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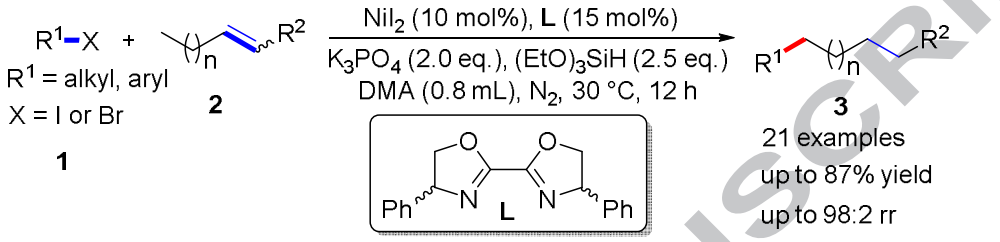

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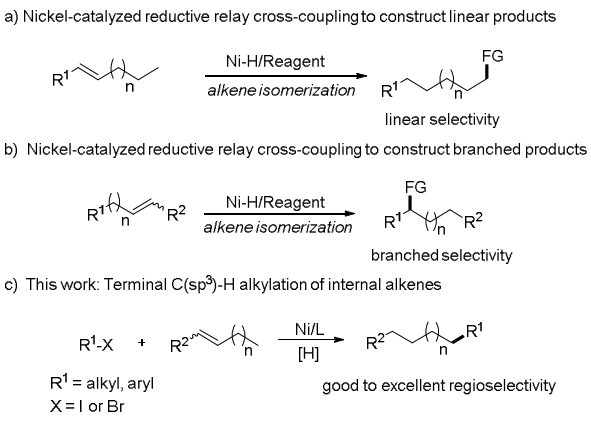
ABSTRACT

An efficient nickel-catalyzed reductive relay cross-coupling of internal alkenes with alkyl (or aryl) halides has been developed. This method has demonstrated broad substrate scope, mild reaction conditions and excellent terminal-selectivity. Moreover, this efficient strategy could be applied to the terminal-selective alkylation of isomeric mixtures of internal alkenes.

Introduction

Transition-metal-catalyzed cross-coupling has emerged as a powerful strategy for effective syntheses of complex organic compounds which are widely used in agricultural, pharmaceutical chemistry and material science.[1] During the past several decades, the widely known cross-coupling between nucleophilic reagents, normally alkyl or aryl organometallic reagents, and electrophilic partners has been developed as an ideal method to forge C-C bonds.[2-3] Since alkyl metal species are always difficult to store, inconvenient to operate and commonly prepared in situ, the discovery of more stable and readily available nucleophiles to avoid the use of organometallic reagents has been regarded as an important issue in this area. As an important feedstock on large scale from petrochemical industry, simple olefins have been used directly as alkyl organometallics equivalents in transition-metal-catalyzed cross-coupling reactions recently, in which silanes were typically used as hydride sources.[4]

As a result of β-hydride elimination and insertion of metal hydride, double bond isomerization along the carbon skeleton often occurs in metal-hydride-catalyzed alkenes functionalization reactions and the isomerization will generate a selective remote transformation of alkenes.[5] However, there are still few reports on the remote C(sp^3)-H functionalization of alkenes with these catalytic systems till date.[5-9] As an abundant and low-cost alternative to precious metal catalyst, nickel-hydride-catalyzed reductive relay cross-coupling has recently been developed as a powerful method to construct C(sp^3)-C bonds from internal olefins via so-called 'chainwalking'.[7-8] Starting from different kinds of alkenes, two chainwalking paths have been demonstrated to produce linear (Scheme 1a) or branched chain products (Scheme 1b), which can be explained by the lower barrier for reductive elimination of terminal nickel species[7] or the thermodynamical stability of some specific alkylnickel intermediates.[7b,8] However, C(sp^3)-C(sp^3) bond forming reaction via such nickel-catalyzed tandem isomerization/hydroalkylation of internal alkenes is rare and remains as a challenge.[9] As part of our continuous efforts to develop novel methods on nickel-catalysis,[10] we envisioned that ligands would play an important role in the remote C(sp^3)-H



Scheme 1. Remote C(sp^3)-H functionalization of alkenes via Ni/H-catalyzed chainwalking.

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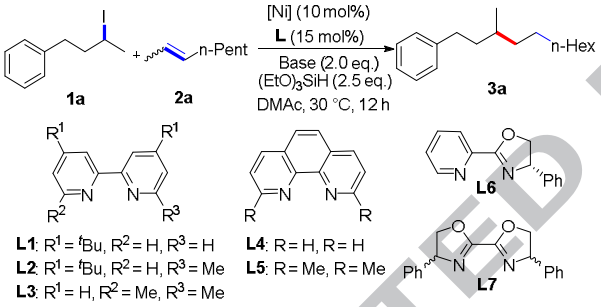
alkylation of internal olefins. Herein, we report a nickel-catalyzed reductive relay cross-coupling reaction between internal alkenes and alkyl (or aryl) halides, in which excellent terminal-selectivity, broad substrate scope and mild conditions have been demonstrated (Scheme 1c). The key to success is the use of bis(oxazoline) as the ligand to improve the reactivity of both olefin isomerization and cross-coupling in this nickel-catalyzed reaction.

Results and discussion

Our initial study commenced with 2-iodo-4-phenylbutane **1a** and 2-octene (*cis*- and *trans*- mixture) **2a** as the model substrate, in the presence of a catalytic amount of NiI_2 (10 mol%) and $(EtO)_3SiH$ as hydrogen source in DMAc at 30 °C. As expected, the desired product **3a** was obtained successfully in 22% yield, albeit with a relatively low regioselectivity (61:39 regioisomeric ratio) when dtbbpy **L7** was used as the ligand (Table 1, entry 1). Considering the key role of ligand to improve the reactivity and regioselectivity, different kinds of nitrogen ligands, including bipyridine (**L1-L3**), phenanthroline (**L4-L5**), pyrox (**L6**), and box (**L7**), were next examined. To our delight, the desired product **3a** was obtained with excellent regioselectivity (97:3 regioisomeric ratio) and higher yield (38%) using **L7** as the ligand (Table 1, entry 7). To improve the yield further, a careful survey of bases was then performed, which indicated K_3PO_4 was the best choice with 86% yield and 98:2 rr (Table 1, entry 9).

Table 1. Optimization of reaction conditions.[a]



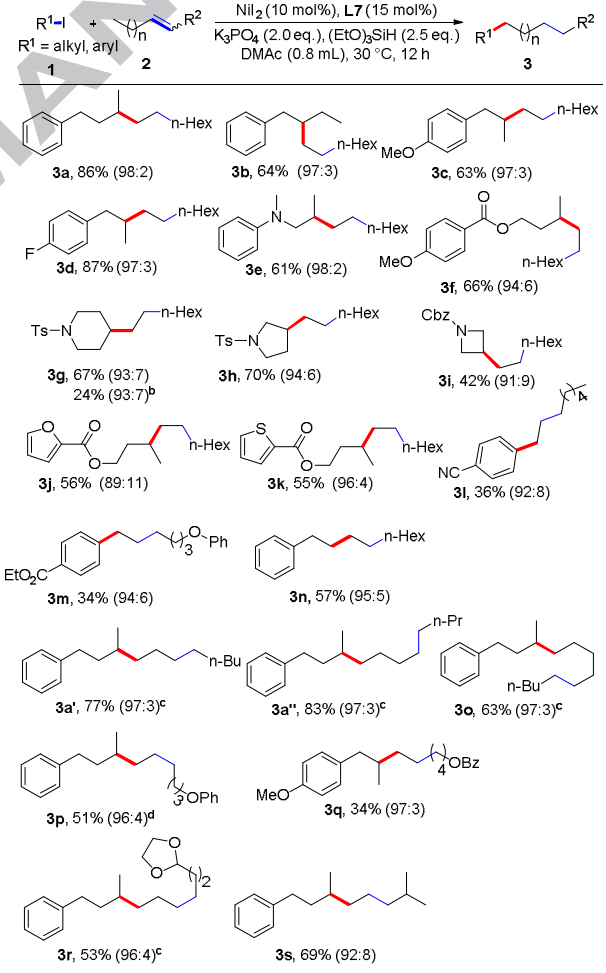
Entry	Ni source	Ligand	Base	Yield[b]/%	rr[c]
1	NiI_2	**L1**	Na_2CO_3	22	61:39
2	NiI_2	**L2**	Na_2CO_3	0	-
3	NiI_2	**L3**	Na_2CO_3	0	-
4	NiI_2	**L4**	Na_2CO_3	14	93:7
5	NiI_2	**L5**	Na_2CO_3	0	-
6	NiI_2	**L6**	Na_2CO_3	0	-
7	NiI_2	**L7**	Na_2CO_3	38	97:3
8	NiI_2	**L7**	K_2CO_3	35	96:4
9	NiI_2	**L7**	K_3PO_4	86[d]	98:2
10	NiI_2	**L7**	KF	76	96:4
11	NiI_2	**L7**	NaOAc	0	-
12	$NiCl_2$	**L7**	K_3PO_4	72	95:5
13	$NiCl_2{\cdot}6H_2O$	**L7**	K_3PO_4	84	95:5
14	$NiBr_2$	**L7**	K_3PO_4	31	95:5
15	$Ni(OTf)_2$	**L7**	K_3PO_4	72	96:4
16[e]	NiI_2	**L7**	K_3PO_4	0	-
17	NiI_2	**-**	K_3PO_4	0	-
18	-	**L7**	K_3PO_4	0	-

[a]Reaction conditions: **1a** (0.3 mmol, 1.5 eq.), **2a** (0.2 mmol, 1.0 eq.), [Ni] (10 mol%), **L** (15 mol%), Base (2.0 eq.), $(EtO)_3SiH$ (2.5 eq.), DMAc (0.8 mL), 30 °C, 12 h, N_2.
[b]Yield was determined by GC analysis using dodecane as an internal standard.
[c]The rr is regioisomeric ratio, represents the ratio of the linear product to the sum of all other isomers as determined by GC analysis.
[d]Isolated yield.
[e]Without $(EtO)_3SiH$.

Meanwhile, the examination of nickel source effects showed that the use of other nickel catalysts failed to improve yields (entries 12-15), and NiI_2 was proved to be the best nickel sources. In addition, control experiments demonstrated that nickel catalyst, ligand and reduce agent were all crucial to the reductive relay cross-coupling reaction (Table 1, entries 16-18).

With the optimized reaction conditions in hand, a range of alkyl or aryl halides and internal olefins with different functional groups could undergo the tandem isomerization and hydroalkylation to afford terminal selective products with modest to excellent yields and good to excellent regioselectivity (Table 2). Firstly, the scope of the electrophiles (R-I) were investigated with 2-octene (*cis*- and *trans*- mixture) **2a** used as the alkene source. Not surprisingly, increasing the side chain length of the secondary alkyl iodides has almost no impact on the reactivity (**3b**). To our delight, a variety of functional groups, including ether (**3c**), fluoride (**3d**), amine (**3e**), ester (**3f**), sulfonamide (**3g**, **3h**) and amide (**3i**) were well compatible with this terminal alkylation reaction system. In addition, heterocycles such as furan (**3j**) and thiophene (**3k**) could also be used as suitable substrates in this transformation. Moreover, both alkyl bromide (**3g′**) and aryl iodides (**3l**, **3m**) offered the desired products

Table 2. Substrate scope.[a]

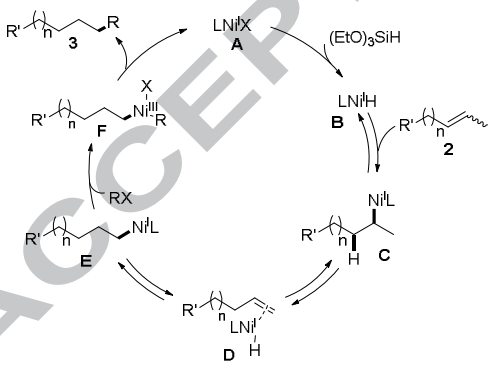


[a]Reaction Conditions: **1** (0.3 mmol, 1.5 eq.), **2** (0.2 mmol, 1.0 eq.), NiI_2 (10 mol%), **L7** (15 mol%), K_3PO_4 (2.0 eq.), $(EtO)_3SiH$ (2.5 eq.), DMAc (0.8 mL), 30 °C, 12 h, N_2; Isolated yield; Ratios in parentheses are regioisomeric ratios determined by GC analysis, which represents the ratio of the linear product to the sum of all other isomers.
[b]alkyl bromide.
[c]24 h.
[d]**1** (2.0 eq.), NiI_2 (15 mol%), **L7** (22.5 mol%).

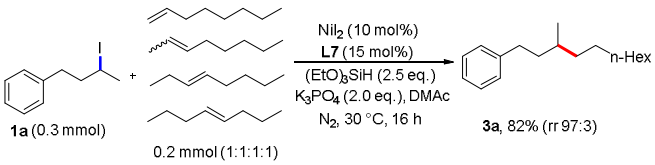
successfully, albeit with relatively lower yields. It was noteworthy that primary alkyl iodide (**3n**) underwent the reaction smoothly with modest yield and good regioselectivity (95:5 rr). Importantly, this catalytic system worked pretty well for the tandem isomerization-hydroalkylation of various internal alkenes. Both *trans*-3-octene (**3a′**) and *trans*-4-octene (**3a″**) could be selectively alkylated to give the terminal alkylation products in good yields with excellent selectivities. To our interest, *trans*-5-decene was also hydroalkylated smoothly in moderate yield and high selectivity (**3o**), in which a long chainwalking was required before the terminal alkylation. Finally, internal alkenes with various functional groups, such as ether (**3p**), ester (**3q**) and acetal (**3r**), could be well tolerated in this transformation.

On the basis of the above results and previous reports,[11] a plausible mechanism involving a Ni(I)/Ni(III) catalytic cycle is proposed as shown in Scheme 2. Firstly, the Ni-H species **B** could be generated via transmetalation between the Ni(I) species **A** with the silane under the activation of K_3PO_4. Subsequently, the insertion of internal alkene into Ni-H species **B** generates alkyl-nickel intermediate **C**, which undergoes β-hydride elimination to afford the intermediate **D**. After readdition of Ni-H species, a new primary alkyl-nickel(I) species **E** is formed. This alkyl-nickel intermediate **E** thus reacts preferentially with the alkyl halide (R-X) to generate Ni(III) species **F**.[12] Finally, the terminal selective coupling product **3** is obtained after the reductive elimination from intermediate **F**, and Ni(I) catalyst **A** is regenerated to complete the catalytic cycle.

To demonstrate the application prospect of this method, our newly developed catalytic system has been applied to the isomerization-hydroalkylation of isomeric mixtures of aliphatic olefins, which are usually obtained from petrochemical sources and thus substantially cheaper and more easily accessible than pure olefin isomers. As shown in Scheme 3, under the standard conditions, a mixture of octenes with equimolar amounts of four octene isomers afforded the terminal alkylated product with good yield (82%) and excellent regioselectivity (97:3 rr). This result suggested the great potential of this transformation in organic synthesis.



Scheme 2. Proposed mechanism.



Scheme 3. Terminal-selective alkylation of mixture of alkene isomers.

Conclusions

In conclusion, we have developed a novel and efficient terminal-selective alkylation of internal alkenes via nickel-catalyzed isomerization/hydroalkylation reaction. This method demonstrated broad scope, mild conditions and excellent regioselectivity. The key to success is the use of bis(oxazoline) as the ligand to improve the reactivity of this nickel-catalyzed tandem reaction. Further studies of the mechanistic details of this transformation and the application of this method for the late-stage modification of some complex bioactive molecules are still ongoing in our laboratory.

Acknowledgments

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12. A TEMPO-quench experiment in mechanism studies indicated that the catalytic cycle might proceed via a radical pathway. For details, see the SI.

Research highlights

1. An efficient nickel-catalyzed reductive relay cross-coupling of internal alkenes with alkyl/aryl halides has been developed;
2. This method has demonstrated broad substrate scope, mild reaction conditions and excellent terminal-selectivity;
3. The efficient strategy can be applied to the terminal-selective alkylation of isomeric mixtures of internal alkenes.