Synthetic Methods

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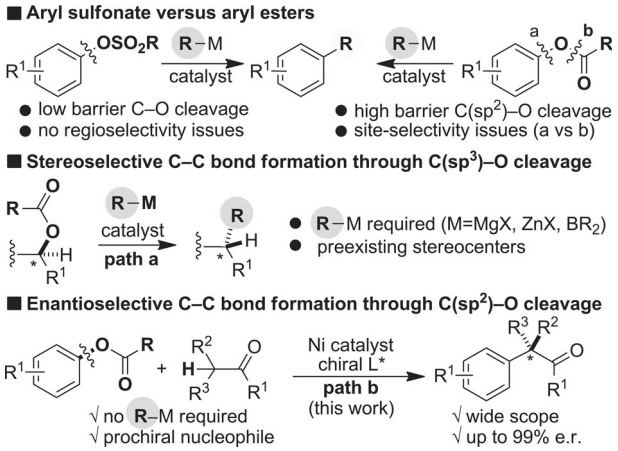
Nickel-Catalyzed Enantioselective C–C Bond Formation through C_{sp^2}–O Cleavage in Aryl Esters**

*Josep Cornella, Evan P. Jackson, and Ruben Martin**

Abstract: *We report the first enantioselective C–C bond formation through C–O bond cleavage using aryl ester counterparts. This method is characterized by its wide substrate scope and results in the formation of quaternary stereogenic centers with high yields and asymmetric induction.*

Over the past decade, C–O electrophiles have gained momentum as powerful alternatives to aryl halides in the cross-coupling arena.[1] Such popularity is largely due to the availability and lack of toxicity of phenols compared to organic halides, representing a significant step forward for their utilization in cross-coupling techniques. Among the phenol series, the utilization of aryl sulfonates, particularly aryl triflates, has become routine due to their high reactivity, low barrier for C–O oxidative addition, and the lack of regioselectivity issues for C–O bond cleavage (Scheme 1, top left).[1] In sharp contrast, the employment of simpler and cheaper aryl esters as C–O electrophiles still poses formidable challenges due to the higher activation energy required for the cleavage of the rather unreactive C_{sp^2}–O bond, the site selectivity among multiple C–O bonds and their inherent tendency for hydrolysis under basic conditions (Scheme 1, top right).[1] Not surprisingly, a rather limited number of C–C bond-forming reactions have been reported using aryl ester counterparts; importantly, the vast majority of these processes employ stoichiometric and well-defined organometallic species, thus constituting a drawback from a practical standpoint (Scheme 1, top right).[2,3]

Despite the advances realized,[1] the development of asymmetric C–O bond cleavage reactions using ester derivatives remains largely undeveloped. In recent years, elegant stereoselective transformations have recently been reported by the groups of Jarvo[4] and Watson[5] (Scheme 1, path a) using ester counterparts; unfortunately, these methods are restricted to the formation of tertiary stereocenters, requiring the installation of a preexisting stereogenic center. In sharp contrast, an enantioselective C–C bond formation through C_{sp^2}–O bond cleavage with prochiral nucleophilic entities that obviates the need for organometallic reagents and results in the rather elusive quaternary stereogenic centers has not yet been described in the literature.[6] Unquestionably, the ability to promote such a reaction would not only dramatically expand the utility of C–O electrophiles, but would also open up new and unconventional strategies for preparing valuable and enantioenriched complex molecules. As part of our ongoing studies in C–O bond cleavage reactions,[7] we summarize our investigations aimed at the development of the first metal-catalyzed enantioselective C–C bond formation of aryl esters through C_{sp^2}–O bond cleavage (Scheme 1, path b).[8] This transformation utilizes in situ-generated prochiral ketone enolates and replaces commonly employed organic halides or activated aryl sulfonates by simpler aryl esters derived from phenol.[9,10] This method is distinguished by a high asymmetric induction and wide scope, including the coupling of rather challenging nonextended π-systems.



Scheme 1. C–C bond formation with ester counterparts.

We began our study by examining the reactivity of 2-methyl-1-indanone (**1a**) with 2-naphthyl pivalate (**2a**), and the effects of the metal catalyst, ligand, base, and solvent employed were systematically investigated (Scheme 2).[11] Initial evaluation of a number of metal complexes identified $Ni(cod)_2$ as a competent catalyst in combination with NaO*t*Bu

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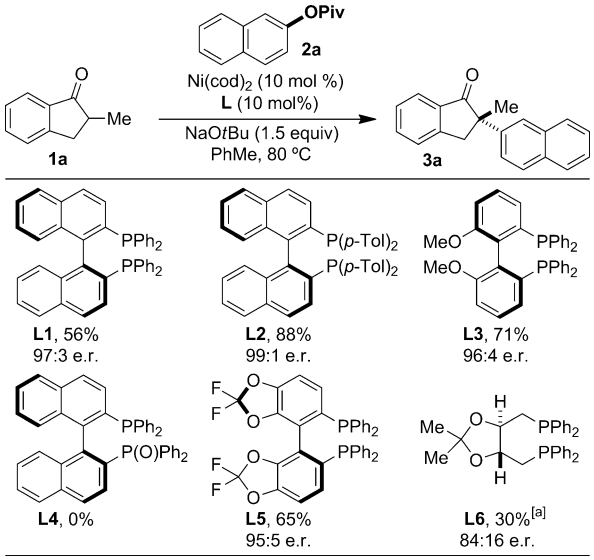
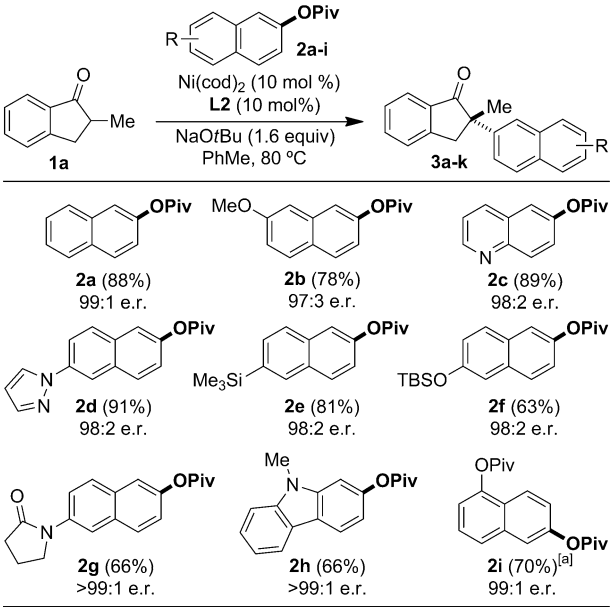


Scheme 2. Enantioselective α-arylation of ketones with aryl esters. Reaction conditions: **1a** (0.25 mmol), **2a** (0.40 mmol), $Ni(cod)_2$ (10 mol%), **L** (10 mol%), NaO*t*Bu (0.40 mmol), toluene (0.17 M) at 80 °C for 12 h. Yields were determined by GC using decane as internal standard. Enantiomeric ratios (e.r.) were determined by HPLC of the crude mixtures on a chiral stationary phase. [a] (*R*)-**3a** was formed.

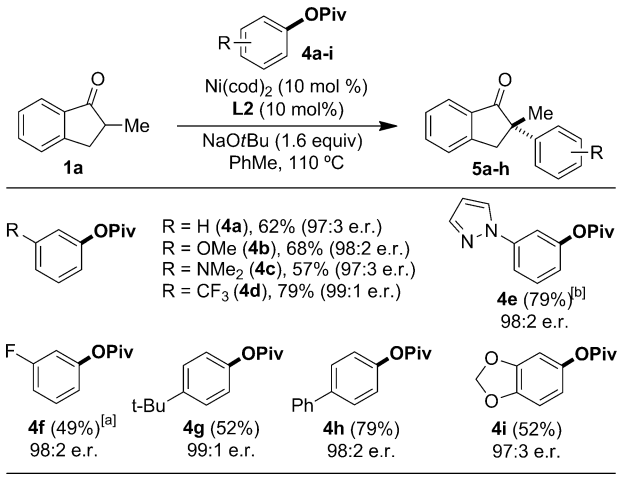


Scheme 3. Scope of naphthyl pivalates. Reaction conditions: **1a** (0.25 mmol), **2a**–**2i** (0.40 mmol), $Ni(cod)_2$ (10 mol%), **L2** (10 mol%), NaO*t*Bu (0.40 mmol), PhMe (0.17 M) at 80 °C for 12 h. Yields are of isolated products; average of at least two independent runs. Enantiomeric ratios (e.r.) were determined by HPLC on a chiral stationary phase. [a] LiHMDS (0.25 mmol) was used as the base.

as the base in toluene at 80 °C. After a judicious screening of the available chiral ligands,[11] we observed a promising asymmetric induction when operating under a **L1** regime. A similar pattern was found for **L3** and **L5**,[10d] reinforcing the notion that a chiral bidentate ligand bearing a biaryl axis was critical for success. In line with these results, we found little reactivity, if any, and low asymmetric induction for **L4** and **L6**. Intriguingly, the inclusion of more electron-rich and sterically demanding ligands had a detrimental impact on the reaction outcome.[11] Similarly, we found that subtle changes on the biaryl backbone of the ligand employed had a marked influence on enantioselectivity. After considerable experimentation, we found that commercially available **L2** provided the best results, obtaining **3a** in 88% yield and with an excellent asymmetric induction (99:1 e.r.). The absolute configuration of **3a** was unambiguously determined by X-ray crystallographic analysis,[12] thus concluding that *S*-configured **3a** was obtained when the reaction was performed with (*S*)-Tol-BINAP (**L2**). As anticipated, control experiments showed that all reaction components were critical for obtaining **3a** in high yield and asymmetric induction.[13]

With the optimized conditions, we sought to examine the scope and the generality of our enantioselective C–C bond formation through C–O bond cleavage. As shown in Scheme 3, the Ni-catalyzed ketone α-arylation of naphthyl pivalates turned out to be widely applicable when utilizing a diverse set of naphthyl derivatives. Interestingly, substrates with pyrazoles (**2d**), quinolines (**2c**), silanes (**2e**), silyl ethers (**2f**), amides (**2g**), and esters (**2i**) posed no problems and remained intact under our optimized reaction conditions. Of particular interest is the fact that nitrogen-containing heterocycles do not interfere (**2c**, **2d**), indicating that these motifs do not compete with **L2** for substrate binding at the Ni center. Equally interesting is the ability to couple carbazole motifs in good yields and without an erosion in enantioselectivity (**2h**). In light of these results, we anticipated that site selectivity would be within reach with similarly reactive C–O bonds. As shown for **2i**, this was indeed the case, obtaining a single regioisomer with excellent yield and asymmetric control.

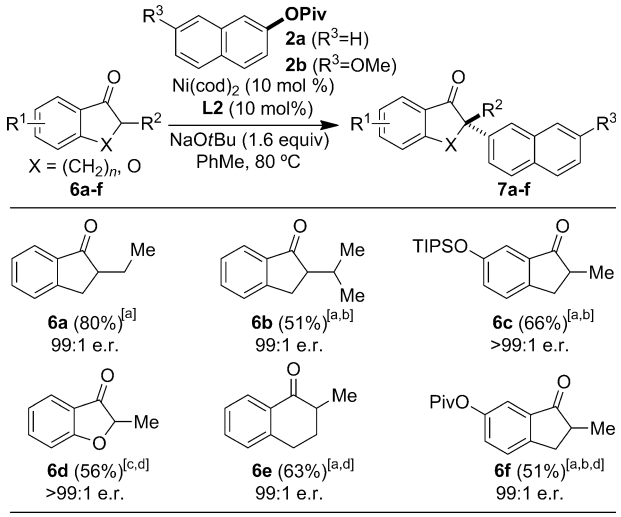
A close inspection of literature data indicates that the use of extended π-systems has typically been a requisite in a wide number of catalytic C–O bond cleavage processes.[14] Most likely, the ease for η^2-coordination to the metal center and the intermediacy of Meisenheimer-type complexes makes extended π-systems several orders of magnitude more reactive than regular arenes.[15,16] Therefore, it was unclear whether a Ni-catalyzed enantioselective C–C bond formation through C–O bond cleavage could ever be conducted with less activated and rather challenging phenyl pivalates. Gratifyingly, this turned out to be the case (Scheme 4). As shown, the coupling of a host of challenging phenyl pivalates could be conducted under otherwise similar reaction conditions to those in Scheme 3. These results reinforce the perception that our protocol based upon Ni/**L2** represents a general technique for preparing α-arylated compounds with quaternary stereogenic centers from simple aryl ester coupling partners. Although aryl pivalates afforded significantly lower reaction rates than naphthyl pivalates (Scheme 3), excellent enantioselectivities were found in all substrates analyzed (Scheme 4). As judged by the results in Scheme 4, it becomes evident that the outcome of the α-arylation event was largely insensitive to electronic changes at the *para* and *meta* positions on the aromatic ring. Unfortunately, *ortho*-substituted phenyl pivalates could not be employed as substrates. Notably, amines



Scheme 4. Scope of aryl pivalates. Reaction conditions: **1a** (0.25 mmol), **4a**–**4i** (0.40 mmol), $Ni(cod)_2$ (10 mol%), **L2** (10 mol%), NaO*t*Bu (0.40 mmol), PhMe (0.17 M) at 110°C for 12 h. Yields are of isolated products; average of at least two independent runs. Enantiomeric ratios (e.r.) were determined by HPLC on a chiral stationary phase. [a] **4** (0.75 mmol).

(**4c**), nitrogen-containing heterocycles (**4e**), acetals (**4i**), and aryl fluorides (**4f**) were all well accommodated, thus illustrating the chemoselectivity and robustness of our protocol.

Next, we turned our attention to explore the reactivity of differently substituted aryl ketones in our Ni-catalyzed enantioselective reaction (Scheme 5). As shown, aryl ketones containing ethyl or even bulkier isopropyl substituents in the α-position (**6a** and **6b**) did not significantly hamper the reactivity and the targeted products were obtained in good yields and high enantioselectivities. The successful preparation of benzofuranone **7d** and tetralone **7e** tacitly indicates



Scheme 5. Scope of aryl ketone counterparts. Reaction conditions: **6a**–**6i** (0.25 mmol), **2a**,**b** (0.40 mmol), $Ni(cod)_2$ (10 mol%), **L2** (10 mol%), NaO*t*Bu (0.40 mmol), PhMe (0.17 M) at 80°C for 12 h. Yields are of isolated products; average of at least two independent runs. Enantiomeric ratios (e.r.) were determined by HPLC on a chiral stationary phase. [a] Using **2b**. [b] $Ni(cod)_2$ (20 mol%). [c] Using **2a**. [d] NaHMDS (0.25 mmol) was used as the base.

that medium-sized rings other than indanone can be equally effective. As anticipated, the inclusion of functional groups such as silyl ethers (**6c**) posed no problems. Particularly noteworthy was the observation that a pivalate motif in the indanone core does not interfere (**6f**), resulting in the selective C–O bond cleavage of **2b** when employing NaHMDS as the base.[17] Taken together, we believe that the results in Schemes 3–5 will not only have broader implications for the utilization of rather unconventional aryl esters as C–O electrophiles in cross-coupling reactions, but will also lead to the implementation of new enantioselective protocols based on C–O bond cleavage.[18]

In summary, we have described the first asymmetric C–C bond forming reaction utilizing aryl esters as C–O electrophiles and in situ-generated prochiral ketone enolates. The transformation is distinguished by its wide substrate scope, high asymmetric induction, and diverse set of substitution patterns. We anticipate that our study will lead to the foundation of new asymmetric protocols when utilizing simpler C–O electrophiles. Further investigations along these lines are currently underway in our laboratories.

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[17] No reaction took place under our optimized reaction conditions when employing aliphatic or nonfused aromatic ketone counterparts.

[18] Whether these results indicate a direct oxidative addition into the targeted C_{sp^2}–O bond or if there are other mechanistic implications via the intermediacy of Ni^0-ate complexes is the subject of ongoing mechanistic studies in our laboratory.

Communications

Synthetic Methods

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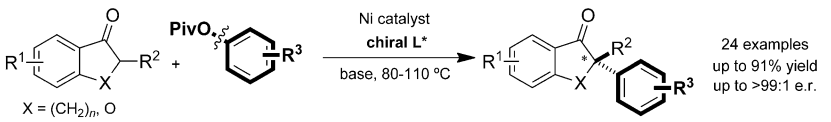
Nickel-Catalyzed Enantioselective C—C Bond Formation through C_{sp^2}—O Cleavage in Aryl Esters



Aryl ester electrophiles are used in an enantioselective C—C bond formation through C—O bond cleavage. This reaction proceeds under nickel catalysis by means of an axially chiral bidentate ligand, allowing the formation of enantioenriched quaternary stereocenters. This protocol is characterized by its high asymmetric induction and remarkable wide scope.