

Regioselective Pd-catalyzed hydroamination of
substituted dienesArnaud Perrier, Michel Ferreira,[†] Joost N. H. Reek and Jarl Ivar van der Vlugt*

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The regioselective addition of hydrazones and related *N*-nucleophiles to substituted terpene-based substrates can be steered to either 1,2- or 1,4-addition products, making this a potentially powerful protocol for the preparation of amines from biorelevant feedstocks *via* C–N bond formation.

Introduction

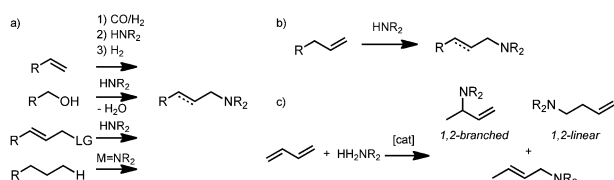
Amines are very versatile building blocks for a plethora of application areas, including dyes, polymers, pharmaceuticals and agrochemicals. The industrial production of amines still depends, at least to a large extent, on stoichiometric conversion of alkyl halides or alcohols as starting materials, which results in undesirable waste-streams or highly energy-intensive process conditions.^{1,2} Several catalytic methodologies for the selective formation of C–N bonds based on vinylic or allylic substrates have recently been developed (Scheme 1a).^{3–8} However, these methodologies generally rely on leaving-group chemistry, multi-step transformations, the inherent generation of by-products or suffer from drawbacks such as limited functional group tolerance.

The direct, atom-efficient hydroaddition of amines across a C=C double bond – hydroamination⁹ – is a very attractive approach to generate amines from readily available starting

materials (Scheme 1b). It would also be of high value to integrate this reaction step with other transformations in a cascade-like sequence. Furthermore, the use of ammonia as starting material, which would lead to valuable primary amines upon addition to alkenes, is a major challenge in this area, despite recent progress in the use of NH₃ as a substrate for homogeneous catalysis.¹⁰ One particular recent example is the direct amination of allyl alcohols using aqueous ammonia to furnish allylic amines, generating water as a by-product.¹¹ Besides (un)functionalized alkenes, allylic substrates or vinylarenes, dienes have recently emerged as an interesting substrate class for the regioselective hydroamination, potentially giving rise to selective 1,2- or 1,4-addition products (Scheme 1c).¹²

Given the recent surge toward the valorization and utilization of biorenewables for the production of high-value, highly functionalized chemicals,¹³ the exploration of catalytic methodologies for C–N bond formation that are orthogonal to existing functional groups is of prime interest and importance, as this would result in more atom-efficient processes, avoid side-product formation (like water) and retain optimal synthetic diversity in the resulting molecules.

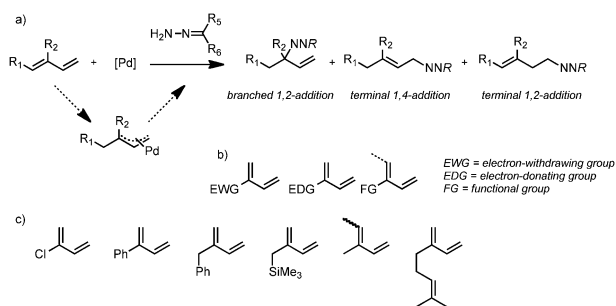
Among the different types of biobased feedstocks available, the class of terpenes appears to be ideally suited to allow easy access to introduction of additional N-containing functionalities. Initial advances concerning interesting terpene-based substrates have recently been reported. Behr and coworkers established the selective Pd-catalyzed 1,4-addition of morpholine to myrcene, resulting in a mixture of (*E*)- and (*Z*)-isomers in high yield, using dppb as a ligand.¹⁴ This procedure could provide an alternative synthesis route to (–)-menthol, for which the current route, as commercialized by Takasago, includes Li-catalyzed intermolecular hydroamination of diethylamine to myrcene that suffers from low activity.¹⁵ The group of Hartwig has investigated the Pd-catalyzed hydroamination of isoprene with a variety of hydrazine or hydroxyl amine derived *N*-nucleophiles, including hydrazones, and employing large bite angle ligands such as Xantphos.¹⁶



Scheme 1 (a) Previously reported catalytic procedures for C–N bond formation; (b) atom-efficient coupling of an alkene with an amine to generate a substituted (allylic) amine; (c) hydroamination of 1,3-diene to yield linear 1,4-, branched 1,2- and linear 1,2-isomers.

Homogeneous & Supramolecular Catalysis, van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH, Amsterdam, The Netherlands. E-mail: j.i.vandervlugt@uva.nl; Fax: +31 (0)20 525 5604; Tel: +31 (0)20 525 6459

[†] Present address: Université Artois, Unité de Catalyse et de Chimie du Solide (UCCS – UMR CNRS 8181) F-62307 Lens, France.



Scheme 2 (a) General Pd-catalyzed reaction between dienes and hydrazones via a π -allyl intermediate and the regioisomeric 1,2- and 1,4-products generated. (b) Potential substrate scope and (c) different substrates employed in this work.

Remarkably, selective nucleophilic addition at the 2-position of the diene skeleton was observed, leading to the formation of branched hydrazines.

However, to date no investigations of the use of substituted dienes other than 2,3-dimethyl-1,3-butadiene, isoprene (2-methyl-1,3-butadiene) and 1,3-cyclohexadiene have been reported for the hydroamination with hydrazones (formally hydrohydrazonation) as nucleophiles (Scheme 2). 2-Substituted dienes can potentially deliver a range of interesting *N*-functionalized products upon regioselective hydroaddition of an amine or derivative thereof, including chiral hydrazines and ultimately branched amines, in the case of selective 1,2-addition.¹⁷

Hydrazones may function as protected or masked amines or hydrazines *via* post-catalysis modification procedures, *i.e.* N–N bond cleavage or N–C bond hydrolysis, although the former is likely not a trivial conversion. At present, it is unknown if and how the regioselectivity of the hydroaddition reaction can be controlled and to what extent the substitution pattern of the diene plays a governing role in tuning the outcome. We herein report initial studies on the regioselective hydroamination of substituted dienes to explore these issues, unraveling some subtle factors that affect the overall reaction outcome, including the choice of ligand and nucleophile and the character of the diene substituent group.

Results and discussion

The 3-chloro-1-amino-2-butenyl fragment is an often encountered motif in biorelevant organic compounds, but introduction of this functional group, *e.g.* in a total synthesis procedure, is currently only available *via* atom-inefficient *amination* of 1,3-dichloro-2-butene.¹⁸ Curiously, the parent primary amine 3-chloro-1-amino-2-butene has so far eluded major attention in the literature. An efficient route to obtain this compound, or a masked version thereof with a protected amine, would be of considerable synthetic interest.

Chloroprene as a substrate for hydroamination

We therefore started our investigations of the regioselective hydroamination of functionalized dienes by surveying the reactivity of commercially available 2-chloro-1,3-butadiene

(chloroprene) in the Pd-catalyzed hydroamination with various nitrogen nucleophiles. The readily available technical grade chloroprene (50% solution in xylene) can be efficiently upgraded by distillation to obtain pure chloroprene, although we have found that the as-received solution also provides satisfactory results in most cases with no sign of catalyst deactivation.

Using benzophenone hydrazone as a nucleophile and an *in situ* generated Pd catalyst, derived from $[\text{Pd}(\eta^3\text{-allyl})(\mu\text{-Cl})]$ dimer (1 mol%) and Xantphos (2 mol%) as a ligand (the same system Hartwig reported¹⁶), and after a reaction time of 24 hours at r.t., the only compound obtained after work-up was the linear 1,4-addition product, according to NMR spectroscopy, with a *Z:E* isomer ratio of 75:25. This stereoisomeric ratio remained constant with increasing reaction time, which implies that the mechanism of the reaction does not change with conversion, an indication for catalyst stability. We did not observe any diene oligomerization as unwanted side-reaction.

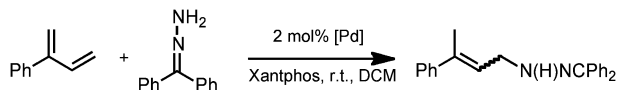
Ligand screening

Strikingly, a screening of diphosphorus ligand systems revealed very strong differences between quite similar frameworks. Well-established diphosphorus ligands with related bite angle dimensions to Xantphos, such as DPEPhos, DBFphos, dppf, BINAP and JosiPhos, did not lead to any activity, even at increased temperature, and only starting materials could be recovered after 24 hours (Table 1). Modification of the xanthene backbone led to ambiguous results: the 4,5-di(*tert*-butyl) substituted derivative (*t*Bu-Xantphos) showed similar results to parent Xantphos, whereas Nixantphos (–NH instead of C(CH₃)₂ as the central fragment) showed no activity. Furthermore, the amine nucleophile proved to be of essential influence to steer reactivity, since hydrazine or phenyl hydrazine, benzyl hydroxylamine, urea or phenyl urea, aniline and morpholine resulted in recovery of chloroprene as starting material. Hence, the reactivity *and* the regioselectivity observed in the hydroamination with chloroprene as substituted diene is markedly different than for

Table 1 Pd catalyzed hydroamination of chloroprene^a

Nucleophile	Ligand	Conversion (%)	Regioselectivity ^b
BH ^c	Xantphos	90	< 1 : 99
BH	<i>t</i> Bu-Xantphos	88	< 1 : 99
BH	Nixantphos	N.R. ^d	—
BH	DPEPhos	N.R.	—
BH	JosiPhos	N.R.	—
BH	BINAP	N.R.	—
PhNHNH ₂	Xantphos	N.R.	—
Urea	Xantphos	N.R.	—
Aniline	Xantphos	N.R.	—

^a [Pd] = 0.02 M; [L] = 0.02 M; [S]:[Pd] = 50:1; Pd = $[\text{Pd}(\eta^3\text{-allyl})(\mu\text{-Cl})]$, 1 mL CH₂Cl₂, r.t., 24 h. ^b Ratio (1,2):(1,4) of 1,2- and 1,4-isomers formed, as determined by NMR spectroscopy. ^c BH = benzophenone hydrazone. ^d N.R. = no reaction.



Scheme 3 Chemo- and regioselective hydroamination of 2-phenyl-1,3-butadiene with benzophenone hydrazone to yield a mixture of (*E*)- and (*Z*)-1,4-addition products.

seemingly related (unsubstituted) dienes such as isoprene discussed by Hartwig *et al.*¹⁶ or the addition of aliphatic amine nucleophiles to myrcene as disclosed by Behr *et al.*¹⁴ The origin of this dichotomy is not understood so far but might be related to the nature of the 2-substituent and its imposing electronic effect on the diene fragment upon transformation to a π -allyl fragment.

2-Phenyl-1,3-butadiene as a substrate for hydroamination

Intrigued by the regioselectivity observed for chloroprene, we also studied 2-phenyl-1,3-butadiene as electron-poor 2-substituted diene (Scheme 3) using the same *in situ* catalyst system, *i.e.* [Pd(η^3 -allyl)-(μ -Cl)]₂ and Xantphos, as this combination provided good activity; additional ligand screening was not performed. This compound is synthesized in a straightforward manner from chloroprene *via* a Ni-catalyzed reaction with phenylmagnesium chloride in good yield after work-up by distillation. To the best of our knowledge, the reactivity of this compound has not been investigated to any significant extent for hydroamination or other hydroaddition reactions to date. Also for this substrate, full conversion with formation of only the 1,4-addition product was observed after 16 hours. In principle, the primary amine should then be accessible *via* reductive cleavage or hydrolysis of the N–N bond, analogous to published procedures for related masked amine functionalities.¹⁹ This amine has previously only been generated *via* classic and cumbersome synthetic procedures.²⁰

Other 2-substituted dienes as substrates for hydroamination

Remarkably, we noted very different behaviour for a different set of 2-alkyl-substituted dienes with benzophenone hydrazone, including 2-benzyl-1,3-butadiene and myrcene, which show preferential 1,2-addition of benzophenone hydrazone (Table 2). Use of 2-(trimethylsilyl)methyl-1,3-butadiene as a substrate led to selective desilylation and formation of the same product as was previously reported from isoprene by Hartwig *et al.*,¹⁶ judging from the ¹H NMR spectrum of the crude reaction mixture.

2-Benzyl-1,3-butadiene, which is readily obtained from chloroprene *via* a Grignard reaction with BzMgBr, was hydroaminated in 83% yield, with a branched to linear (b/l) ratio of 4. However, a pronounced byproduct, formed during reaction, even under ambient conditions, was found to be the isomeric 2-methyl-1-phenylbutadiene, based on comparison of available NMR spectroscopic data for this substituted styrene derivative.²¹ This byproduct was not observed at the end of the reaction, implying an as-yet unidentified reversible isomerization or subsequent hydroamination of the internal double bond to furnish the same products. The latter would provide a new

Table 2 Pd catalyzed hydroamination of various 2-substituted 1,3-dienes^a

2-Ph	R ₁ = H, R ₂ = C ₆ H ₅			
2-Bz	R ₁ = H, R ₂ = CH ₂ C ₆ H ₅			
3-Me-C5	R ₁ = CH ₃ , R ₂ = CH ₃			
myrcene	R ₁ = H, R ₂ = CH ₂ CH ₂ CH=CMe ₂			
Substrate	Nucleophile	Ligand	Conv. ^b (%)	b/l ratio ^c
2-Ph	BH ^d	Xantphos	88	0/100
2-Bz	BH	Xantphos	83	80/20
3-Me-C5	BH	Xantphos	83	80/20
Myrcene	BH	Xantphos	53	95/5
Myrcene	BH	BINAP	12	100/0
Myrcene	Aniline	Xantphos	100	60/40
Myrcene	Morpholine	Xantphos	100	70/30
Myrcene	Piperidine	Xantphos	100	75/25

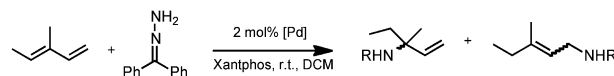
^a [Pd] = 0.02 M; [L] = 0.02 M; [S]:[Pd] = 50:1; Pd = [Pd(η^3 -allyl)(μ -Cl)]₂, 1 mL CH₂Cl₂, r.t., 24 h. ^b Determined by NMR spectroscopy. ^c Branched-to-linear ratio. ^d BH = benzophenone hydrazone.

entry into the application of (biorelevant) trisubstituted dienes as substrates.

Based on this finding, we investigated 3-methyl-1,3-pentadiene as a possible substrate to test the hypothesis that dienes with an internal double bond may also be efficiently hydroaminated to branched products (Scheme 4). Indeed, monitoring the reaction using the same standard conditions, we observed 83% conversion with a b/l ratio (branched 1,2- vs. linear 1,2- and 1,4-products) of 80:20 under the standard catalytic conditions.

Myrcene as a biorenewable diene substrate for hydroamination

We were delighted to see that the bioavailable terpene 7-methyl-3-methylene-1,6-octadiene (myrcene) was also selectively converted to the *branched* 1,2-addition product upon reaction with benzophenone hydrazone using Xantphos as a ligand (95:5 regioselectivity), with 53% conversion after 24 h at room temperature. Employing BINAP as a ligand led to slower reaction (12% conversion) but with exclusive formation of the 1,2-branched isomer product. Interestingly, also primary and secondary amines, *e.g.* aniline, piperidine and morpholine, could be used as nucleophiles under mild conditions, but with regioselectivities between 60:40 and 75:25 for the 1,2-:1,4-addition products. The chiral diene nopadiene did not show any reactivity in the same reaction.



Scheme 4 Hydroamination of 3-methyl-1,3-pentadiene with benzophenone hydrazone to generate branched 1,2-addition products (R=Ph₂CN).

Conclusions

In summary, we have reported on subtle differences occurring in the regioselective Pd catalyzed hydroamination of terpene-like dienes under mild catalytic conditions using hydrazone nucleophiles as protected amines. The choice of ligand, nucleophile and substrate were all found to affect the rate and fate of the reaction. Electron-poor 2-substituted butadienes (chloroprene, 2-phenyl-1,3-butadiene) gave rise to sole formation of the linear 1,4-addition product, whereas electron-rich analogues (2-benzyl-1,3-butadiene, 3-methyl-1,3-pentadiene, myrcene) were predominantly converted (60–95%) to the branched 1,2-addition product. The electronic character of the starting diene most likely impacts the hypothesized allylic intermediate, although further investigations are required to elucidate this aspect. We believe that this protocol may lead to novel pathways for the production of chiral amines from readily available biofeedstocks in an atom-efficient manner, if N–N bond cleavage of hydrazones can be achieved using a mild protocol.

Experimental section

General methods

All manipulations were carried out under an inert atmosphere using a nitrogen-filled glovebox or standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. Dichloromethane was of ACS reagent grade, degassed by purging with nitrogen and dried over appropriate drying agents. 2-Phenyl-1,3-butadiene,²² 2-benzyl-1,3-butadiene²² and 2-trimethylsilylmethyl-1,3-butadiene²³ were prepared following published procedures. All other reagents and solvents were obtained from commercial sources and used without further purification. ¹H NMR spectra were obtained at 300 MHz and recorded relative to residual protio-solvent. ¹³C NMR spectra were obtained at 126 MHz and chemical shifts were recorded relative to the solvent resonance.

Procedure for the Pd-catalyzed hydroamination of dienes with benzophenone hydrazone

In a glovebox, [Pd(η³-allyl)(μ-Cl)]₂ (3.7 mg, 0.010 mmol), Xantphos (11.6 mg, 0.020 mmol), diene substrate (1.00 mmol) and benzophenone hydrazone (196 mg, 1.00 mmol) were placed into a small vial, dissolved in dichloromethane (1.00 mL), and sealed with a cap containing a PTFE septum. The reaction mixture was stirred at RT for 24 h. The reaction mixture was then purified by alumina flash chromatography (ethyl acetate–hexanes 5:95) and analyzed by NMR spectroscopy. Alternatively, a flame-dried Schlenk tube was charged with a solution of [Pd(η³-allyl)(μ-Cl)]₂ (0.020 mmol), Xantphos (0.040 mmol), benzophenone hydrazone (2 mmol) and diene (2 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at appropriate temperature for appropriate time.

1-(3,7-Dimethylocta-1,6-dien-3-yl)-2-(diphenylmethylene)hydrazine

¹H NMR (300 MHz, CDCl₃): δ 1.34 (s, 3H), 1.57 (s, 3H), 1.68 (m, 5H), 1.91 (dd, *J* = 8.1 Hz, 2H), 5.07 (m, 2H), 5.31 (s, 1H), 5.92 (dd, *J* = 17.7 Hz, 11.1 Hz, 1H), 7.23–7.29 (m, 5H), 7.46–7.51

(m, 5H) ppm; ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 17.5, 22.7, 24.4, 25.6, 39.9, 60.3, 112.4, 124.6, 126.2, 127.4, 128.1, 128.5, 128.8, 129.2, 129.6, 130.1, 131.6, 132.6, 134.0, 139.5, 144.2, 145.0 ppm. HRMS *m/z* calculated for C₂₂H₂₈N₂: 320.2252; found: 320.2260 (M)⁺.

1-(Diphenylmethylene)-2-(2-methyl-1-phenylbut-3-en-2-yl)-hydrazine

¹H NMR (300 MHz, CDCl₃): δ 1.35 (s, 3H), 3.04 (m, 2H), 5.05 (dd, *J* = 1.1 Hz, 17.7 Hz, 1H), 5.11 (dd, *J* = 1.1 Hz, 11.0 Hz, 1H), 6.07 (dd, *J* = 17.7 Hz, 11.0 Hz, 1H), 7.18–7.38 (m, 10H), 7.47–7.62 (m, 5H) ppm; ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 17.5, 41.6, 60.3, 113.4, 126.8, 127.4, 128.5, 128.9, 130.6, 133.9, 136.2, 138.5, 138.7, 146.2 ppm. HRMS *m/z* calculated for C₂₄H₂₄N₂: 340.1939; found: 340.1899 (M)⁺.

1-(Diphenylmethylene)-2-(3-methylpent-1-en-3-yl)-hydrazine

¹H NMR (300 MHz, CDCl₃): δ 0.82 (t, *J* = 7.8 Hz, 3H), 1.32 (s, 3H), 1.70 (m, 2H), 5.06 (m, 2H), 5.94 (dd, *J* = 17.7 Hz, 10.6 Hz, 1H), 7.22–7.35 (m, 5H), 7.43–7.60 (m, 5H) ppm; ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 7.7, 21.5, 30.6, 62.4, 117.7, 127.5, 127.7, 128.9, 138.5, 138.6, 140.3, 147.1 ppm. HRMS *m/z* calculated for C₁₉H₂₂N₂: 278.1783; found 278.1726 (M)⁺.

1-(3-Chlorobut-2-en-1-yl)-2-(diphenylmethylene)hydrazine

¹H NMR (300 MHz, CDCl₃): δ 2.03 (s, 3H), 5.95 (s, 1H), 7.21–7.38 (m, 5H), 7.44–7.59 (m, 5H) ppm; ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 21.3, 112.2, 127.5, 128.1, 128.5, 128.8, 138.4, 138.7, 144.8 ppm. HRMS *m/z* calculated for C₁₆H₁₅ClN₂: 270.0924; found: 270.1010 (M)⁺.

1-(Diphenylmethylene)-2-(3-phenylbut-2-en-1-yl)hydrazine

¹H NMR (300 MHz, CDCl₃): δ 2.12 (s, 3H), 6.81 (s, 1H), 7.17–7.35 (m, 10H), 7.41–7.52 (m, 5H) ppm; ¹³C{¹H} NMR (126 MHz, CDCl₃): δ 18.7, 120.2, 123.0, 125.5, 125.6, 128.0, 128.3, 128.5, 128.6, 138.3, 138.9, 141.2, 144.7 ppm. HRMS *m/z* calculated for C₂₂H₂₀N₂: 312.1626; found: 312.1593 (M)⁺.

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