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# Ni-Catalyzed Regiodivergent and Stereoselective Hydroalkylation of Acyclic Branched Dienes with Unstabilized C(sp<sup>3</sup>) Nucleophiles

Wen Shao,<sup>†</sup> Céline Besnard,<sup>‡</sup> Laure Guénée,<sup>‡</sup> Clément Mazet\*,<sup>†</sup>

<sup>†</sup> Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva, Switzerland.

<sup>‡</sup> Laboratory of Crystallography, University of Geneva, 24 quai Ernest Ansermet, 1211 Geneva, Switzerland.

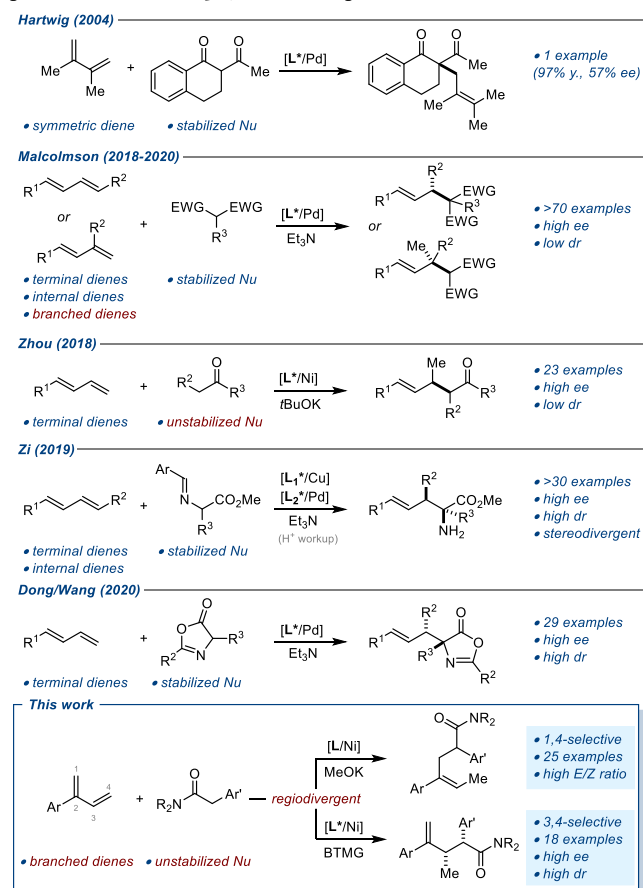
**ABSTRACT:** Two complementary regiodivergent [(P,N)Ni]-catalyzed hydroalkylations of branched dienes are reported. When amides are employed as unstabilized C(sp<sup>3</sup>) nucleophiles, a highly regioselective 1,4-addition process is favored. The addition products are obtained in high yield and with excellent stereocontrol of the internal olefin. Using a chiral ligand and imides as carbon nucleophiles, a 3,4-addition protocol was developed enabling construction of two contiguous tertiary stereocenters in a single step with moderate to high levels of diastereocontrol and excellent enantiocontrol. Both methods operate under mild reaction conditions, display broad scope and show excellent functional group tolerance. The synthetic potential of the 3,4-hydroalkylation reaction was established via a series of post-catalytic modifications.

## INTRODUCTION

The development of novel methods for the diastereoselective and enantioselective construction of adjacent stereocenters based on C–C bond forming reactions is a resounding challenge in chemical synthesis.<sup>1</sup> The atom-economical intermolecular hydroalkylation of conjugated dienes has recently emerged as an enabling strategy because it provides access to synthetically useful compounds with an allylic stereocenter, compounds that would be difficult to prepare using conventional protocols. The influence of the substitution pattern of dienes on reactivity and selectivity and the diversity of insertion modes conceivable for a transition metal catalyst across the conjugated double bonds pose major difficulties for their selective functionalization. Consequently, in its most demanding version, the successful development of a metal-catalyzed hydroalkylation of dienes requires addressing altogether chemoselectivity, regioselectivity, diastereoselectivity and –ultimately– enantioselectivity challenges.<sup>2,3</sup>

To date, there is only a handful of reports on the selective intermolecular hydroalkylation of 1,3-dienes (Figure 1). In 2004, Hartwig described the first Pd-catalyzed enantioselective addition of a stabilized C(sp<sup>3</sup>) nucleophile to a symmetric diene (which obviated potential regioselectivity issues), furnishing the product in excellent yield but modest enantiomeric excess.<sup>4</sup> Over a decade later, a series of breakthrough studies were reported by the Malcolmson group, which disclosed highly enantioselective Pd-catalyzed additions of a variety of activated C-centered nucleophiles to terminal, internal and even branched dienes.<sup>5</sup> The products were typically obtained with excellent level of enantiocontrol and the combined scope of these methods is particularly broad. Zhou and coworkers demonstrated that, in presence of a Ni catalyst and a catalytic amount of a strong

base, linear 1,3-dienes could be coupled with unstabilized C-nucleophiles using in situ generated enolates from simple ketones.<sup>6</sup> The 3,4-addition products were obtained



**Figure 1.** Transition metal-catalyzed intermolecular enantioselective and diastereoselective hydroalkylations of acyclic 1,3-dienes.

preferentially with high enantioselectivity but in low diastereomeric ratio when vicinal stereocenters were formed. The Zi group disclosed an elegant [Cu/Pd] dual catalytic system for the addition of weakly nucleophilic aldimine esters to linear dienes, affording the products in high yield, excellent *ee* and high *dr*. Particularly worthy of note is the perfectly stereodivergent nature of the process, which provided access to all four possible stereoisomeric products when 2 adjacent stereocenters were generated.<sup>7</sup> Inspired by seminal work from the Meek group,<sup>8</sup> Dong and Wang recently reported an enantioselective Pd-catalyzed hydroalkylation of linear dienes using azlactones as stabilized C-nucleophiles.<sup>9</sup> The products were isolated in good yield, high *dr* and high levels of enantiocontrol. In spite of the above achievements, the number of efficient diastereo- and enantioselective hydroalkylations of dienes remains limited. The development of selective methods based on the combination of unstabilized carbon-centered nucleophiles and underexplored –yet valuable– diene subclasses would undeniably represent an important addition to the protocols currently available.

We disclose here the identification of two regiodivergent and complementary Ni-catalyzed stereoselective hydroalkylations of branched dienes using unstabilized C(sp<sup>3</sup>) nucleophiles derived from simple amides and imides.<sup>10</sup>

## RESULTS AND DISCUSSION

We recently reported a Ni-catalyzed enantioselective 3,4-hydroamination of 1,3-dienes using primary aliphatic amines, which occur with excellent Markovnikov selectivity.<sup>11</sup> Therefore, we initially set out to develop a related system for the 3,4-hydroalkylation of branched dienes with amides as carbon nucleophiles. Unfortunately, subjecting the model coupling partners **1a** and **2a** to our original protocol did not deliver any addition product (Table 1, entry 1). No reaction took place under the conditions developed by the Zhou group for the hydroalkylation of linear dienes using simple ketones despite the relatively similar pK<sub>a</sub> values of the C-nucleophiles (entry 2; pK<sub>a</sub> (**2a**/DMSO) = 26.6, pK<sub>a</sub> (acetone/DMSO) = 26.5).<sup>12</sup> With **L1**, when *t*BuOK was employed as base in THF, quantitative conversion to alkylation products resulting from 3,4-addition (**4aa**) and 1,4-addition (**5aa**) was observed, with a marked preference for the latter (entry 3). Although **5aa** was not our initial target, the presence of two stereogenic elements and two functional handles in its structure prompted us to further explore conditions favoring its formation. Pleasingly, with a catalytic amount of MeOK, an extended reaction time and only 1.2 equivalents of **2a**, **5aa** was generated as the sole regioisomeric hydroalkylation product with excellent control of the internal olefin geometry (*rr* >25:1, *E/Z* 15:1) (entries 4–5). We found that the product of 3,4-hydroalkylation (**6aa**), could be obtained majoritarily by substituting amide **2a** for imide **3a** (entry 6).<sup>13</sup> The use of Barton's base (BTMG) for the in situ generation of the carbon-centered nucleophile gave a homogeneous solution and led to slightly improved regioselectivity and diastereoselectivity (entry 7).<sup>14</sup> Of note, no addition reaction occurred when attempting to generate the enolate of **2a** with BTMG (entry 8).

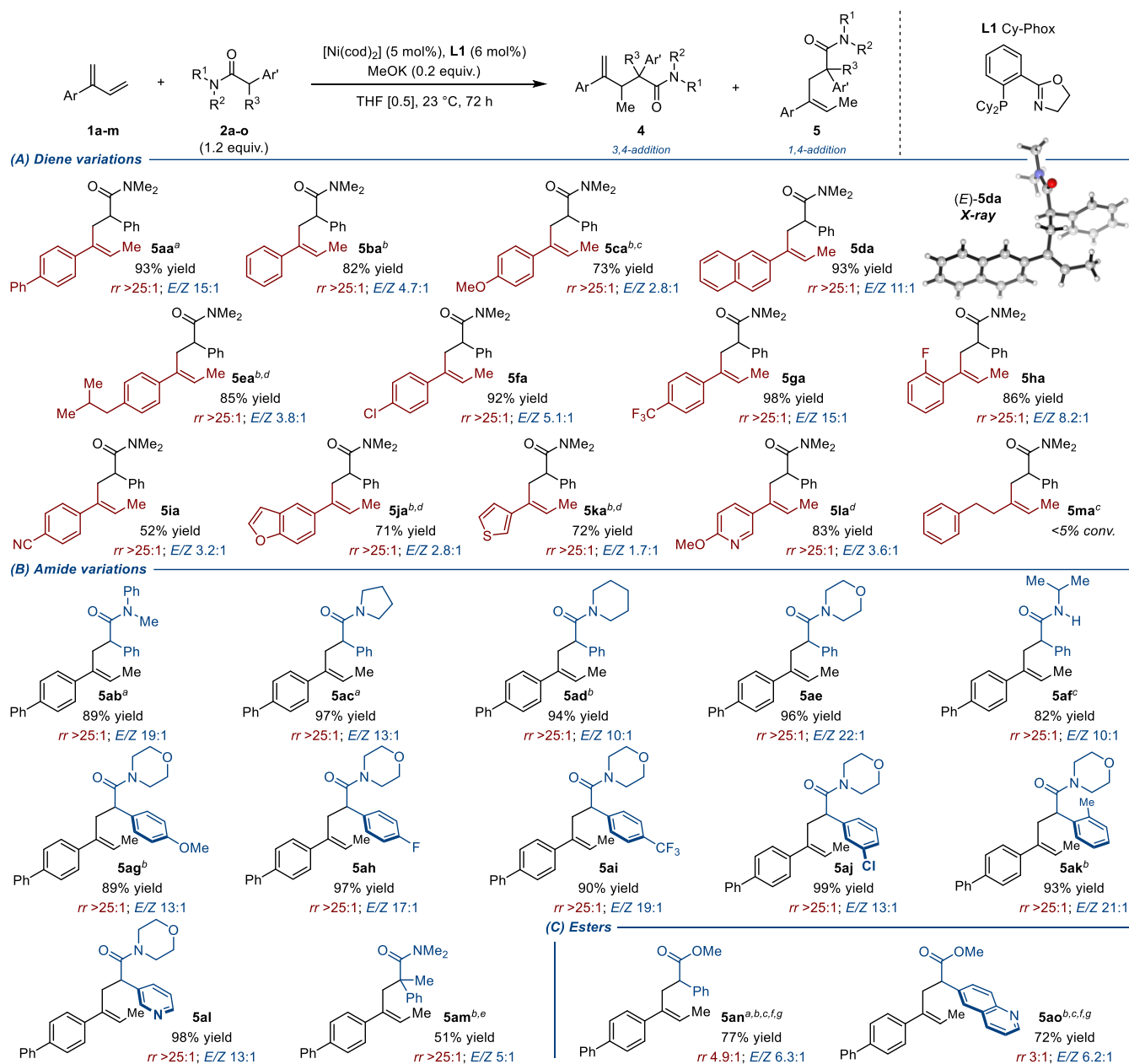
**Table 1. Reaction optimization<sup>a</sup>**

entry	Nu	L	base (n equiv)	solvent	conv. (%) <sup>b</sup>	3,4-/1,4-addition <sup>b</sup>
1	<b>2a</b>	<b>L1</b>	none <sup>c</sup>	mesitylene	<5	-
2 <sup>d</sup>	<b>2a</b>	<b>L2</b>	<i>t</i> BuOK (0.2)	EtOH <sup>e</sup>	<5	-
3 <sup>f</sup>	<b>2a</b>	<b>L1</b>	<i>t</i> BuOK (2.0)	THF	>95	1:19 ( <i>E/Z</i> 2.5:1)
4 <sup>f</sup>	<b>2a</b>	<b>L1</b>	MeOK (0.2)	THF	>95	1:>25 ( <i>E/Z</i> 9:1)
5 <sup>g</sup>	<b>2a</b> <sup>h</sup>	<b>L1</b>	MeOK (0.2)	THF	>95	1:>25 ( <i>E/Z</i> 15:1)
6	<b>3a</b>	<b>L1</b>	MeOK (0.2)	THF	>95	6.2:1 ( <i>dr</i> 2.7:1)
7	<b>3a</b>	<b>L1</b>	BTMG (1.0)	THF	>95	6.5:1 ( <i>dr</i> 2.8:1)
8	<b>2a</b>	<b>L1</b>	BTMG (1.0)	THF	<5	-

**L1** Cy-Phox      **L2** DTBM-Seqphos      **BTMG** (Barton's base)

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** or **3a** (0.2 mmol). <sup>b</sup> Determined by <sup>1</sup>H NMR using an internal standard. <sup>c</sup> 1.0 equiv. trifluoroethanol. <sup>d</sup> 100 °C. <sup>e</sup> 0.2 M. <sup>f</sup> 50 °C. <sup>g</sup> 48 h. <sup>h</sup> 1.2 equiv.

Having identified two complementary protocols for the hydroalkylation of branched dienes, we first decided to explore the scope of the Ni-catalyzed 1,4-regioselective process using amides as carbon nucleophiles (Figure 2). For 2-aryl substituted 1,3-dienes, independently of any electronic perturbation, the regioselectivity was uniformly high and the addition products were isolated in good to excellent yield with stereoselectivity varying from 1.7:1 to 15:1. Notably, 2-heteroaryl dienes (**1j–1l**) and a cyano-containing substrate (**1i**) were compatible with the mild reaction conditions. By contrast, 2-alkyl 1,3-dienes such as **1m** did not participate productively in the reaction. Variation of the structure of the C-nucleophile proved to be particularly informative. A variety of secondary amides, containing for instance a pyrrolidine, a piperidine or a morpholine unit, were suitable candidates for the addition reaction (**5ab–5ae**). Remarkably, *N*-isopropyl-2-phenylacetamide, a primary amide derivative, was engaged successfully in the hydroalkylation reaction with perfect chemoselectivity (**5af**). Introduction of electron-donating or electron-withdrawing substituents at the *para*-, *ortho*- or even *meta*- position of the aryl ring was also well-tolerated (**5ag–5ak**), as was the case with a 3-pyridine moiety (**5al**). In all these reactions, regioselectivity and stereoselectivity were excellent. Of particular note, using *N,N*-dimethyl-2-phenylpropanamide and LiHMDS/*t*BuOK as a combination of bases, **5am** a product with a congested α-quaternary center was generated, albeit in a slightly diminished yield and stereoselectivity (51% yield, *E/Z* 5:1). Finally, even though the regioselectivity and stereoselectivity decreased markedly, we found that esters could be employed as C(sp<sup>3</sup>) nucleophiles using 2 equiv of base and by running the reaction at 50 °C

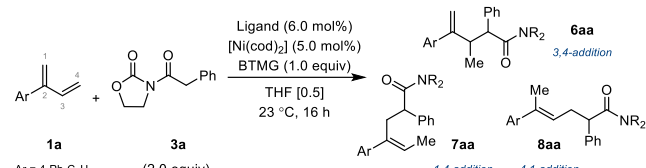


**Figure 2.** Scope of the stereoselective Ni-catalyzed 1,4-hydroalkylation of branched dienes using 2-phenylacetamide derivatives. **1a-m** (0.2 mmol) and **2a-o** (1.2 equiv.). Yield of isolated product after purification by column chromatography. Regioisomeric ratio and stereoselectivity determined by  $^1\text{H}$  NMR. <sup>a</sup> 48 h. <sup>b</sup> 2.0 equiv. of nucleophile (amide or ester). <sup>c</sup> 50 °C. <sup>d</sup> 120 h. <sup>e</sup> LiHMDS (1.0 equiv.) and *t*BuOK (0.1 equiv.) instead of MeOK. <sup>f</sup> 2.0 equiv. of base. <sup>g</sup> Combined yield (**4**+**5**).

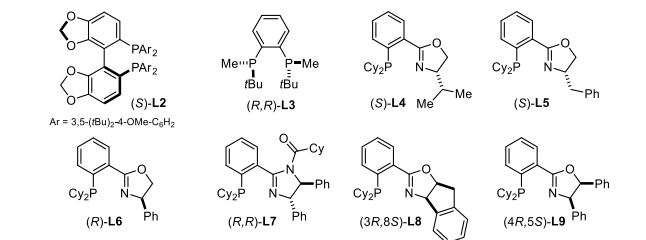
(**5an**, **5ao**). The stereochemistry of the internal double bond initially assigned on the basis of 2D NMR experiments was confirmed with the resolution of the X-ray structure of **5da**. Much to our dismay, all efforts to develop an enantioselective variant of this addition process were unsuccessful, despite an extensive screening of chiral (P,N) and (P,P) ligands (See SI for details). The absence of stereoinduction can be ascribed either to poor facial selectivity upon nucleophilic addition and/or poor control of the enolate stereochemistry. Nonetheless, because no enantioinduction was observed both with **2a** and **2m**, post-catalytic enantiomerization can be reasonably excluded.<sup>15</sup>

Reasoning that the use of imides in place of amides in the Ni-catalyzed 3,4-hydroalkylation of diene may positively influence the stereoselective outcome of the reaction, we directly set out to develop an enantioselective variant of this process. Several chiral ligands were surveyed using the optimized conditions developed with **L1** (Table 2). Whereas DTBM-Segphos (**L2**), the chiral ligand employed by Zhou and coworkers for the hydroalkylation of linear dienes using simple ketones proved ineffective, BenzP\* (**L3**) which we used in the enantioselective hydroamination of branched dienes led to a mixture of 3 regioisomers (entries 1-2). These isomeric products, which result from formal 3,4-addition (**6aa**), 1,4-addition (**7aa**) and 4,1-addition (**8aa**), were obtained quasi-quantitatively



Table 2. Chiral ligand survey<sup>a</sup>


entry	L	Conv. (%) <sup>b</sup>	6aa : 7aa : 8aa <sup>b</sup>	dr <sub>6aa</sub> <sup>b</sup>	ee <sub>6aa</sub> (%) <sup>c</sup>
1	<b>L2</b>	<5	-	-	-
2	<b>L3</b>	>95	3.8 : 4.2 : 1	2.8:1	77
3	<b>L4</b>	95	7.3 : 1 : 1.1	3.3:1	18
4 <sup>d</sup>	<b>L5</b>	80	16.3 : 2.8 : 1	3.3:1	3
5	<b>L6</b>	>95	11.3 : 1 : 1.9	5.3:1	87
6	<b>L7</b>	51	6.1 : 1 : 6	5.3:1	70
7	<b>L8</b>	59	5.7 : 1 : 1.7	2.3:1	-79
8	<b>L9</b>	>95	11.1 : 1 : 1.9	5.3:1	92
9 <sup>e</sup>	<b>L9</b>	>95	13 : 1 : 2.1	7.0:1	92



<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **3a** (0.2 mmol). <sup>b</sup> Determined by <sup>1</sup>H NMR using an internal standard. <sup>c</sup> Determined by HPLC using a chiral stationary phase. <sup>d</sup> Using MeOK (0.2 equiv.) as base. <sup>e</sup> **3a** (1.2 equiv.), BTMG (0.2 equiv.), 48 h.

in a 3.8:4.2:1 ratio. Furthermore, **6aa** was generated with promising diastereo- and enantioselectivity levels (*dr* 2.8:1; 77% ee). A series of chiral phosphino-oxazoline ligands derived from **L1** were tested next and the most representative results are disclosed in entries 3–8 of Table 2 (See SI for details). Overall, the highest regioselectivity, diastereoselectivity and enantioselectivity were obtained for derivatives possessing an aromatic substituent at the stereogenic center  $\alpha$  to the N-donor atom, and **L9**—a novel member of this ligand class—was the optimal candidate. Extending the reaction time and adjusting the relative stoichiometry between all reagents enabled us to further improve the catalytic performances (*rr* 4.1, *dr* 7.0:1, 92% ee; entry 9).<sup>16</sup>

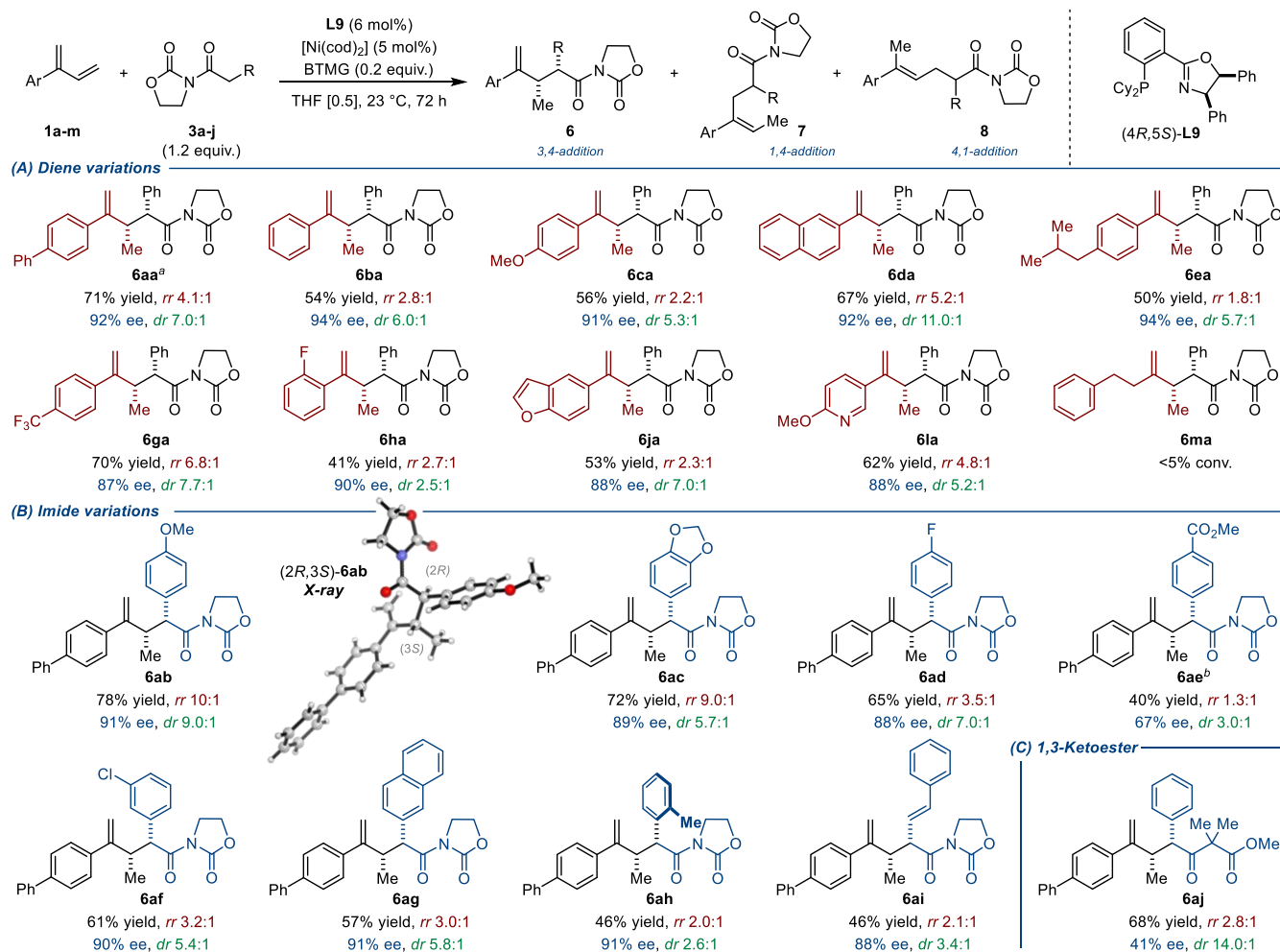
These mild conditions were subsequently used to delineate the scope of the 3,4-hydroalkylation of branched dienes by first varying the nature of the electrophilic component (Figure 3, A). Isolation of the major diastereoisomeric product in pure form was strongly influenced by the extent of regio- and diastereocontrol. Thus, regioselectivity ranging from 1.8:1 to 6.8:1 were paralleled by yields varying between 41% and 71%. Most diastereoselectivity levels were greater than 5:1. The lowest value was obtained for **1h**, a diene with an *ortho*-fluoro substituent (*dr* 2.5:1), while the highest was obtained for **1d**, a diene with an extended  $\pi$  system (*dr* 11:1). Modulations of the electronic density of the 2-(hetero)aryl substituent were well tolerated. Enantioselectivity was very high in all cases (87–94% ee). No reaction took place when a 2-alkyl substituted diene was

tested (**6ma**). Several imides, readily prepared from 2-oxazolidinone and the appropriate acyl chloride, were explored next (Figure 3, B). The product of 3,4-hydroalkylation was always generated preferentially (*rr* 1.3:1–10:1) in excellent enantioselectivity (88–91% ee), with the exception of **6ae** (67% ee). Products with a *para* methoxy- (**6ab**), a *para* fluoro- (**6ad**), a *meta* chloro-substituent (**6af**), a naphthyl group (**6ag**) as well as a dioxolane moiety (**6ac**) were formed with appreciable catalytic efficiency, in high diastereo- and enantioselectivity and with acceptable regioselectivity (*dr* > 5:1, ca. 90% ee). Although the net catalytic performances were affected, we found that a *para*-methyl ester could be accommodated by using MeOK instead of BTMG as base (**6ae**). A sterically demanding *ortho*-methyl arene affected reactivity, regio- and diastereoselectivity, but not enantioselectivity (**6ah**: 91% ee). Similar data were obtained for a substrate with a cinnamyl substituent (**6ai**). When the imide moiety was substituted by a 1,3-ketoesters preferential 3,4-hydroalkylation occurred with reduced regioselectivity and enantioselectivity but with excellent diastereoselectivity (**6aj**). Finally, an X-ray analysis was obtained for **6ab**, and the absolute and relative configurations of all other hydroalkylation products were assigned by analogy.

To demonstrate the synthetic potential of the 3,4-hydroalkylation protocol, several post-catalytic derivatizations were conducted using diastereomerically pure **6aa** (Figure 4). Complete reduction of the imide moiety into the corresponding primary alcohol **9** was achieved without epimerization using lithium borohydride. Subsequent acidic treatment led to the selective formation of tetrahydrofuran derivative **10**, the structure of which is characterized by three contiguous stereocenters (*dr* 19:1). Ester **11** was obtained in excellent yield and enantiospecificity using the ytterbium-catalyzed esterification of imides independently developed by the Evans and Stevens/Frantz groups.<sup>17</sup> Hydrogenation of the 1,1-disubstituted alkene unit in **6aa** was accomplished under mild reaction conditions using Pd(C). The reduced product (**12**) was generated quantitatively in a 5.3 *dr*. The relative stereochemistry of the major isomer was established by X-ray crystallographic analysis. Hydrolysis of **6aa** was conducted under basic conditions using H<sub>2</sub>O<sub>2</sub> as nucleophile under strongly basic conditions (LiOH).<sup>18</sup> Finally, we demonstrated that the corresponding carboxylic acid (**13**) could be engaged in late-stage modifications using highly functionalized synthetic intermediates. Sitagliptin, an anti-diabetic drug containing a primary amine and Ciproflaxin ester, a broad-spectrum antibiotic containing a secondary amine, were both efficiently converted to the corresponding amides **14** and **15** respectively using EDC·HCl as peptide coupling reagent.

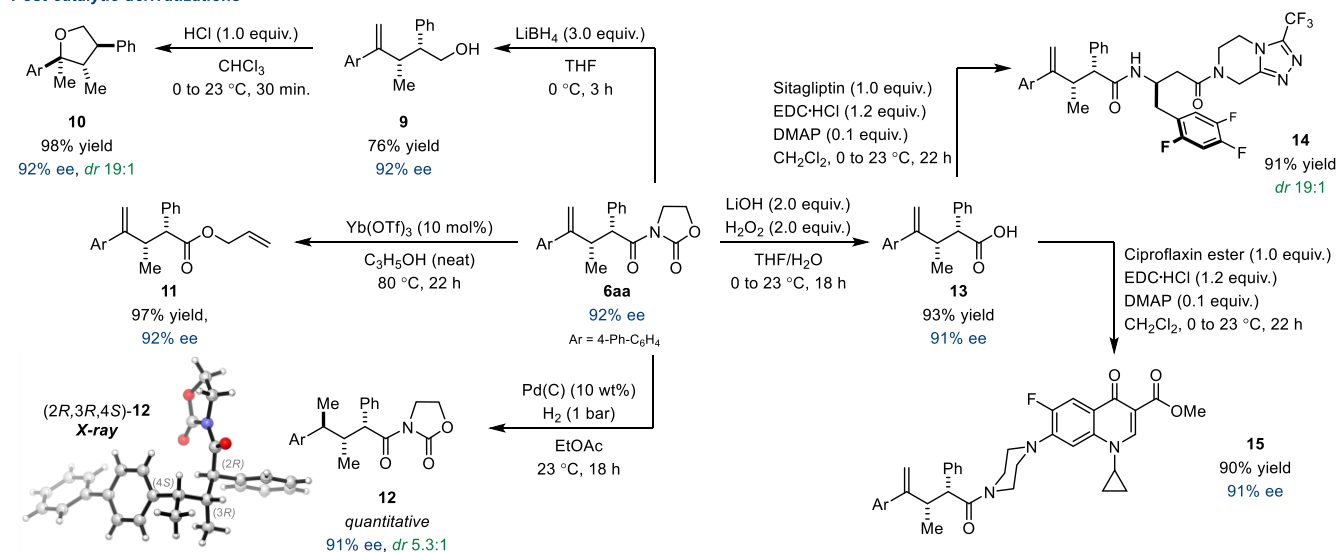
## CONCLUSION

In addition to stereoselectivity, regioselectivity is often a major challenge in diene hydrofunctionalization reactions. In this article, we have reported two complementary regiodivergent Ni-catalyzed hydroalkylations of branched



**Figure 3.** Scope of the diastereoselective and enantioselective Ni-catalyzed 3,4-hydroalkylation of branched dienes using imides and a  $\beta$ -ketoester. 1a-m (0.2 mmol) and 3a-j (1.2 equiv.). Yield reported for the major diastereoisomer, isolated after purification by column chromatography. Regioisomeric ratio (rr) expressed as the ratio between 6 and all other isomers (7+8) as determined by <sup>1</sup>H NMR with an internal standard. Enantiomeric excess determined by HPLC using a chiral stationary phase. <sup>a</sup> 48 h. <sup>b</sup> MeOK (0.2 equiv.) as base.

#### Post-catalytic derivatizations



**Figure 4.** Post-catalytic derivatizations starting from diastereomerically pure 6aa. Yields of isolated products after purification. Diastereomeric ratio determined by <sup>1</sup>H NMR with an internal standard. Enantiomeric excess determined by HPLC using a chiral stationary phase.

dienes with unstabilized C(sp<sup>3</sup>) nucleophiles. The first system uses an achiral C<sub>1</sub>-symmetric phosphinooxazoline ligand and simple amides which, once deprotonated in situ, undergo a highly 1,4-selective addition process with excellent stereocontrol of the trisubstituted C=C bond generated. The method displays a broad scope in both the nucleophilic and electrophilic component, enabling the use of sensitive functionalities and heteroaromatic-containing precursors. Switching to imides as carbon nucleophiles favored formation of the 3,4-addition products. The construction of the two vicinal tertiary stereocenters was achieved with moderate to high diastereoselectivity and excellent enantioselectivity by means of a novel chiral (P,N) ligand. Notably, a wide range of functional groups were compatible with the mild conditions employed and several post-catalytic derivatizations were conducted to measure the synthetic potential of the method. Studies aiming at understanding the factors that determine reactivity and selectivity for both systems are currently ongoing in our laboratories.<sup>19</sup>

## ASSOCIATED CONTENT

Experimental procedures, characterization of all new compounds and X-ray data for compounds (*E*)-**5da**, (2*R*,3*S*)-**6ab** and (2*R*,3*R*,4*S*)-**12** (CCDC 2018944-2018946). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\* clement.mazet@unige.ch

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## SYNOPSIS TOC

