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NiH-Catalyzed Asymmetric Remote Hydroalkylation of Alkenes with Racemic α-Bromo Amides

Fang Zhou, Yao Zhang, Xianfeng Xu, and Shaolin Zhu*

Dedication ((optional))

Abstract: Here we report a terminal-selective, asymmetric remote hydroalkylation of olefins with racemic α-bromo amides, through NiH-catalyzed alkene isomerization and subsequent alkylation reaction that can enantioconvergently introduce an unsymmetrical *sec*-alkyl group from a racemic α-bromo amide onto a terminal sp^3 C–H position along the hydrocarbon chain of alkene. This mild process affords a range of structurally diverse chiral α-alkylalkanoic amides in excellent yields, high regioselectivities, and enantioselectivities. In addition, the synthetic utility of this protocol is further highlighted by the regioconvergent conversion of industrial raw materials of isomeric olefin mixtures into enantioriched α-alkylalkanoic amides on large-scale.

In view of the prevalence of chiral sp^3 carbon stereocenters in pharmaceuticals and materials,[1] introduction of an unsymmetrical secondary alkyl group in an enantioselective fashion is a challenge and is of fundamental importance in chemical synthesis.[2] One attractive strategy to realize this transformation is to couple with the racemic alkyl halides or alkylmetal reagents through an enantioconvergent conversion of both enantiomers into the same enantiomer of the product.[3] This efficient approach has proven successful in a number of transition-metal-catalyzed cross-coupling reactions, including nickel-, palladium-, or cobalt- catalyzed asymmetric Kumada,[4] Negishi,[5] Suzuki-Miyaura,[6] etc.[7] reactions. Over the last two decades, highly enantioselective examples of such transformations were well developed by Fu and co-workers while using racemic alkyl halides as substrates and earth-abundant nickel-based catalysts (Figure 1a).[4g,4h,5,6,7a,7b] However, the requirement for pregenerated organometallic reagents is still less than ideal, leading to inefficient step and atom-economies. An attractive alternative strategy is the direct sp^3 C–H functionalization.

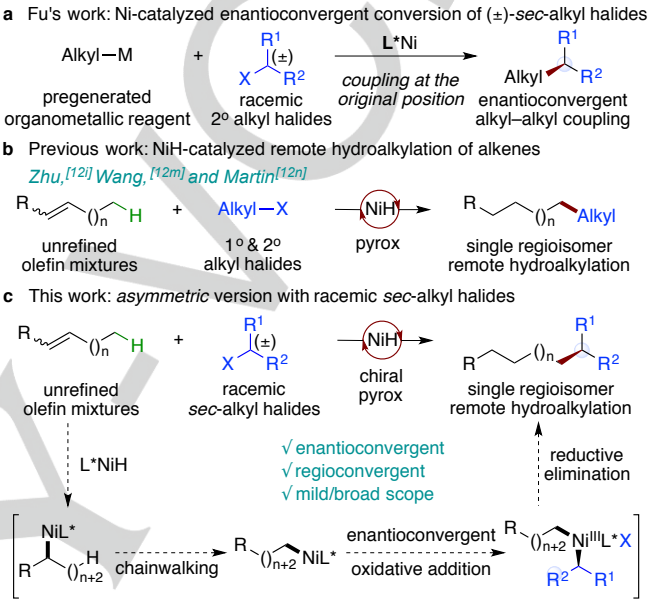

Figure 1. Design plan: chiral nickel/pyrox catalyzed enantioconvergent remote hydroalkylation of alkenes with racemic *sec*-alkyl halides.

Despite recent considerable progress in the sp^3 C–H functionalization,[8] the enantioselective installation of an unsymmetrical *sec*-alkyl group at a remote unfunctionalized site along an alkyl chain is a synthetically valuable but rarely explored process. The synergystic combination of chainwalking and cross-coupling on an aliphatic chain provides an attractive approach towards achieving this goal.[9-12] Previously, starting from the easily accessed and bench-stable alkenes[13] and alkyl halides, our group,[12i] Wang[12m], and Martin[12n] independently reported a terminal-selective, NiH-catalyzed[14] remote sp^3 C–H alkylation process for the direct installation of a primary or secondary alkyl group (Figure 1b). In case of unsymmetrical *sec*-alkyl halides, a stereocenter may be generated at the carbon that bears the halide leaving group. If the stereochemical outcome could be controlled, it would greatly increase their synthetic utility. We wondered whether a suitable chiral nickel/pyrox catalyst could be used to achieve this goal, in which the stereochemical information generated after the oxidative addition of the migrated alkylnickel species with racemic unsymmetrical *sec*-alkyl halides is retained in the product (Figure 1c). Here we disclose the successful execution of these ideals and present a mild and versatile method for the enantioconvergent remote hydroalkylation of alkenes with racemic alkyl halides, specifically, internal alkenes with racemic α-bromoamides, to form enantioriched α-alkylalkanoic amides[15]. We note that during the preparation of this report, independent

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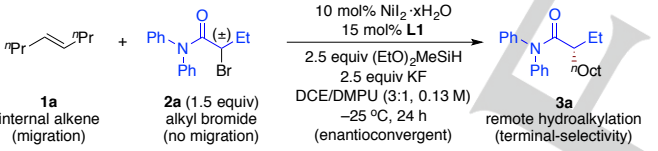
elegant work from Fu and co-workers appeared. In their strategy, with a chiral nickel/bisoxazoline catalyst, enantioconvergent hydroalkylation of terminal alkenes with racemic α-bromocarbonyl compounds was reported with one example of internal alkene.[16]

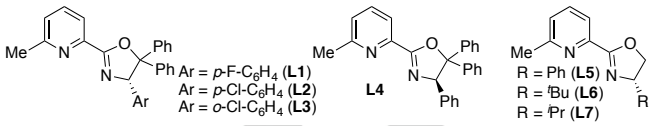
On the basis of our previously reported migratory coupling reaction of olefins with alkyl halides,[12i] we first examined the proposed asymmetric remote hydroalkylation reaction with *trans*-4-octene (**1a**), 2-bromo-*N*,*N*-diphenylbutanamide (**2a**) by employing a variety of nickel sources, ligands, silanes, temperature, and solvents. The highly enantioriched terminal alkylation product (**3a**) was obtained using a combination of $NiI_2{\cdot}xH_2O$ with C6-methyl substituted chiral pyrox ligand **L1** in 84% isolated yield and 97% ee as essentially a single regioisomer at –25 °C (Table 1, entry 1). This result is particularly remarkable taking into consideration the requirement for high chainwalking reactivity at this low temperature (–25 °C). Notably, all of the used pyrox ligands (**L1**–**L5**) bearing a methyl substituent at the C6-position could promote the reaction to give the desired product as a single regioisomer (entries 1–11, >99:1 rr). Interestingly, use of other nickel sources, $NiCl_2$ or $NiBr_2$ led to poor yields (entries 2 and 3). Inferior results were found with other chiral pyrox ligands (**L2**–**L7**, entry 1 *vs* entries 4–9, see SI for detailed discussion). Unlike our previous condition, use of triethoxylsilane resulted in decreased yield and ee. In addition, conducting the reaction at room temperature (25 °C) led to significantly lower yield and ee (entry 9). Likewise, a poor yield was obtained when a single solvent was used (entries 10 and 11), thus showing the subtle interplay of reagents and solvents in this protocol.

Table 1: Variation of reaction parameters.



1a internal alkene (migration) + **2a** (1.5 equiv) alkyl bromide (no migration) → **3a** remote hydroalkylation (terminal-selectivity)

Entry	Variation from standard conditions	Yield (%)[a]	ee[b]
1	none	90(84)	97
2	$NiCl_2$, instead of $NiI_2{\cdot}xH_2O$	19	95
3	$NiBr_2$, instead of $NiI_2{\cdot}xH_2O$	2	ND
4	**L2**, instead of **L1**	90	97
5	**L3**, instead of **L1**	78	97
6	**L4**, instead of **L1**	70	–96
7	**L5**, instead of **L1**	60	86
8	**L6**, instead of **L1**	9	27
9	**L7**, instead of **L1**	30	90
10	$(EtO)_3SiH$, instead of DEMS	21	81
11	25 °C, instead of –25 °C	24	89
12	DCE only	29	95
13	DMPU only	28	97



[a] Yields were determined by GC using *n*-dodecane as the internal standard, the yield in parentheses is the isolated yield and is an average of two runs (0.10 mmol scale). [b] Enantioselectivities were determined by chiral HPLC analysis; the absolute configuration was determined by chemical correlation or by analogy.

With the optimal catalyst and reaction conditions in hand, we next turned our attention to the scope of alkene partner (Table 2). As anticipated, both *E* (**1a**–**1c**) and *Z* (**1d** and **1i**) alkenes, as well as *E*/*Z* mixtures (**1e**–**1h** and **1j**–**1p**) underwent this transformation smoothly with excellent terminal regioselectivity and enantioselectivity, regardless of the starting position of the C=C bond in the olefinic starting materials. This method is compatible with a diverse spectrum of functional groups, including an acetal (**1i**), ethers (**1j** and **1k**), Boc carbamates (**1l**, **1s**, and **1t**), an ester (**1m**), and a nitrile (**1u**). Notably, even with an ester (**1m**) or a (hetero)aromatic ring (**1n**–**1p**) at the other terminus of the alkyl chain, migration towards the terminal position and subsequent enantioselective alkylation was still observed. Furthermore, migration toward to the less steric primary sp^3 C–H site was preferred when there were multiple methyl positions on the alkyl chain (**1h** and **1j**). Interestingly, even a hindered unactivated trisubstituted internal alkene substrate (**1q**) could undergo the desired process, although under the current conditions, the conversion was still not so good. Perhaps less surprising, but equally useful, is the hydroalkylation of terminal alkenes (**1r**).[13,17] Accordingly, 1,1-disubstituted alkenes also cross-coupled efficiently (**1s**–**1u**).

Table 2: Scope of alkene coupling component.[a]

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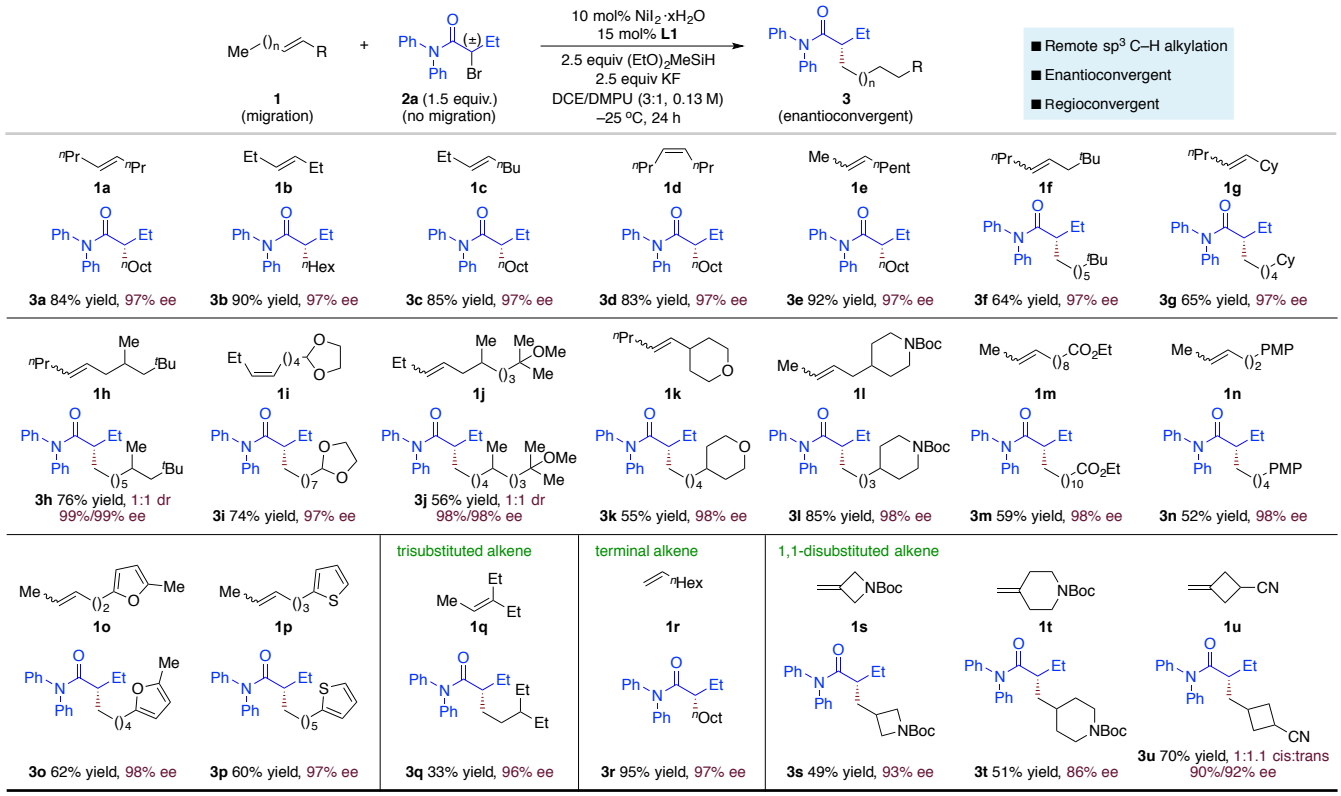
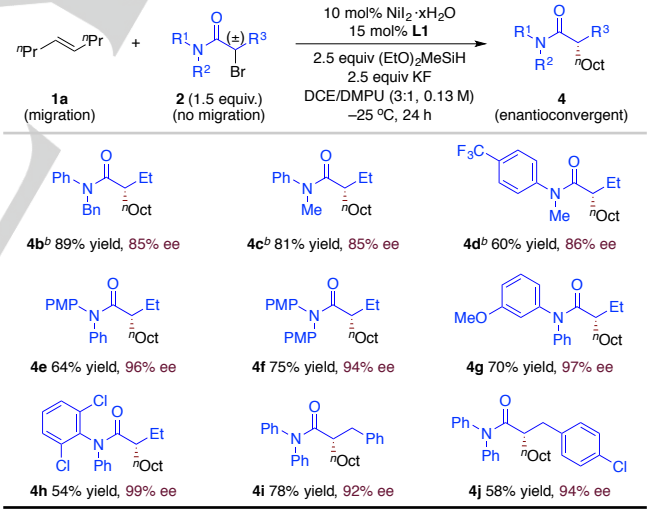


[a] Under each product is the percentage isolated yield and enantioselectivity (ee) (0.10 mmol scale, average of two runs); regioselectivities (rr) were determined by GC and GCMS (for **3l**, **3s**, and **3t**, the regioselectivities were determined by crude ^{1}H NMR), single regioisomer was observed in all cases.

We next evaluated the scope of alkyl electrophile and were pleased to find that a number of α-bromo amides derivatives were compatible (Table 3). In general, substitution of one aryl group of the amide with an alkyl group led to a slight lower ee than those with the diarylamide (**4b**–**4d** *vs* **4e**–**4h**). Nevertheless, high levels of enantioselectivity were obtained when substitution of the two phenyl groups with either electron-rich (**4e** and **4f**) or electron-withdrawing (**4g** and **4h**) aryl groups. Of particular interest is that potential cross-coupling partners, aryl chlorides (**4h** and **4j**), remained intact and were available for further derivatization. It is noteworthy that the β-hydride elimination products of the α-bromo amide substrates were not detected in all cases.

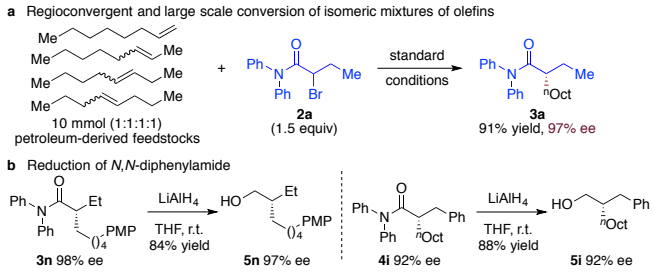
Table 3: Scope of the α-bromo amide component.[a]



[a] Yield, ee, and rr are as defined in Table 2. [b] DCE/DMPU (1:1, 0.50 M) was used.

Furthermore, because the isomeric mixtures of unactivated alkenes from petroleum-derived feedstocks, such as butenes, hexenes, pentenes, and octenes, are generally available in bulk and substantially cheaper than pure isomers.[18] Utilizing such mixtures in a regioconvergent process on a large scale to produce the single isomer of value-added product is of considerable interest. As a proof-of-concept, using mixtures of

octenes (equimolar amounts of the four linear octene-isomers) on 10 mmol scale, the reaction produced enantiopured terminal alkylation product (**3a**) in an effective fashion (Scheme 1a). Moreover, diphenylamides are attractive carboxylic acid derivatives and can be easily converted into other useful functional groups without erosion of enantiomeric excess.[6e] For example, reduction of **3n** and **4i** with $LiAlH_4$ cleaved the amide group to deliver free primary alcohol **5n** and **5i** in 97% ee and 91% ee, respectively (Scheme 1b).



Scheme 1. Regioconvergent and derivatization experiments.

In summary, we have developed a NiH-catalyzed asymmetric remote hydroalkylation process from two readily accessed starting materials, unactivated alkenes and racemic α-bromo amides. With a chiral nickel-pyrox-based catalyst, excellent regio- and enantioselectivity were observed with broad substrate scope. This mild, enantioconvergent reaction provides rapid access to a variety of enantioriched α-alkylalkanoic amides in good yields and ee. Furthermore, the practical value of this transformation is highlighted by the regioconvergent and enantioconvergent conversion of petroleum-derived isomeric mixtures of olefins feedstocks into a single region- and stereoisomer of the product. The further development and application of this reaction as well as mechanistic investigations are currently in progress.

Acknowledgements

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Keywords: nickel • C–H activation • isomerization • alkylation • enantioselectivity

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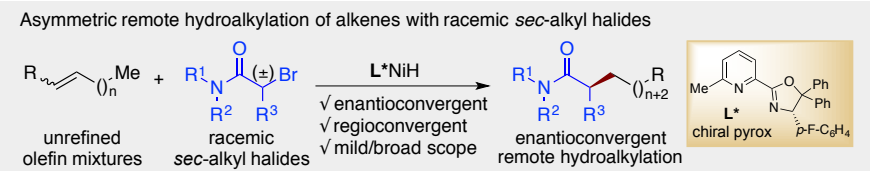
NiH-Catalyzed Asymmetric Remote Hydroalkylation of Alkenes with Racemic α-Bromo Amides



Regio- and enantioselective installation of an unsymmetrical *sec*-alkyl group at a distal position to form an enantioriched C(sp^3) center is a valuable process for organic synthesis. By using a chiral nickel-pyrox-based catalyst, we realized a NiH-catalyzed asymmetric remote hydroalkylation of alkenes with racemic α-bromo amides under mild conditions.