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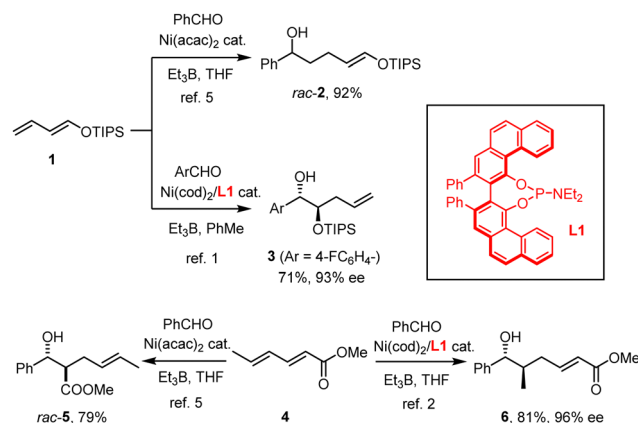
# Aminoalcohol derivatives by nickel-catalyzed enantioselective coupling of imines and dienol ethers†

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**The reductive coupling of dienol ethers with *N*-tosylimines catalyzed by Ni(0) in the presence of a VAPOL-derived phosphoramidite ligand follows an unprecedented regiochemical course; it furnishes *syn*-configured 1,2-aminoalcohol derivatives in good chemical yields with up to 94% ee.**

Our group has recently reported that the nickel-catalyzed reductive coupling of aldehydes with dienol ethers, when carried out in the presence of the VAPOL-derived phosphoramidite ligand **L1**, takes an unprecedented regiochemical course.<sup>1–4</sup> Whereas classical “Tamaru–Mori”-type reactions are distinguished by C–C-bond formation at the diene terminus leading to products such as *rac*-2,<sup>5–9</sup> Ni(0)/**L1** compels the electron-rich diene **1** to react at the least nucleophilic and arguably most hindered C-atom carrying the oxygen substituent to give the mono-protected 1,2-diol derivative **3** in good yield and appreciable optical purity (Scheme 1).<sup>1</sup> Shortly thereafter, we showed that this outcome is no singularity; rather, electron-deficient sorbate esters **4** (and related dienes) also follow an “inverse” course relative to all literature precedent<sup>5,10</sup> in that they furnish compounds such as **6** rather than aldol-type products of type *rac*-5.<sup>2</sup> In addition to the unorthodox connectivity pattern manifested in **6**,<sup>11</sup> the high level of enantioselectivity is noteworthy, since asymmetric Tamaru-type reactions in general were even recently called a “largely unresolved challenge”;<sup>12</sup> indeed, only a few examples were known prior to our work.<sup>10,13–16</sup> Although mechanistic studies<sup>17</sup> into these transformations proved exceptionally challenging and the reasons for the observed reversal enforced by the ligand **L1** therefore remain elusive, a more systematic exploration of this unorthodox yet arguably enabling reactivity pattern is warranted.

In this context, an extension to imines as electrophilic partners seemed particularly attractive for the prospect of gaining access to valuable *vic*-aminoalcohol derivatives. Under the standard conditions employed for the preparation of **3**,<sup>1</sup> the reaction of benzaldehyde *N*-tosylimine **8** with silyl dienol ether **1** (R = TBS) proceeded extremely slowly, not least because of the poor solubility of the substrate in toluene (Scheme 2(A)). To remedy the issue, amidosulfone **7** was tested as an imine surrogate,<sup>18</sup> which led to an apparently homogeneous solution upon addition of di-isopropylethylamine to the mixture; this base gently releases imine **8** in solution yet is too bulky to quench the Et<sub>3</sub>B as the promoter of choice. The fact that product **9a** was obtained in moderate yield but with excellent optical purity was deemed encouraging; surprisingly though, transformation into aziridine **10** and comparison with literature data<sup>19</sup> suggested that the product was *syn*-configured (see below), whereas diols such as **3** derived from aldehydes under the same conditions had invariably been *anti*-configured.<sup>1</sup> Unfortunately, however, the material contained substantial amounts of **11a**, in which the double bond is shifted by one position (**9a**:**11a** ≈ 4:1).



**Scheme 1** The VAPOL-derived phosphoramidite ligand **L1** as a “game-changer” in Ni-catalyzed reductive coupling reactions.

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As this isomer is virtually impossible to remove by any method other than HPLC, its formation had to be suppressed from the outset. To this end, the solvent, the reaction temperature, the nickel source,<sup>§</sup> the promoter,<sup>¶</sup> the *N*-substituent on the imine,<sup>||</sup> the *O*-substituent of the dienol ether were varied and numerous additives tested, without much success. It was not until an attempt was made to form an imine *in situ* from benzaldehyde and *p*-methoxybenzylamine that a key observation was made: although the desired product was almost racemic in this case, the rate of reaction was massively enhanced as compared to what was seen with preformed *N*-PMB imine.<sup>20</sup> This comparison suggested that water generated *in situ* might play a critical role; therefore, further attempts at optimization focussed on this particular parameter.<sup>21</sup> Indeed, addition of three equivalents of degassed H<sub>2</sub>O proved optimal, provided THF (rather than toluene) was used as the solvent (for details, see the ESI†). Under these conditions, product **9a** (R = TBS) was obtained in 75% yield and 94% ee with a notably improved regioisomer ratio of  $\approx 7.6:1$ ; slightly better results were obtained for **9b** bearing a smaller TES-group. Gratifyingly though, recourse to the more bulky TIPS dienol ether **1** (R = TIPS) furnished product **9c** virtually as a single isomer; the regioisomeric alkene could not be detected by <sup>1</sup>H NMR in the crude material (rr > 20:1). Moreover, the *N*-tosylimine **8** itself performed even better in this case than the sulfone surrogate **7** (Scheme 2(B)), which is an advantage in terms of atom economy. Cleavage of the TIPS group with TBAF afforded alcohol **12**; its structure in the solid state confirmed the relative and absolute configuration as originally deduced based on the data recorded for the derived aziridine **10** (Fig. 1).<sup>22</sup> The MOM-protected dienol ether



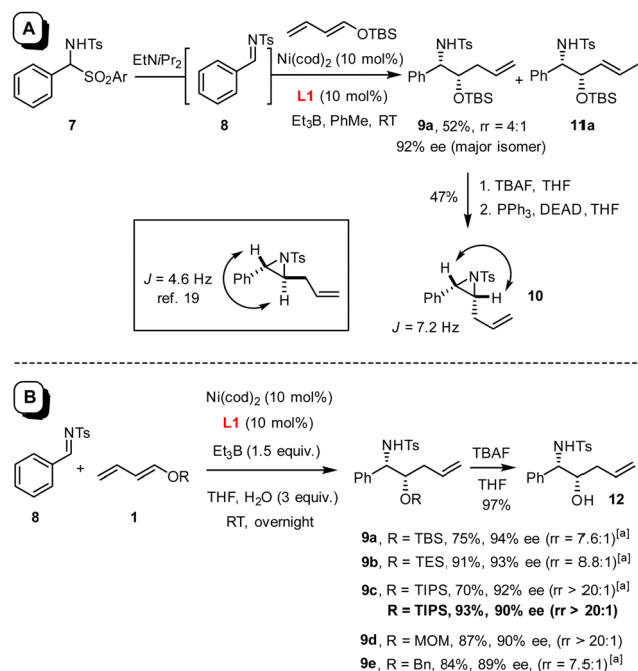
Fig. 1 Structure of compound **12** in the solid state.

proved similarly suitable for reductive coupling to give **9d** exclusively, whereas the corresponding benzyl dienol ether resulted in an isomer mixture and was therefore not used any further.

Fig. 2 shows an assortment of aminoalcohol derivatives obtained by this new procedure from aromatic and heteroaromatic tosyl aldimines; their configuration was assigned in analogy to compound **12**. Electron-rich as well as electron-deficient substrates proved suitable, although the latter tend to give better ee's. The fact that an aryl chloride and even a bromide as well as a thiophene ring remained intact is a remarkable virtue of this catalyst system based on Ni(0). Equally relevant is the compatibility with a pinacolboronate ester, which constitutes an excellent handle for downstream functionalization. It is also noteworthy that placement of a methyl substituent *ortho* to the aldimine did not prevent the reductive coupling from occurring. In cases such as **17**, in which the optical purity was insufficient, recrystallization of the sample from *t*BuOMe/*n*-hexane allowed the issue to be addressed.

*N*-Tosyl aldimines derived from aliphatic aldehydes also participate in reductive coupling with dienol ethers **1** (Scheme 3). In this case, only one equivalent of degassed water should be added to the reaction mixture to minimize formation of the corresponding internal alkene isomer. Although traces of this side product were always present in the crude material, chromatographic purification allowed this impurity to be removed after cleavage of the silyl ether. The ee's obtained with the aliphatic aldimines were in the range of 81–86%, but recrystallization proved again serviceable for solid materials.

The reaction scales well. Thus, product **9c** was formed in essentially the same yield and unchanged ee of 90% when the



Scheme 2 Panel A: lead finding (Ar = Ph); panel B: preparation of *syn*-configured aminoalcohol derivatives by reductive coupling under optimized conditions; <sup>a</sup> starting from sulfone **7** (Ar = *p*-tolyl) (rather than imine **8**) in the presence of EtN(iPr)<sub>2</sub> (1.2 equiv.).

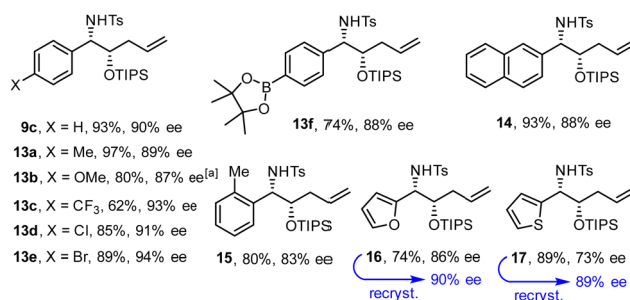
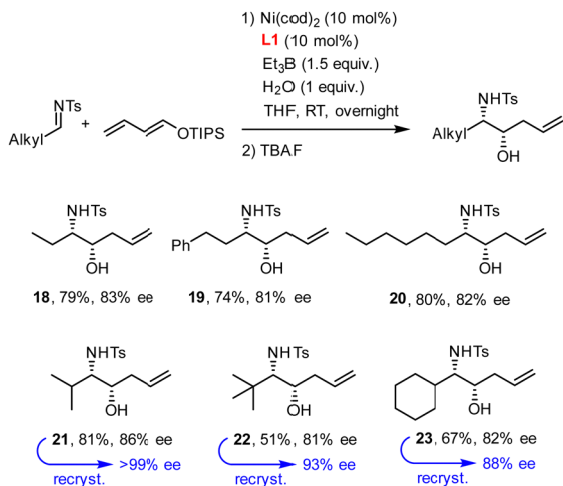
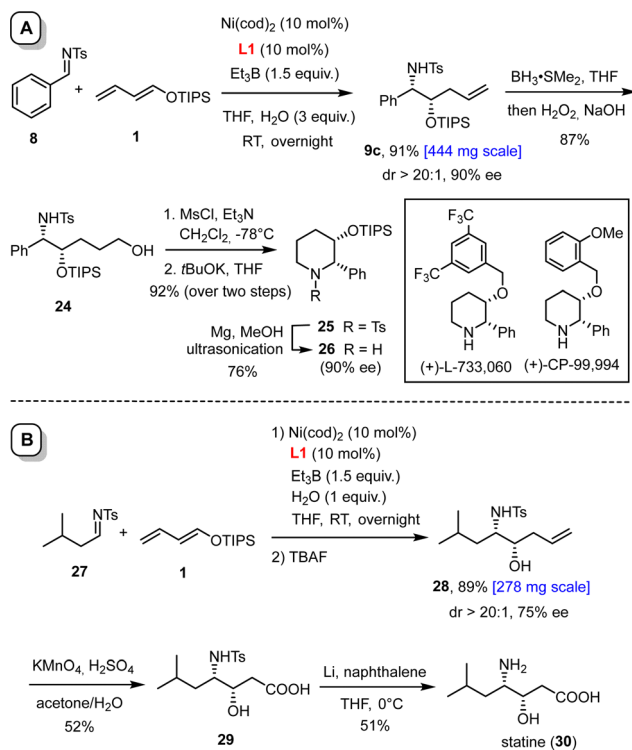


Fig. 2 Aminoalcohol derivatives formed by reductive coupling of (hetero)aromatic tosyl aldimines with silyl dienol ether **1** (R = TIPS); for the conditions, see Scheme 2(B); <sup>a</sup> at 0 °C.



**Scheme 3** Reductive coupling of aliphatic tosyl aldimines with silyl dienoether **1** (R = TIPS).

reductive coupling was performed on 1 mmol scale (Scheme 4(A)). Subsequent hydroboration/oxidation furnished alcohol **24**; treatment of the derived mesylate with *t*BuOK in THF gave the disubstituted piperidine derivative **25**, which is a valuable building block for the formation of non-peptidic neurokinine NK1 receptor antagonists such as L-733,060 or CP-99,994.<sup>23</sup> In this context, it is important to note that the tosyl group of **25** can be readily cleaved with magnesium powder in MeOH upon ultrasonication of the suspension in a laboratory cleaning bath.<sup>24</sup> This method is so mild



**Scheme 4** Synthetic applications. Panel A: preparation of a building block for non-peptidic neurokinine NK1 receptor antagonists; panel B: synthesis of the naturally occurring  $\gamma$ -amino acid statine.

that the TIPS-ether survives, as demonstrated by the formation of compound **26**, which was obtained with unaltered optical purity.

Scalability was also demonstrated for compound **28**, which can be elaborated in only two steps into statine (**30**, Scheme 4(B)). This  $\gamma$ -amino acid is the essential constituent responsible for the activity of the potent aspartyl protease inhibitor pepstatin.<sup>25</sup> To this end, the double bond of **28** was oxidatively cleaved with acidic permanganate and the sulfonamide of the resulting acid **29** deprotected with lithium naphthalene in THF; the moderate yields are solely due to the very high polarity of the compounds.

In summary, this study extends our recent finding that Ni(0) allies with a VAPOL-derived phosphoramidite ligand to give a so far unique catalyst system that imposes unprecedented regioselectivity as well as appreciable enantioselectivity onto reductive coupling reactions of dienes with different electrophilic partners. Future studies in our laboratory will try to extend the portfolio of this novel type of transformation, optimize the attained level of induction by ligand tuning, and gain basic mechanistic understanding for how this specific nickel/ligand combination exerts its function. Pertinent results along these lines will be reported in due course.

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## Conflicts of interest

There are no conflicts to declare.

## Notes and references

§ The use of the bench-stable Ni(0) stilbene complex [Ni(*t*Bu-stb)<sub>3</sub>]<sup>26</sup> instead of [Ni(cod)<sub>2</sub>] led to markedly lower yields of product, although this precatalyst had been very active in the reductive coupling of sorbate esters.<sup>2</sup>

¶ For reasons that are not entirely clear, Et<sub>3</sub>B worked much better than Et<sub>2</sub>Zn, although the latter has often been used in Tamaru–Mori-type reactions.

|| PhCH = NTs and PhCH = NSO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> gave good ee's; low ee's and/or low yields were obtained with PhCH = NSO<sub>2</sub>Me, PhCH = NSO<sub>2</sub>*t*Bu, PhCH = NSO<sub>2</sub>Bn, PhCH = NBn, PhCH = NPMB, PhCH = N(2-pyridyl), PhCH = NP(O)Ph<sub>2</sub> and PhCH = NP(O)(OEt)<sub>2</sub>.

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