Nickel-Catalyzed Asymmetric Reductive Cross-Coupling of α-Chloroesters with (Hetero)Aryl Iodides

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ABSTRACT: An asymmetric reductive cross-coupling of α-chloroesters and (hetero)aryl iodides is reported. This nickel-catalyzed reaction proceeds with a chiral BiOX ligand under mild conditions, affording α-aryl esters in good yields and enantioselectivities. The reaction is tolerant of a variety of functional groups, and the resulting products can be converted to pharmaceutically-relevant chiral building blocks. A multivariate linear regression model was developed to quantitatively relate the influence of the α-chloroester substrate and ligand on enantioselectivity.

Carboxylic acid derivatives containing α-aryl stereogenic centers are useful synthetic building blocks and are found in a number of biologically active compounds, including non-steroidal anti-inflammatory drugs such as naproxen and ibuprofen (Figure 1a). Often these compounds are synthesized in enantioenriched form by chiral resolution or through the use of chiral auxiliaries. In order to streamline the synthesis of such compounds, there has been significant effort aimed at the development of enantioselective transition metal-catalyzed enolate arylation reactions. A challenge of this approach is the need for a strong base, which can give rise to racemization of the newly formed stereocenter under the reaction conditions. As an alternative, several teams have investigated the cross-coupling of α-halo carbonyl compounds with aryl nucelophiles using chiral Ni, Co, or Fe catalysts, which can proceed under mild conditions to give products with good levels of enantiomeric excess (Figure 1b).

As an alternative approach to enantioenriched α-aryl carboxylic acids, we envisioned developing a Ni-catalyzed asymmetric reductive cross-coupling of α-chloroesters with (hetero)aryl iodides. Such cross-electrophile couplings have emerged as versatile methods for C(sp²)–C(sp³) bond formation. One advantage over traditional cross-coupling reactions is that no pre-generated organometallic reagents are required, which can improve the functional group tolerance. In this context, our laboratory has developed Ni-catalyzed enantioselective cross-electrophile couplings for a range of electrophile pairs. In the racemic sense, early studies by Durandetti and coworkers established that Ni catalyzes the reductive cross-coupling of α-chloroesters and aryl iodides using either Mn⁰ or electrochemical reduction to turn over the catalyst; however, the scope of investigations were limited to methyl 2-chloropropanoate and methyl 2-chloroacetate. As we were completing our own investigations, Mao, Walsh, and coworkers reported a Ni-catalyzed asymmetric coupling of α-chloroesters and aryl iodides using a metallaphotoredox approach. Here, we report the development of a nickel-catalyzed enantioselective reductive cross-coupling between α-chloroesters and a variety of aryl and heteroaryl iodides (Figure 1c). This system performs particularly well for β-branched substrates, providing access to α-aryl carboxylic acid derivatives that are both difficult to prepare and underrepresented in reported methods. Additionally, multivariate linear regression (MLR) informs how steric matching between the ligand and substrate controls the enantioselectivity observed for the reaction.

Figure 1. Enantioenriched α-aryl carboxylic acid derivatives.

a) Biologically active α-aryl carboxylic acid derivatives.

b) Asymmetric reductive coupling to form α-aryl esters.

c) This work: Ni-catalyzed asymmetric reductive coupling of α-chloroesters.
We began our study investigating the coupling between phenyl 2-chloropropanoate (1a) and pyridyl iodide 2a. An initial evaluation of reaction parameters identified the BiOX family of ligands as most promising for this transformation, using NiBr₂-diglyme as the Ni source, THF as the solvent, and Mn⁺ as the terminal reductant (Table 1, entry 1). The use of NaBF₄ (1.0 equiv) as an additive was found to be critical for the formation of 3a (entry 2). Butyl bromide failed to afford any of the desired product (entry 5).

Table 1. Effects of Reaction Parameters.

| entry | deviation from standard conditions | yield (%) | ee (%) |
|-------|-----------------------------------|-----------|--------|
| 1     | None                              | 92        | 86     |
| 2     | No NaBF₄                          | 0         | –      |
| 3     | L₂ instead of L₁                   | 62        | 76     |
| 4     | L₃ instead of L₁                   | 89        | 70     |
| 5     | L₄ instead of L₁                   | 0         | –      |
| 6     | 10 mol % L₁                        | 81        | 83     |
| 7     | Zn⁶ instead of Mn⁶                 | 29        | 81     |
| 8     | TDAE instead of Mn⁶                | 0         | –      |
| 9     | DMA instead of THF                 | 67        | 84     |
| 10    | 1,4-dioxane instead of THF         | 0         | –      |
| 11    | Methyl ester                      | 40        | 84     |
| 12    | t-Butyl ester                     | 20        | 89     |
| 13    | 1 equiv 2a                        | 85        | 84     |
| 14    | 4 instead of 2a                    | 10        | 84     |
| 15    | 5 instead of 1a                    | 0         | –      |
| 16    | No NiBr₂-diglyme                   | 0         | –      |
| 17    | No L₁                             | 0         | –      |
| 18    | No Mn⁶                            | 0         | –      |

Reactions conducted in duplicate on 0.2 mmol scale. Determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Determined by SFC using a chiral stationary phase. TDAE = tetrakis(dimethylamino)ethylene.

Zn⁶ proved less effective than Mn⁶ as a reductant (entry 7), and use of TDAE failed to afford any of the desired product (entries 8). Whereas the reaction performed reasonably well in DMA, no reaction was observed in 1,4-dioxane, a solvent previously applied to other [L₁-Ni]-catalyzed asymmetric reductive coupling reactions (entries 9 and 10). Use of the methyl or tert-butyl esters instead of the phenyl ester gave coupled product in similar enantioselectivity but reduced yields (entries 11 and 12). The amount of 2a could be reduced to 1.0 equiv with only a slight decrease in the yield of 3a (entry 13). When pyridyl bromide 4 was employed instead of 2a, substantially lower yields of 3a were obtained (entry 14), while use of α-bromoester 5 failed to give any of the desired product (entry 15).

Control experiments confirmed that nickel, ligand, and Mn⁺ are all required for product formation (entries 16–18).

Figure 2. Scope of (Hetero)Aryl Iodides.

[Table and diagrams showing reaction results]

To investigate the scope of the reaction, a series of aryl iodides were coupled with 1a under standard conditions (Figure 2). The reaction tolerates both electron-rich (3g and 3k) and electron-poor (3c and 3e) aryl iodides, as well as heteroaryl iodides (3a, 3d, and 3j). Protected heteroatoms (3j and 3k) and an aryl chloride (3l) were tolerated, giving enantioenriched products poised for further elaboration. Whereas para- and meta-tolyl substrates 3g and 3h coupled efficiently, ortho-tolyl iodide resulted in significantly reduced yield and enantioselectivity. Analysis of this series of substrates suggests that the reaction is relatively insensitive to the electronic properties of the arene.

In contrast to the aryl iodides, the enantioselectivity of the reaction was found to be quite sensitive to the structure of the α-chlorosteres (Figure 3). For a series of substrates where the α-substituent is changed from methyl (3a) to ethyl (6a) to iso-propyl (6b), the ee of the product increased from 85% to 88% to 96%, respectively. A similar trend was observed in the formation of 3b, 6c, and 6e. The α-iso-propyl chloroester 1c can be coupled with a variety of aryl i-
didates to give the corresponding α-arylesters in good yield and uniformly high ee (6b, 6c, 6e, 6j, and 6k). Similar yields and ee were obtained with the α-cyclopentyl and α-cyclohexyl substituents (6f and 6g). Using the α-chloroester derived from L-isoleucine (1f), either the S,S- or le-R,S-diastereomer (6h and 6i) could be obtained simply by changing the enantiomer of L1 that was used, demonstrating that products with vicinal stereogenic centers can be prepared with catalyst control over the configuration of the α-carbon. We note that, qualitatively, the increase in enantioselectivity with large substituents does not come at the expense of yield, in contrast to related transformations.4d,13

Figure 3. Scope of α-Chloroesters.

Reactions conducted in duplicate on 0.2 mmol scale. Isolated yields are provided; ee was determined by SFC using a chiral stationary phase. (S,S)-L1 was used. Reaction time was 48 h.

Given that the enantioselectivity improves as a function of the size of the α-substituent, we hypothesized that a synergistic interaction between the substrate and the ligand may be at play. In order to quantify this, we used statistical modelling of substrate/ligand features with the observed enantioselectivity by evaluating a matrix of five α-chloroesters with five BiOX ligands.14 Utilizing a workflow previously reported by one of our labs,15,16 conformers with a 2.4 kcal/mol energy range were identified via a conformational search using the OPLS3e force field (see SI for details).17 Each conformer was then submitted to DFT level geometry optimization, followed by single point energy calculations of the optimized structures at the M06-2x/def2-TZVP level of theory.18,19 Various molecular features, including Boltzmann-weighted descriptors, were acquired from these optimized structures.14 The ensuing library was then split into a training set (18 points) and a test set (6 points) by an automated process20 using a test ratio of 0.25. Using both the experimental ee (expressed as ln(er)) and the computationally derived molecular features, a forward stepwise linear regression algorithm was used to yield a statistical model (Figure 4b).21 The resulting statistical model reveals a clear correlation between the observed enantioselectivity and the Boltzmann-weighted minimum width (B1) of both the ligand and the substrate (Figure 4a). The statistics of the model indicate a high level of accuracy (R2 = 0.93) and the model robustness is also high as indicated by cross-validations (leave-one-out (LOO) Q2 = 0.89 and K-fold = 0.89). The model indicates that steric matching between the catalyst and substrate is responsible for high selectivity, as evidenced by the fact that the substrate and ligand with the largest Boltzmann B1 value (6g and L1) give the best selectivity while those with the smallest values give the worst selectivity. Both ligand and substrate parameters were required to describe the reaction output (see SI for details). This simple model should be highly predictive if either a new catalyst or a new substrate is considered for application of this reaction.

Figure 4. Multivariate linear regression shows correlation between ligand and α-chloroester size.

a) Model for Observed Enantioselectivity

\[
\ln(er) = 2.74 + 0.69B1_{\text{Ligand}} + 0.70B1_{\text{Substrate}}
\]

\[R^2 = 0.93, \quad \text{LOO } Q^2 = 0.89, \quad \text{K-fold } R^2 = 0.88\]

b) Relevant Molecular Features

To demonstrate the utility of this method to access pharmaceutically-relevant α-aryl carboxylic acids, we prepared the nonsteroi-dal anti-inflammatory drug (S)-naproxen (9, Scheme 1). Coupling of α-chloroester 1a with naphthyl iodide 7 under standard conditions...
afforded ester 8 in 93% yield and 84% ee on 1.0 mmol scale. Hydrolysis of the phenyl ester gave 9 in 84% ee. This synthesis allowed the unambiguous assignment of the configuration of 8 as $S$.

**Scheme 1. Product Elaboration to Naproxen.**

It is has become accepted that many Ni-catalyzed cross-coupling reactions of alkyl halides involve oxidative addition by a radical mechanism. However, $\alpha$-chlo-roesters such as 1 could potentially react via an in situ-generated manganese enolate. To investigate this possibility, Mn enolate 10 was prepared and subjected to aryl iodide 2g under the standard reaction conditions; however, no product 3g was observed (Figure 5a). Control experiments determined that the reductive cross-coupling could still proceed in 73% yield and 81% ee when the byproducts from Mn enolate formation were doped into the standard reaction (LiCl, hexanes, and Pr$_2$NH). A stoichiometric experiment was carried out in which pre-complexed [L1-Ni$^{0}$] was added dropwise to aryl iodide 2g; subsequent addition of chloroester 1a afforded 3g in 72% yield and comparable ee to the catalytic reaction. Taken together, these experiments do not support the formation of a Mn enolate, but do indicate that product formation does not require reduction of [L1-Ni$^{0}$ArX]. Similar studies were used by Weix and coworkers to implicate oxidative addition of the alkyl halide by a radical chain mechanism in the coupling between aryl halides and unactivated alkyl halides; unfortunately, efforts to further interrogate this possibility for the present reaction, using a variety of radical trapping experiments, have not been conclusive (Figure 5c).

**Figure 5. Mechanistic Experiments**

a) Viability of a Mn enolate.

10 (1 equiv) + 2g (1.5 equiv)

\[
\text{PhO} \quad \text{Cl} \quad \text{Me} \quad \text{OMe} \quad \text{NiBr}_2 \cdot \text{diglyme} \\
(10 \text{ mol} \%) \quad (10 \text{ mol} \%) \quad \text{L1} \quad (20 \text{ mol} \%) \quad \text{THF} \quad 18^\circ \text{C} \quad 14 \text{ h} \\
\rightarrow \text{Me} \quad \text{OMe} \quad \text{PhO} \\
\text{PhO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{KOH} \quad \text{H}_2\text{O} \quad \text{PhMe} \\
\text{Me} \quad \text{OMe} \quad \text{PhO} \\
\text{Me} \quad \text{OMe} \quad \text{PhO} \\
\text{96\% yield, 83\% ee} \\
\text{93\% yield, 84\% ee} \\
\]

b) Stoichiometric reaction.

2g (1 equiv) + NaBF$_4$ (1 equiv) + NaBF$_4$ (1 equiv) + L1 (1 equiv) Ni(cod)$_2$ (1 equiv) THF, 18°C added dropwise

\[
\text{L1-Ni}^{0} \quad \text{Me} \quad \text{OMe} \\
\text{Me} \quad \text{OMe} \quad \text{PhO} \\
\text{Me} \quad \text{OMe} \quad \text{PhO} \\
\text{72\% yield, 81\% ee} \\
\]

In conclusion, we have developed a nickel-catalyzed asymmetric reductive cross-coupling of $\alpha$-chlo-roesters and (hetero)aryl iodides. The transformation is enabled by a chiral BiOX ligand previously developed by our group, and forms $\alpha$-arylated esters in good yields and enantioselectivities under mild conditions. These products are useful chiral building blocks with potential applications in pharmaceuticals, agrochemicals, and materials. The reaction proves especially selective when $\beta$-branched substrates are employed. An MLR model has been developed to quantitatively demonstrate the cooperative influence of the substrate and ligand steric profiles on enantioselectivity.

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The manuscript was written through contributions of all authors. *These authors contributed equally to this manuscript.*

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**ABBREVIATIONS**

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