Asymmetric Ni-Catalyzed Radical Relayed Reductive Coupling

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Abstract: Alkene dicarbofunctionalizations enable the streamlined construction of aliphatic structures and have thus been the subject of intense research efforts. Despite significant progress, catalytic asymmetric variants remain scarce. Inspired by the advantages of reductive cross-coupling approaches, we present here a highly efficient asymmetric intermolecular Ni-catalyzed reductive dicarbofunctionalization of alkenes. Two distinct readily available electrophiles, namely, Csp2- and Csp3-halides, are added simultaneously across a variety of olefins (vinyl amides, vinyl boranes, vinyl phosphonates) at room temperature in a highly regio- and enantioselective manner. The reaction, devoid of sensitive organometallic reagents, takes advantage of an in situ generated chiral alkyl Ni(III)-intermediate to ensure a stereodefined outcome in the Csp3–Csp2 bond-forming reaction. An (l)-(+)-isoleucine chiral bisoxazoline ligand and the presence of coordinating sites on the alkene are key for the successful outcome in these “asymmetric radical relayed reductive couplings” (ARRRCs). Further, multiple transformations of the chiral amides obtained in this process showcase the potential of this new methodology for the straightforward assembly of chiral building blocks such as primary and secondary amines and oxazolines, highlighting its synthetic utility.

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Asymmetric Ni-catalyzed Radical Relayed Reductive Coupling

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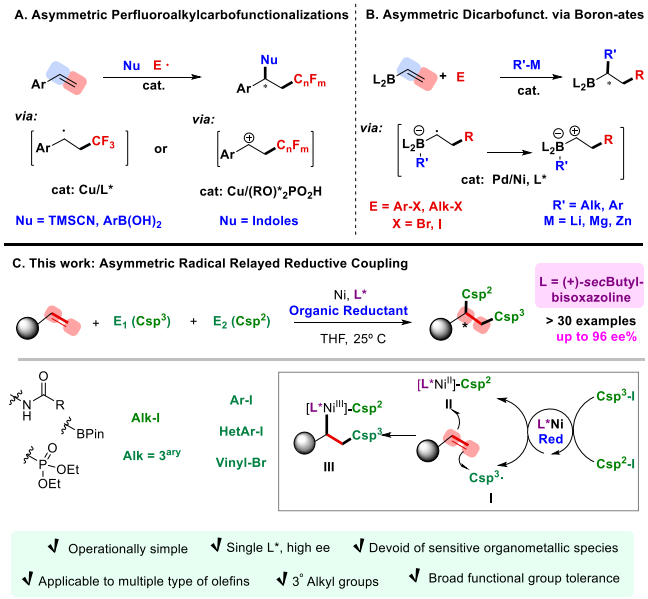
KEYWORDS Nickel, Asymmetric dicarbofunctionalization, Alkenes, Reductive coupling.

ABSTRACT: Alkene dicarbofunctionalizations represent streamline the construction of aliphatic structures and have thus been the subject of intense research efforts. Despite significant progress, catalytic asymmetric variants remain scarce. Inspired by the advantages of reductive cross-coupling approaches, we present here a highly efficient asymmetric intermolecular Ni-catalyzed reductive dicarbofunctionalization of alkenes. Two distinct readily available electrophiles, namely Csp^2- and Csp^3- halides are added simultaneously across a variety of olefins (vinyl amides, vinyl boranes, vinyl phosphates) at room temperature in a highly regio- and enantioselective manner. The reaction, devoid of sensitive of organometallic reagents, takes advantage of an *in situ* generated chiral alkyl Ni(III)-intermediate to ensure a stereodefined outcome in the Csp^3-Csp^2 bond forming reaction. An (L)-(+)-isoleucine chiral bisoxazoline ligand and the presence of coordinating sites on the alkene are key for the successful outcome in these "Asymmetric Radical Relayed Reductive Coupling" (ARRRC). Further, multiple transformations of the chiral amides obtained in this process showcase the potential of this new methodology for the straightforward assembly of chiral building blocks such as primary and secondary amines, oxazolines, etc. highlighting its synthetic utility.

Introduction

Olefins represent excellent platforms for regio- and enantioselective transformations. Because of their ubiquitous presence in pharmaceuticals and orthogonal reactivity with respect to carbonyls and other polar functional groups, they have also been used in late-stage functionalization efforts.[1] In recent years, three-component alkene dicarbofunctionalizations have triggered significant attention based on their unique ability to streamline the assembly of complex aliphatic structures through the simultaneous construction of two new C-C bonds across the π system. Transition metals,[2] in particular paladium[3] and more recently nickel,[4] have played a significant role in developing catalytic versions of these transformations, the latter enabling the utilization of a wide variety of Csp^3-based partners. Still, and despite significant progress, catalytic asymmetric dicarbofunctionalizations of alkenes, in particular those dealing with intermolecular three-component reactions,[5] remain largely underdeveloped. Remarkable examples by Liu and co-workers showed that, *in situ* generated trifluoromethyl radicals undergo addition across double bonds to produce intermediates which are subsequently intercepted by chiral copper species to yield efficient enantioselective trifluoromethylarylation and cyanotrifluoromethylation reactions.[6] Interestingly, oxidation of such radical intermediates to the corresponding carbocations was also recently harvested by Liu et al. to produce the corresponding chiral perfluoroalkylarylated products in the presence of a chiral phosphoric acid organocatalyst (Scheme 1A).[7] Chiral phosphoric acids were also employed in a photocatalyzed three component Minisci reaction recently reported by Studer et al.[8] In a different approach, Morken´s group has taken advantage of well-established 1,2-metallate rearrangements at Boron[9] developing a series of Pd- and Ni-catalyzed conjuctive cross-coupling reactions. Boron-ate intermediates produced *in situ* by addition of stoichiometric amounts of an organo-lithium or –magnesium reagents to a vinyl borane, undergo arylation or alkylation in the β position delivering, upon 1,2-rearrangement, the corresponding alkylboronate esters with excellent levels of stereocontrol (Scheme 1B).[10] Recently, a Ni-catalyzed asymmetric dicarbofunctionalization of vinyl boranes using organozinc reagents was also reported.[10f] Despite the profound impact of these transformations, multiple challenges still lay ahead. First, methods remain highly tailored to olefinic partners able to stabilize the fast-paced radical/cationic intermediates involved in these transformations.



Scheme 1. Strategies towards metal-catalyzed asymmetric intermolecular dicarbofunctionalization of alkenes.

Further, many of these protocols rely on highly reactive and thus sensitive organometallic species such as organo-lithium, -zinc or -magnesium reagents. In this context, the ability to promote asymmetric intermolecular dicarbofunctionalizations for a variety of olefins that would rely on neutral precursors would be highly desirable. Readily available, both Csp^2- and Csp^3-halides would be ideal reaction partners, as they would prevent the use of stoichiometric, highly reactive, organometallic reagents thus improving the operational simplicity, functional group compatibility and cost-efficiency of these transformations. Multiple obstacles including the inherent low reactivity of these electrophiles an their potential side reactions (i.e. homocoupling, β-hydride elimination, direct cross-coupling etc.) would need to be overcome in order to ensure a successful outcome.[11] Inspired by the advantages of reductive cross-coupling approaches,[12,13] several nickel-catalyzed intermolecular alkene dicarbofunctionalizations have been recently disclosed.[14] Here, we have devised a highly efficient asymmetric example of this type of transformations (Scheme 1c). Mechanistically, our design relies on the activation of an alkyl iodide with nickel[15] to produce an alkyl radical **I** under the reductive conditions.[16] Further, Csp^2-X precursors (Csp^2 = Ar, vinyl; X = Br, I) are activated via oxidative addition producing Csp^2-nickel intermediates of type **II**. Instead of the direct coupling between these two species,[17] alkyl radical **I** is trapped by different olefins so that, in a relay process, a new alkyl-Ni(III) complex is formed (**III**). The combination of complexes **II** and **III** enable the second C-C bond forming reaction via reductive elimination. A novel (L)-(+)-Isoleucine-based chiral bisoxazoline ligand has been identified to control the stereochemical outcome in this process.[18] Two distinct readily available electrophiles, namely Csp^2- and Csp^3- halides are thus simultaneously added across multiple, readily available olefins including vinyl amides, vinyl boranes, vinyl phosphates in a completely regio- and stereoselective manner. This process, termed "Asymmetric Radical Relayed Reductive Coupling" (ARRRC), is thus devoid of sensitive of organometallic reagents and proceeds at room temperature. Further, and in the case of the chiral amides obtained in these transformations, subsequent derivatization showcased the potential of this new methodology for the straightforward assembly of chiral building blocks such as primary and secondary amines, oxazolines, etc.

Results and Discussion

N-vinylbenzamide, iodobenzene and *tert*-butyl iodide were chosen as reaction partners to find the optimal conditions for this transformation. After a screening including different nickel sources, solvents, reductants and additives (see Supporting Information for further details)[19], different chiral ligands including mono- and bisoxazoline templates were evaluated (Figure 1). Commercially available **L1** and **L2** ligands, which have been successfully applied in nickel catalyzed enantioselective reductive coupling reactions,[18] failed to produce the desired product. In contrast, the reaction with PYBOX ligands **L3** and **L4** produced compound **1** in 13% and 94% yields, respectively with promising levels of stereocontrol in both cases. These results highlight the importance of rigidity and the bite angle of the N^N ligand for a successful reaction outcome. Next, we turned our attention to C2-symmetric bisoxazoline ligands. Interestingly, while **L5** furnished moderate levels of stereocontrol, the steric demand imposed by the substituents in α-position to the nitrogen atom seemed to play a major role in the reaction outcome.

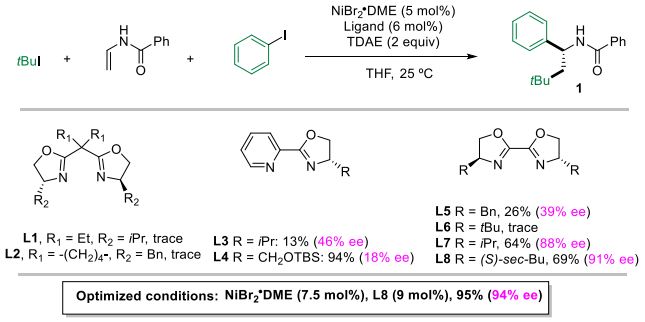
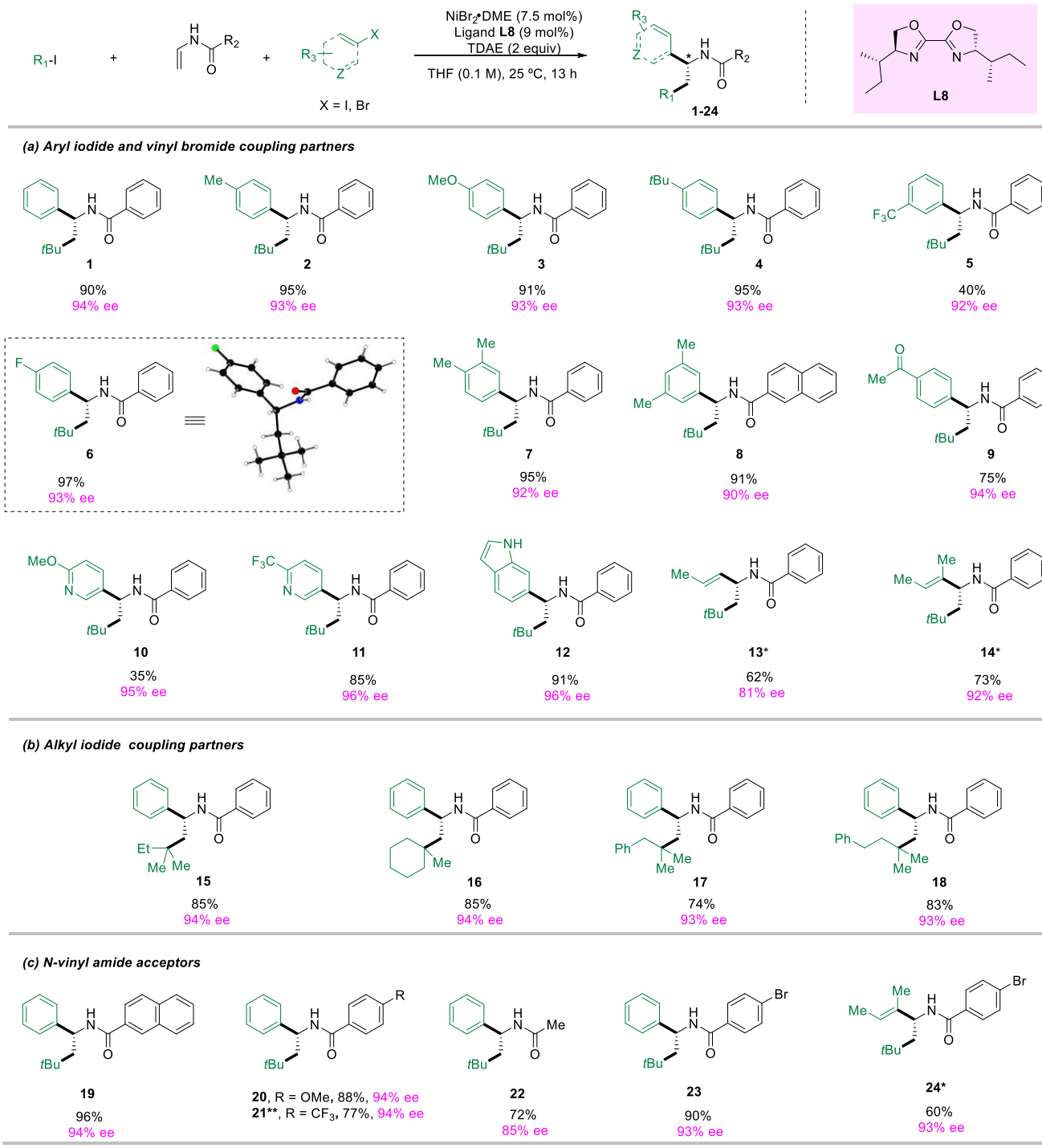


Figure 1. Ligand optimization. For preliminary experiments to find optimal conditions, see Supporting Information.[19] Standard protocol uses vinyl amide (0.1 mmol), *t*BuI (0.3 mmol), PhI (0.15 mmol), TDAE (2 equiv.) $NiBr_2$·glyme (5 mol%), Ligand (6 mol%), in 1 mL of THF at 25 ºC for 13 hours. Yield determined by ^1H NMR using mesitylene as internal standard. The ee value was determined by HPLC with a chiral stationary phase.

Thus, whereas the use of a more bulky *tert*-butyl derivative **L6** resulted in decreased reactivity, *iso*-propyl-derivative **L7** delivered compound **1** in good yields with high level of stereocontrol. Interestingly, a rather unexplored *sec*-butyl bisoxazoline ligand **L8**,[20] readily synthesized from (L)-(+)-Isoleucine, delivered the corresponding dicarbofunctionalized amide in 69% yield and 91% ee. Finally, the combination of **L8** (9 mol%) with $NiBr_2$·DME catalyst (7.5 mol%) furnished the chiral amide **1** in almost quantitative yield (95%) with excellent stereocontrol (94% ee).

With the optimized reaction conditions in hand, the substrate scope of this transformation was examined next (Scheme 2). A broad range of electronic and sterically differentiated substituted iodoarenes (Ar-I with Ar = Ph, Tol, *p*-$OMeC_6H_4$, *p*-$tBuC_6H_4$, *m*-CF_3-C_6H_4, *p*-F-C_6H_4, 2,3- and 3,5-$(CH_3)_2$-C_6H_3, *p*-$COMe$-C_6H_4) delivered the corresponding products **1-9** in good to excellent yields (40 to 97%) with high enantioselectivities (90 to 94% ee). Hetereocycles such as pyridine and indoles, which are also challenging partners for reported processes using vinyl boron-ate species,[9] were well-tolerated in this mild three-component reaction as shown by the efficient formation of products **10**-**12**. Interestingly, vinyl bromides could also be successfully incorporated in these transformations by increasing the Ni-catalyst load to 10 mol% so that the corresponding chiral allyl amides **13** and **14** could be isolated in 62 and 73% yield with 81 and 92% ee, respectively. In all abovementioned cases, excellent regio- and enantioselectivities were observed across the panel of utilized iodoarenes (Scheme 2a). The absolute configuration of the relayed cross-coupling products was unambiguously confirmed as by X-ray diffraction analysis of *p*-fluoro substituted amide (*R*)-**6**.

As shown in Scheme 2b, the reaction could be successfully extended to different tertiary halides. Both acyclic and cyclic, alkyl iodides were incorporated into the corresponding amides delivering the desired products with excellent level of enantiocontrol (**15-18**, 74-85% yield, 93-94% ee).

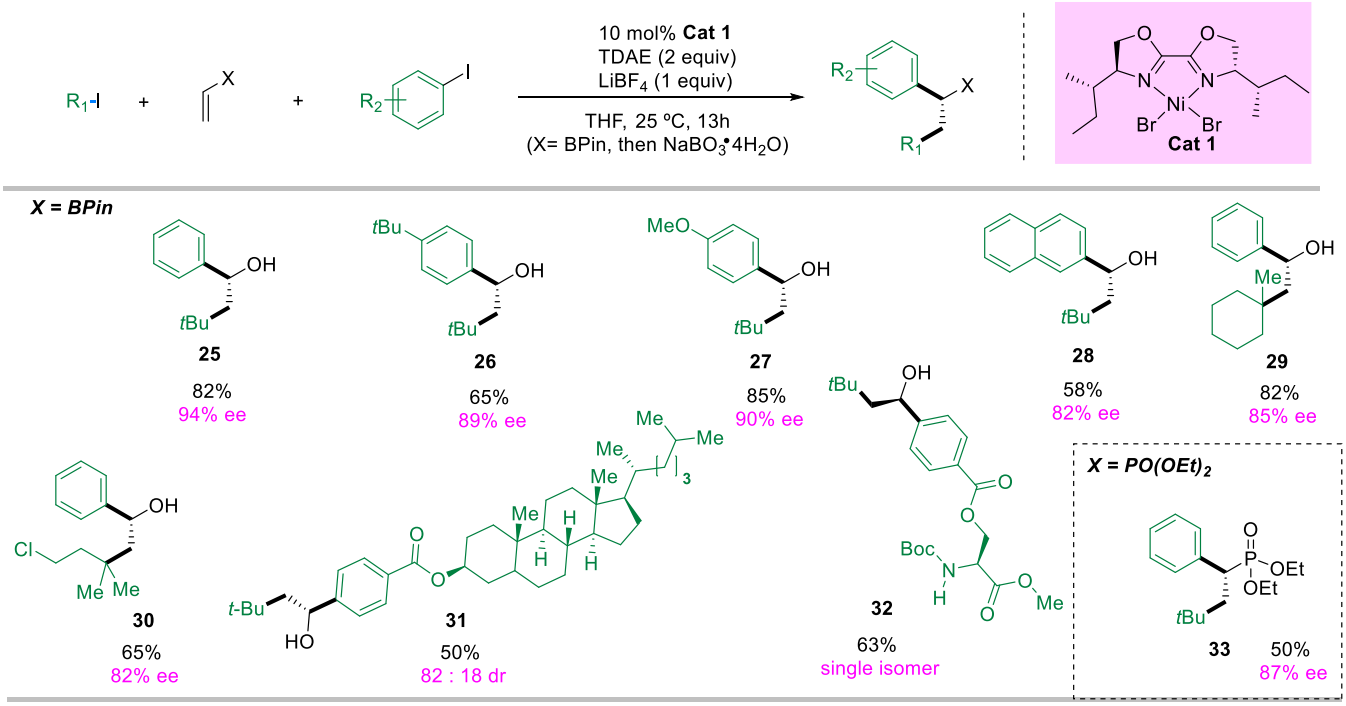


Scheme 2. (a) Substrate scope of Csp^2 partners (Ar-I and and vinyl-Br). (b) Substrate scope of Alkyl-I partners (c) Scope on vinyl-amides. All yields are isolated yields of pure products obtained after purification of the reaction mixtures via column chromatography on silica gel. *Reaction was conducted using 10 mol% catalyst loading at -5 ºC for 13 h. ** Reaction was conducted using 15 mol% $NiBr_2$·DME and 18 mol% **L8**. Absolute configuration of products was assigned by analogy to that determined by X-Ray diffraction analysis for compound **6**.

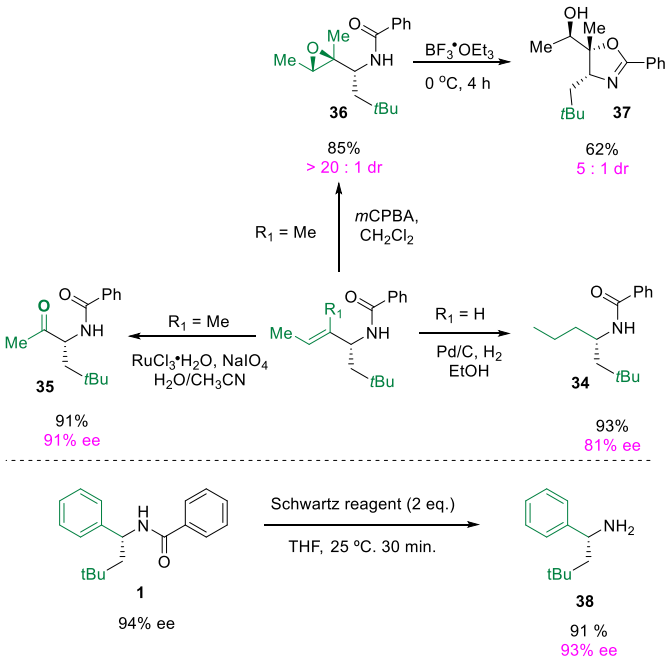
The ability to incorporate tertiary alkyl groups represent an attractive feature as highly sterically hindered electrophiles are typically difficult to engage in these transformations.[10] Unfortunately, perfluoroalkyl iodides could not be successfully incorporated under these conditions.[21] The methodology is also amenable to the utilization of different of vinyl amide acceptors (Scheme 2c). Interestingly, both electron-donating as well as electron-withdrawing substituents on the aryl group bound to nitrogen were well tolerated, although higher catalyst loading was required to accomplish the transformation with electron-deficient derivative **21**. Naphthalene carboxamide as well as acetamides were also nicely compatible with the optimized reaction conditions. Orthogonal functionalities, such as Csp^2-Br

bonds, remained intact under the standard protocol, opening the possibility of subsequent functionalizations via classical Pd-cross coupling reactions (**23** and **24**). Next, we sought to further expand the scope with respect to the olefinic acceptor in these transformations. To our delight, vinyl boronic esters, which are useful intermediates[22] in a wide range of transformations, proved to be amenable to this asymmetric radical relayed reductive cross-coupling upon minor modifications of the previously optimized conditions. To this end, nickel complex **Cat1** was prepared by stirring of $NiBr_2$·glyme with **L8**.[19] The use of 10 mol% of **Cat1** in the presence of one equivalent of $LiBF_4$ resulted in clean formation of the desired secondary alkyl boronic ester derivatives. For convenience, the resulting products were oxidized *in situ* into the corresponding secondary alcohols using $NaBO_3 \cdot 4H_2O$ in aqueous THF. As illustrated in Scheme 3, a diverse range of aryl and vinyl halides as well as tertiary alkyl iodides were incorporated across the vinyl boron moiety with consistent yields and excellent regio- and absolute stereocontrol. Substrates resembling steroid natural products as well as amino acid derivatives were also amenable to the asymmetric dicarbonfunctionalization protocol, providing the corresponding products **31** and **32** with high levels of diastereocontrol. Further, we also demonstrate that vinyl phosphates can be transformed into the corresponding enan-tioenriched adducts under our standard conditions, thus highlighting the broad application potential of this mild enantioselective three component coupling strategy (**33**). Despite its broad applicability, our protocol could not be successfully applied to secondary alkyl iodides nor to olefins acceptors such as N-Boc or N-Ts protected vinyl amides or vinylsilanes. For an overview of the unsuccessful substrates, please see Section 2 in the SI.[19]

To further illustrate the synthetic utility of our protocol, several transformations of the chiral amides initially obtained in Scheme 2 were carried out (Scheme 4a). Palladium-catalyzed hydrogenation of **14** furnished the corresponding chiral secondary amine **34** with high levels of stereofidelity. It is important to note that, enantioselective catalytic access to such amines has proven elusive due to minimally differentiated steric and electronic properties of the two aliphatic substituents. The olefin group in **14** could be cleaved via oxidation by $RuCl_3/NaIO_4$ to give α amino ketone **35** in 91% yield and 91% ee. An enantio-enriched trisubstituted epoxide (**36**) containing three contiguous chiral centers, could be assembled by straightforward one-pot diastereoselective epoxidation reaction in the presence of m-CPBA. A subsequent Lewis-acid catalyzed ring opening reaction furnished a chiral mono-oxazoline **37** in a 5:1 d.r. and 62% yield, thus showcasing the potential of our method towards novel routes for ligand discovery. Finally, deprotection of the benzamide moiety in the presence of Schwartz reagent resulted in the clean formation of primary amine **38** in almost quantitative yield almost perfect stereocontrol (Scheme 4b).

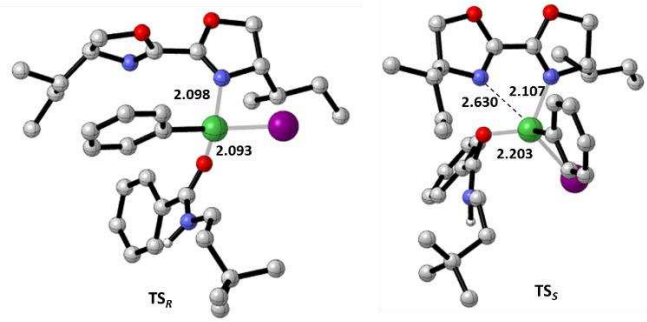


Scheme 3. Extension of the asymmetric reductive dicarbofunctionalization to vinyl boronic esters and vinyl phosphonates as olefin acceptors.



Scheme 4. Derivatization of chiral dicarbofunctionalized amides.

To shed light on the stereochemical outcome of this process, DFT calculations were carried out for the reaction producing amide **1**.[19] The transition state preceding the formation of intermediate **III** for the observed (*R*) configured product (**TS*R***) showcases the interaction of the carbonyl group of the amide with the Ni center ($d_{Ni\text{-}O}$= 2.093 Å). Although weak, this interaction enables the partial decoordination of one of the nitrogen atoms of **L8** ($d_{Ni\text{-}N1}$= 2.098 and $d_{Ni\text{-}N2}$= 4.280 Å) which results in a minimized steric contact between the incoming aryl moiety and the *sec*-butyl chain of the bisoxazoline ligand, thus explaining the *R*-configuration of the final product. The transition state yielding the minor enantiomer (**TS*S***) is energetically disfavored ($\Delta\Delta G^{\ddagger}$ = 2.1 kcal/mol) as a result of a more congested environment around the metal center since no significant interaction between the carbonyl group of the amide and the metal center is observed ($d_{Ni\text{-}O}$= 2.203 Å) and, although to a different extent, the two nitrogen atoms of the ligand remain coordinated to Ni ($d_{Ni\text{-}N1}$= 2.630 and $d_{Ni\text{-}N2}$= 2.107 Å) (Scheme 5).[19,23]



Scheme 5. Stereochemical model supported by DFT calculations. Reaction free energies and activation energies (kcal/mol) calculated at UB3LYP/6-31G(d) (C,H,N), LANL2DZ (Ni, I) level.[19]

Conclusion

In summary, we present here a highly efficient asymmetric intermolecular reductive dicarbofunctionalization of alkenes. A variety of readily available Csp^2- and Csp^3-halides are added simultaneously across alkenes at room temperature in a highly regio- and enantioselective manner. The reaction is devoid of sensitive of organometallic reagents as it relies on an organic reductant. The reaction proceeds through a chiral alkyl Ni(III)-intermediate based on a (L)-(+)-isoleucine chiral bisoxazoline ligand. DFT calculations confirm that in the transition state, coordinating sites present on the alkene stabilize the Ni center contributing to a stereodefined outcome in the Csp^3-Csp^2 bond forming reaction. This transformation, termed "Asymmetric Radical Relayed Reductive Coupling" (ARRRC) is able to engage a variety of olefins (vinyl amides, vinyl boranes, vinyl phosphates) under extremely mild reaction conditions. Further, multiple transformations of the chiral amides obtained in this process showcase the synthetic potential of our methodology towards the straightforward assembly of chiral building blocks such as primary and secondary amines, oxazolines, etc.

ASSOCIATED CONTENT

Supporting Information. Supplementary information including compound synthesis, characterization, additional experiments and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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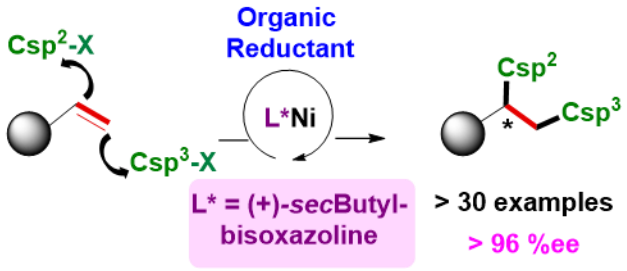
TOC


Organic
Reductant
Csp2-X
Csp3-X
L*Ni
Csp2
Csp3
*
L* = (+)-secButyl-
bisoxazoline
> 30 examples
> 96 %ee