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Asymmetric Catalysis

Asymmetric Cross-Coupling of Non-Activated Secondary Alkyl Halides**

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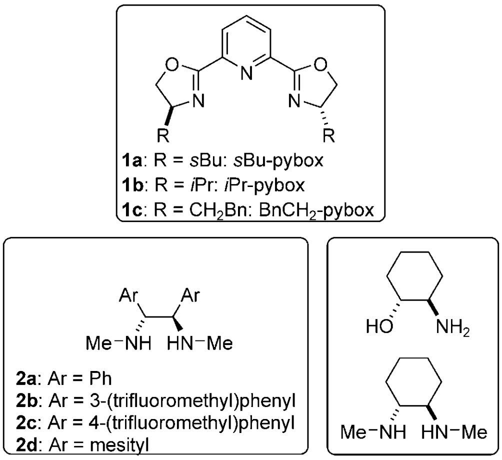
asymmetric catalysis · cross-coupling · Negishi coupling · nickel · Suzuki–Miyaura coupling

Modern transition-metal-catalyzed cross-coupling reactions have altered organic synthesis enormously,[1] and the coupling of aryl and alkenyl electrophiles has become a routine transformation in natural product and fine-chemical synthesis. For a long time, equivalent reactions of alkyl electrophiles, especially those with non-activated β hydrogen atoms, remained elusive. The difficulties encountered in attempts to carry out such reactions have been ascribed to a slow oxidative-addition step and undesired side reactions, such as β-hydride elimination. Palladium complexes of electron-rich phosphines, in particular $P(c\text{-Hex})_3$ and $PtBu_2Me$, were eventually found to be competent catalysts for the Suzuki–Miyaura coupling and related reactions of primary alkyl halides under mild conditions.[2,3]

Even more desirable and challenging is the coupling of secondary alkyl halides: challenging, as the increased steric demand and electron richness of these substrates leads to a reduced rate of oxidative addition; desirable, as a new stereogenic center is often formed. Whereas palladium-catalyzed methods are limited to primary alkyl halide substrates, cheaper nickel complexes were found to be uniquely suited to the catalysis of the cross-coupling of secondary alkyl halides.[4,5] Bi- and tridentate nitrogen ligands (Scheme 1), many of which are commercially available, were found to be key to success of these nickel-catalyzed reactions. These chelate ligands favor the *cis* orientation of the coupling partners at the nickel center. Thus, the rate of reductive elimination is increased relative to that of undesired β-hydride elimination. Recently, Fu and co-workers developed a number of impressive highly enantioselective nickel-catalyzed Negishi,[6] Hiyama,[7] and Suzuki–Miyaura[8] cross-coupling reactions of secondary alkyl halides. The last of these methods is the only asymmetric cross-coupling described to date in which non-activated secondary alkyl halides can be used and thus paves the way for exciting future developments.



Scheme 1. Ligands employed in nickel-catalyzed cross-coupling reactions of secondary alkyl halides (Bn = benzyl, pybox = bis(oxazolinyl)-pyridine).

In 2003, Zhou and Fu reported the high catalytic activity of nickel–pybox complexes formed in situ in the Negishi coupling of non-activated secondary alkyl bromides and iodides with organozinc reagents at ambient temperature.[2,9] Their study served as a starting point for the development of an impressive series of asymmetric Negishi coupling reactions of secondary alkyl halides.[6] Activated racemic alkyl halides, such as α-bromoamides,[6a] benzylic chlorides and bromides,[6b] and allylic chlorides,[6c] were coupled successfully as electrophiles with alkyl zinc reagents with high enantioselectivity (Schemes 2 and 3). The reactions were even carried out below ambient temperature. The reaction conditions were optimized carefully, and it was found that the optimal combination of a solvent, nickel precursor, and additive differed for each class of substrate.[6] Interestingly, in each of these studies, nickel–pybox complexes formed in situ were found to be the most active and most selective catalysts; furthermore, donor solvents, such as 1,3-dimethyl-2-imidazolidinone (DMI), *N*,*N*-dimethylacetamide (DMA), and *N*,*N*-dimethylformamide (DMF), were found to be crucial. The exact mechanism of these transformations still remains to be elucidated. However, in view of the high levels of enantio-

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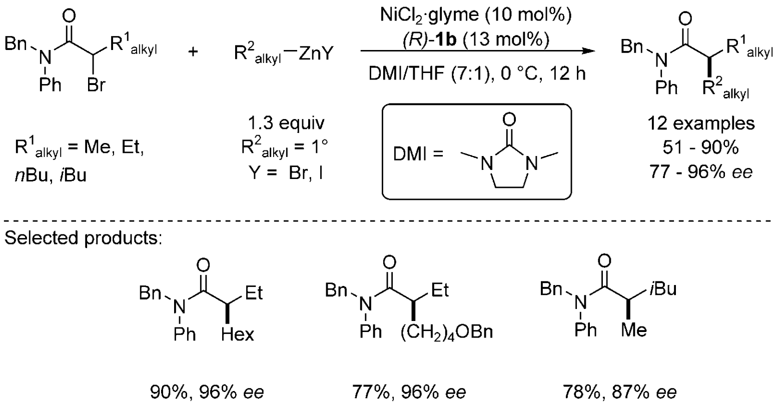
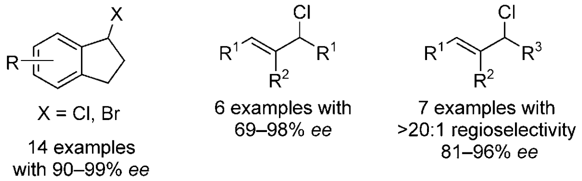


Scheme 2. First asymmetric Negishi coupling of racemic secondary alkyl halides.[6a]

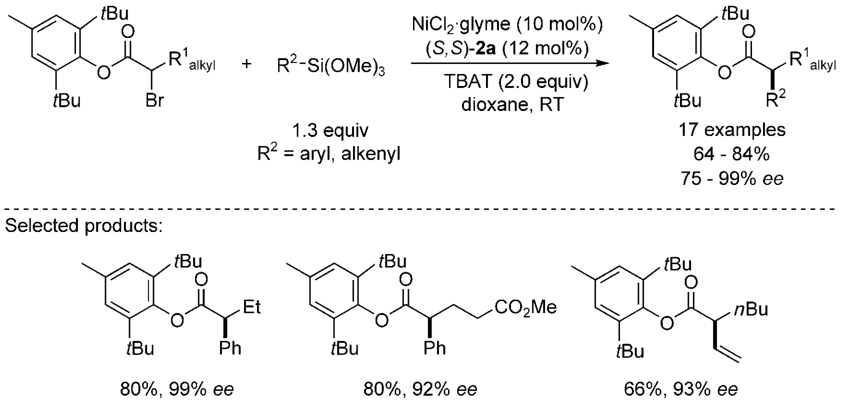


Scheme 3. Racemic secondary alkyl halides used as substrates for asymmetric Negishi cross-coupling reactions.[6b,c]

selectivity observed, a radical–radical coupling mechanism, as proposed initially by Vicic and co-workers, seems unlikely.[10]

The versatility and practicability of these asymmetric Negishi coupling reactions was demonstrated skillfully in a formal total synthesis of fluvirucinine A$_1$ (Scheme 4) in fewer steps and increased overall efficiency relative to the original synthesis.[6c]

Having described the first Hiyama coupling of secondary alkyl halides,[11] Fu and co-workers then developed an asymmetric variant by coupling α-bromoesters with aryl and alkenyl silanes (Scheme 5).[7]

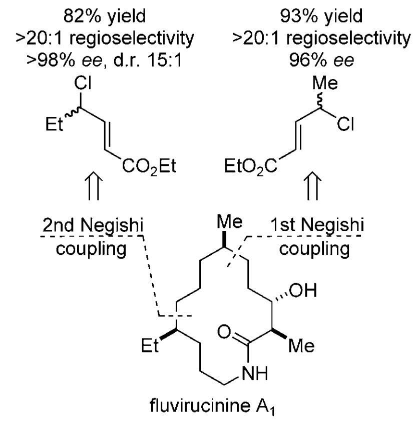


Scheme 5. First asymmetric Hiyama coupling of racemic secondary alkyl halides. TBAT = tetrabutylammonium difluorotriphenylsilicate.

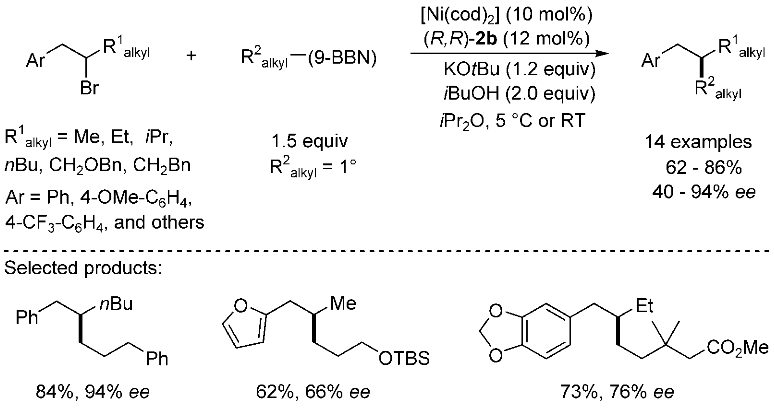
The esters were derived from 2,6-di-*tert*-butyl-4-methylphenol (BHT), as the use of less sterically demanding esters led to a significant deterioration of the enantioselectivity.

The Suzuki–Miyaura coupling is currently perhaps the most popular cross-coupling reaction.[1] However, the C(sp^3)–C(sp^3) Suzuki–Miyaura coupling[12] is especially challenging, as alkyl boranes are generally air and moisture sensitive and can not be stored for long periods of time. Alkyl boranes are usually prepared in situ by the hydroboration of alkenes and used without prior purification. The coupling of non-activated alkyl halides with primary alkyl boranes derived from 9-BBN was made possible by the use of a nickel diamine complex formed in situ under finely tuned basic reaction conditions.[13] Prior to this study, organozinc reagents were the only alkyl metal species to have been coupled successfully with non-activated secondary alkyl halides.

From this point, it was only a small step to another tremendous achievement: the first highly enantioselective alkyl–alkyl cross-coupling of non-activated secondary alkyl halides.[8] This nickel-catalyzed reaction, in which secondary homobenzylic bromides were coupled enantioselectively with primary alkyl boranes, was also the first enantioselective Suzuki–Miyaura coupling of alkyl electrophiles (Scheme 6). Several chiral diaryl-substituted diamine ligands were screened, including **2a**–**2d**, and ligand **2b** was found to provide the most selective catalyst. However, the enantioselectivities observed for this transformation were sometimes lower than those observed for the aforementioned asymmetric cross-coupling reactions (Scheme 6). Deviation from the acyclic homobenzylic bromide structure, that is, the use of cyclic substrates or substrates with a longer side chain, resulted in very low enantioselectivity. Thus, it was concluded that a weak secondary interaction between the catalyst and the CH$_2$Ar group of the substrate is critical for high enantioselectivity.



Scheme 4. Asymmetric Negishi coupling applied twice in the formal total synthesis of fluvirucinine A$_1$.



Scheme 6. First asymmetric (Suzuki–Miyaura) cross-coupling of racemic non-activated secondary alkyl halides. BBN = 9-borabicyclo[3.3.1]nonane, cod = 1,5-cyclooctadiene, TBS = *tert*-butyldimethylsilyl.

Fu and co-workers have amply demonstrated that nickel-based catalysts are uniquely suited for the coupling of activated and non-activated secondary alkyl halides. Impressive levels of enantioselectivity were reported for Negishi, Hiyama, and Suzuki–Miyaura coupling reactions, which will soon be applied in the synthesis of natural products. Future research will lead to an improved mechanistic and stereochemical understanding. Hopefully, the influence of solvents and additives will be elucidated, to enable reactions to be designed more systematically. The door has been opened to the development of general methods for the asymmetric coupling of non-activated secondary alkyl halides. Such methods will certainly alter organic synthesis significantly.

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