
2	(4-Me)-C_4H_6Br	**3b**	78	93
3	(4-*t*-Bu)-C_4H_6Br	**3c**	92	95
4	(4-CN)-C_4H_6Br	**3d**	94	98
5	(3-CN)-C_4H_6Br	**3g**	79	95
6	[4-(2-dioxolane)]-C_4H_6Br	**3f**	90	96
7	(4-CF_3)-C_4H_6Br	**3e**	66	70
8[d]	PhI	**3a**	97	92
9[e]	PhCl	**3a**	59	91

[a] Reaction conditions: $Ni(COD)_2$: (*R*)-P-Phos : 2-methyl-1-tetralone : ArBr : NaO*t*-Bu = 1 : 1.2 : 50 : 150 : 100, for 24 h. [b] Isolated yield. [c] The enantiomer ratios were determined by HPLC (Chiralcel® OB-H or OJ columns). [d] **1** : PhI (1 : 10), at 70 °C. [e] **1** : PhCl (1 : 5), reaction time (48 h).

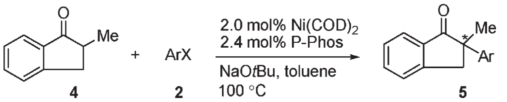


Scheme 2 Ni-P-Phos-catalyzed α-arylation of 2-alkyl-1-tetralone.

aryl bromides, which usually provide coupled product **5** in racemic mixtures.[10] To our delight, the α-arylation of **4** with *para*-substituted aryl bromides in the presence of Ni-P-Phos catalyst proceeded smoothly to afford **5** with moderate-to-good enantioselectivities (Table 3). Thus, this Ni-P-Phos system offers us a wider scope than the Pd(BINAP) system for efficient α-arylation of both tetralone and indanone.

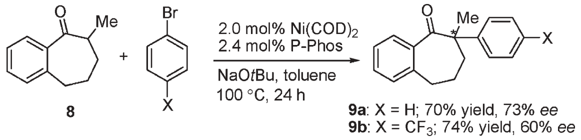
Preliminary results showed that the α-arylation of seven-membered cyclic ketone (benzosuberone) was feasible (Scheme 3). However, our initial results represented that the enantioselective arylation of acyclic 2-substituted propiophenones was unsuccessful.[14] Further investigations are currently underway to cater for this class of substrate.

Table 3 Ni-catalyzed asymmetric α-arylation of indanone **4** with ArX



Entry	ArX	5	% Yield[b]	% ee[c]
1	PhBr	**5a**	78	88
2	(4-Me)-C_4H_6Br	**5b**	69	87
3	(4-F)-C_4H_6Br	**5c**	80	67

[a] Reaction conditions: $Ni(COD)_2$: P-Phos : 2-methyl-1-indanone : ArBr : NaO*t*-Bu = 1 : 1.2 : 50 : 150 : 100, for 24 h. [b] Isolated yield. [c] The enantiomer ratios were determined by chiral HPLC (Chiralcel® OB-H column).



Scheme 3 Ni-P-Phos-catalyzed asymmetric α-arylation of 2-methyl-1-benzosuberone.

In summary, we have achieved the highly enantioselective Ni-P-Phos-catalyzed α-arylation of ketone enolates with aryl halides. Up to 98% ee was obtained with 4-bromobenzonitrile as reactant and it provided the best enantioselectivity accomplished so far for this transformation. In addition, the unactivated aryl chloride can also be applied under these reaction conditions for the first time with good ee values (91% ee). Particularly noteworthy is that the Ni-P-Phos system showed success in the α-arylation of indanone with *para*-substituted aryl bromides, where by contrast the Pd-system failed to provide enantioselectivity. This catalytic system is believed to offer a better scope of efficient asymmetric α-arylation of tetralone, indanone and benzosuberone. Exploration of this catalytic protocol is currently underway.‡

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Notes and references

‡ An oven dried Schlenk tube was charged with Ni(COD)$_2$ (2.8 mg, 2.0 mol%), (*R*)-P-Phos (7.7 mg, 2.4 mol%) and NaO*t*-Bu (96 mg, 1.0 mmol). The Schlenk tube was evacuated and backfilled with N$_2$. Freshly distilled toluene (1.0 mL) was added. After stirring the mixture at RT for 1 min, ArX (1.5 mmol) was added, followed by stirring for another 1 min at RT. To the mixture **1** (76 μL, 0.5 mmol) and toluene (1.0 mL) were added, and the reaction mixture was heated to 100 °C with stirring until **1** was consumed based on GC or TLC monitoring. After cooling to RT, the reaction mixture was quenched with sat. NH$_4$Cl (∼5 mL) and extracted with diethyl ether (2 × ∼10 mL). The combined organic extracts were washed with brine (∼5 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (See supplementary material for details†).

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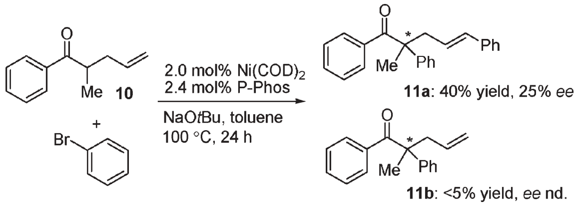

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14 Preliminary results of asymmetric arylation of acyclic ketone **10**.