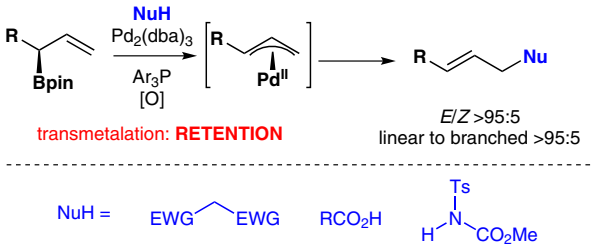
Synlett P. J. Unsworth et al. Letter

Palladium-Catalyzed Reactions of Allylic Boronic Esters with Nucleophiles: Novel Umpolung Reactivity

Phillip J. Unsworth
Lorenz E. Löffler
Adam Noble
Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK
v.aggarwal@bristol.ac.uk

Dedicated to Professor K. Peter C. Vollhardt with deep appreciation, where science and art combine



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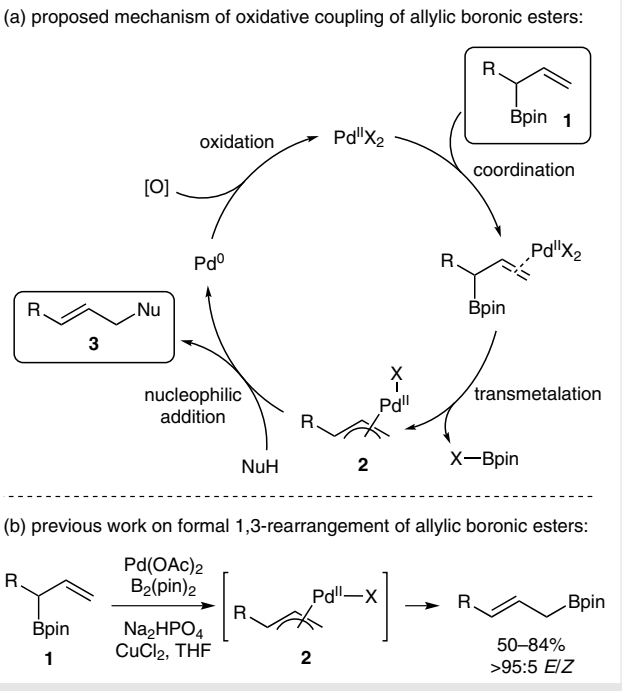
Abstract Oxidative palladium-catalyzed reaction conditions have been developed to allow for regioselective and stereoselective coupling of allylic boronic esters with a range of carbon-, oxygen-, and nitrogen-based nucleophiles. Studies into the mechanism of the reaction have shown that the key transmetalation step occurs with retention of stereochemistry, since overall inversion is observed.

Key words palladium, boronic ester, umpolung, allylation, oxidative coupling

Boronic esters are highly versatile intermediates that undergo a wide variety of useful chemical transformations.[1] In addition, their air and moisture stability, ease of preparation, and low toxicity has further contributed to the popularity of these important reagents. For example, allylic boronic esters have been widely utilized in allylation reactions of aldehydes[2] and ketones[3] as well as palladium-catalyzed cross-couplings with aryl halides[4] and allylic carbonates.[5] A key feature in all of these reactions is that the allylic boronic ester acts as a nucleophile. We believed that it might be possible to reverse this normal mode of reactivity through the use of palladium(II) catalysis, thereby rendering the allylic boronic ester, an electrophilic allylating reagent, that would react with nucleophiles instead of electrophiles. As shown in Scheme 1 (a), we reasoned that conversion of the allylic boronic ester **1** into the π-allyl palladium complex **2** could be achieved by transmetalation with a suitable palladium(II) catalyst.[6,7] This would then react with a nucleophile in a Tsuji–Trost-type reaction giving the allylated product **3** and palladium(0). Oxidation of palladium(0) to palladium(II) with an appropriate oxidant would then complete the catalytic cycle. Not only would such a protocol increase the synthetic utility of boronic esters, it would also expand the scope of allylation reactions through a novel methodology that is complementary to the well-known Tsuji–Trost reaction[8] and allylic C–H activation protocols.[9]

In support of our mechanistic hypothesis, we recently reported a palladium-catalyzed procedure to achieve a formal 1,3-rearrangement of a branched allylic boronic ester to the linear isomer (Scheme 1, b).[10] It was proposed that an intermediate π-allyl palladium complex **2** was captured by a nucleophilic source of boron [$Na_2HPO_4/B_2(pin)_2$].[11] Crucial



Scheme 1 Proposed strategy for oxidative coupling of allylic boronic esters

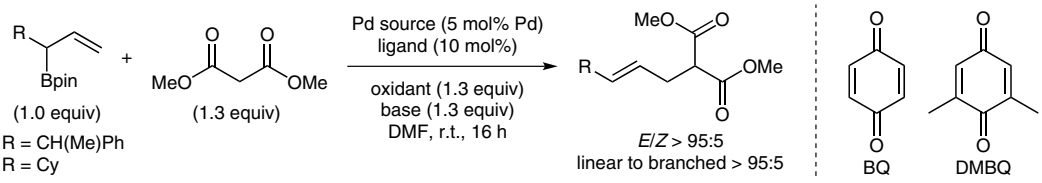
to the success of this reaction was the addition of an oxidant ($CuCl_2$) to re-oxidize palladium(0) to palladium(II). If such a process did indeed occur via an intermediate π-allyl palladium complex then it should be possible to intercept it with other nucleophiles. Herein we describe our success in achieving a palladium-catalyzed coupling of allylic boronic esters with a range of different carbon-, oxygen-, and nitrogen-based nucleophiles, thus demonstrating a novel umpolung reactivity of this important class of reagents.

One of the key challenges in developing our proposed methodology was to find a suitable oxidant that would be capable of oxidizing palladium(0) to palladium(II) while also being compatible with both the allylic boronic ester and the nucleophile. Quinones have been successfully applied as oxidants in palladium(II)-catalyzed formation of π-allyl intermediates by allylic C–H activation of terminal olefins.[9] Furthermore, the resulting π-allyl palladium complexes have been demonstrated to react with a range of nucleophiles. Based on this precedent we initially tested *p*-benzoquinone (BQ) and 2,6-dimethylbenzoquinone (DMBQ) as potential oxidants. Since some reports of allylic C–H activation of terminal olefins have used Ph_3P to suppress the formation of palladium black,[9d] we decided to include phosphine ligands in our initial investigations.

We began by investigating the coupling of allylic boronic ester **4** with dimethyl malonate. Encouragingly, treatment of **4** and dimethyl malonate with $Pd(OAc)_2$ in the presence of Ph_3P and a base (NaOMe), to aid transmetalation of the boronic ester, resulted in the formation of the desired product (Table 1, entry 1). However, as expected, in the absence of an oxidant to complete the palladium catalytic cycle only traces of product were observed with large amounts of **4** remaining. Low conversions were also observed when BQ was used as the oxidant (Table 1, entries 2 and 3). Complete consumption of **4** was observed with DMBQ as the oxidant, however, in the presence of NaOMe only trace amounts of the desired product were obtained (Table 1, entry 4). Pleasingly, it was found that in the absence of any added base the desired product was formed in 30% yield, importantly as a single regioisomer and a single *E*-olefin isomer (Table 1, entry 5). Further evaluation of the reaction conditions showed tri-2-furylphosphine to be a superior ligand (Table 1, entry 6) and that an improved yield could be obtained when using $Pd_2(dba)_3$ (dba = dibenzylideneacetone) in place of $Pd(OAc)_2$ (Table 1, entry 7).[12] In the absence of ligand none of the desired product was formed, instead, the major product was the diene derived from β-hydrogen elimination of the π-allyl intermediate (Table 1, entry 8).[13] Closer inspection of the crude reaction mixtures from entries 5–7 revealed that a small amount of β-hydrogen elimination (ca. 10–20%) also occurred in the presence of phosphine ligands. However, this undesired reaction pathway was completely suppressed in the case of the nonbenzylic substrate **5** (Table 1, entry 9). Furthermore, when using substrate **5** the loading of palladium could be reduced to just 1 mol% without loss in reaction efficiency.

With the optimized conditions in hand we proceeded to examine the scope of the reaction (Scheme 2). It was found that, in addition to malonates, 1,3-diketones and α-nitro-

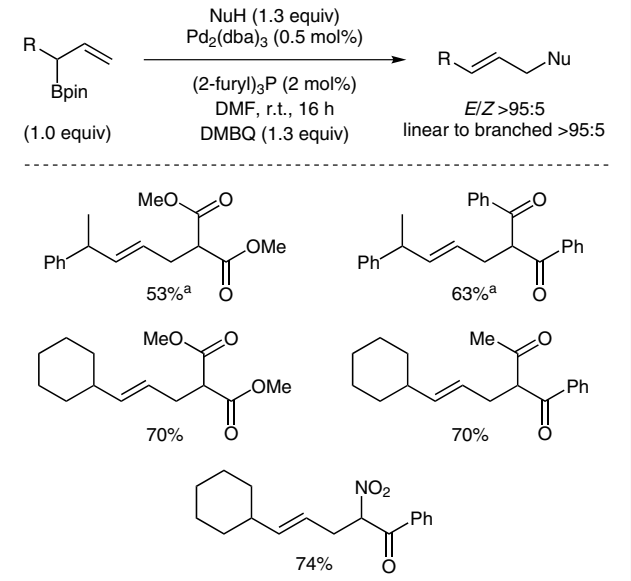
Table 1 Reaction Optimization



Entry	Substrate	Pd Source	Oxidant	Base	Ligand	Yield (%)[a]
1	**4**	$Pd(OAc)_2$	none	NaOMe	Ph_3P	<10
2	**4**	$Pd(OAc)_2$	BQ	NaOMe	Ph_3P	<10
3	**4**	$Pd(OAc)_2$	BQ	none	Ph_3P	<10
4	**4**	$Pd(OAc)_2$	DMBQ	NaOMe	Ph_3P	<10
5	**4**	$Pd(OAc)_2$	DMBQ	none	Ph_3P	30
6	**4**	$Pd(OAc)_2$	DMBQ	none	$(2\text{-furyl})_3P$	51
7	**4**	$Pd_2(dba)_3$	DMBQ	none	$(2\text{-furyl})_3P$	60 (53[b])
8	**4**	$Pd_2(dba)_3$	DMBQ	none	none	0
9[c]	**5**	$Pd_2(dba)_3$	DMBQ	none	$(2\text{-furyl})_3P$	70[b]

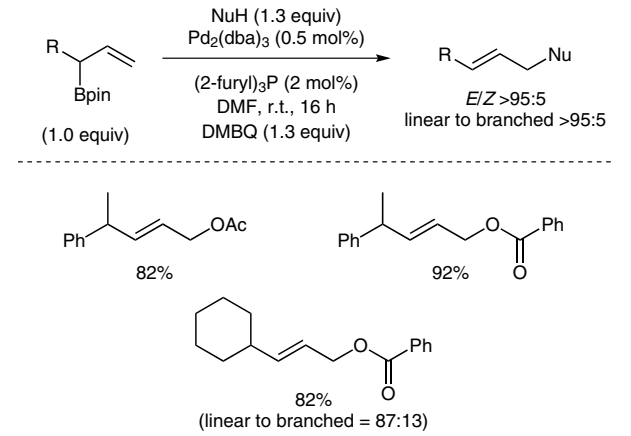
[a] Yields determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated yield.
[c] Reaction conditons: 1 mol% Pd, 2 mol% ligand.

ketones were competent nucleophiles in this allylation reaction. Pleasingly, all products were formed in good yield, with excellent regioselectivity for the linear product and as a single *E*-olefin isomer.



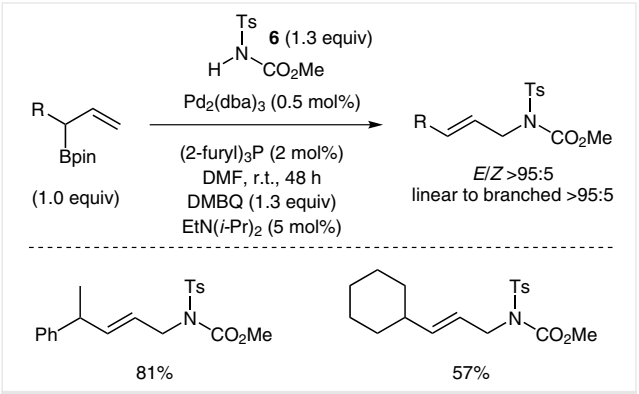
Scheme 2 Carbon-based nucleophiles. [a] Formed using 2.5 mol% $Pd_2(dba)_3$ and 10 mol% phosphine.

We were also able to expand the scope of this reaction to oxygen-based nucleophiles (Scheme 3). With no further optimization of the reaction conditions, simply replacing the malonate with a carboxylic acid resulted in high yields of allylic ester products with excellent *E* selectivities. While those derived from boronic ester **4** were formed exclusively as the linear regioisomer, the reaction of boronic ester **5** with benzoic acid resulted in an 87:13 mixture of linear and branched isomers, respectively. The origin of this reduction in selectivity for the linear regioisomer upon switching from boronic ester **4** to **5** is currently unclear.



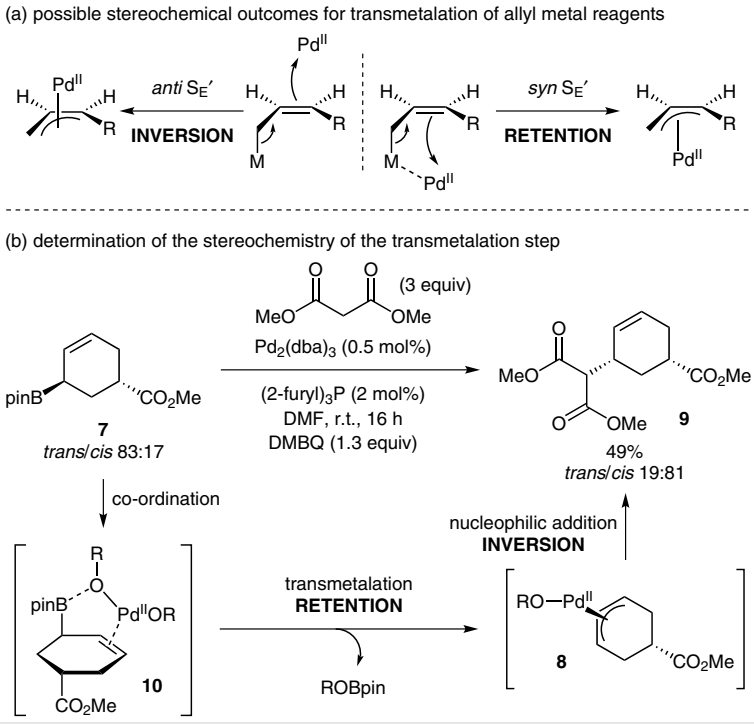
Scheme 3 Oxygen-based nucleophiles

We next looked at applying our conditions to nitrogen-based nucleophiles, for which we chose the acidic *N*-tosylcarbamate nucleophile **6** (pK_a = ca. 3.7).[14] Unfortunately, application of **6** to our standard reaction conditions led to the formation of only trace amounts of product. However, in the presence of 5 mol% $EtN(i\text{-}Pr)_2$[9h] the allylic amine products were obtained in good yields and, again, as single stereoisomers and regioisomers (Scheme 4).



Scheme 4 Nitrogen-based nucleophiles

When considering our proposed mechanism for this allylation reaction (Scheme 1, a), we realized that while the reactivity of π-allyl palladium complexes **2** has been well studied, their generation from allylic boronic esters has not been reported.[15] Therefore, we wished to study the mechanism of this transmetalation process (Scheme 5). The transmetalation of allyl metal reagents (e.g., allyl boronates[4c,g] and silanes[16]) with palladium(II) complexes has been demonstrated to proceed via an S_E' mechanism, in which the palladium(II) can approach either *syn* or *anti* to the metal center (Scheme 5, a). For example, Hiyama et al. demonstrated that in the cross-coupling of allyl silanes with aryl triflates, depending on the reaction conditions, the transmetalation step could proceed via either *syn* or *anti* S_E' mechanisms.[16a] In order to determine which of these two possible transmetalation mechanisms is operative we used cyclohexenyl boronic ester **7** to study the stereochemistry of our allylation reaction (Scheme 5, b). Substituted cyclohexenyl acetates have been used extensively to probe the mechanism of Tsuji–Trost reactions[17] and related processes involving π-allyl palladium intermediates.[18] In particular, comparison of the relative stereochemistry of the substrate and product is used to determine whether the allylation reaction proceeds with overall retention or inversion of stereochemistry. These substituted cyclohexenyl substrates have been used to show that reactions of π-allyl palladium complexes of type **8** (see Scheme 5, b) with soft nucleophiles proceed with inversion of configuration,[17b] whereas those with hard nucleophiles proceed with retention.[18] As dimethyl malonate is a soft nucleophile it will react with π-allyl palladium complex **8** with inversion of con-



Scheme 5 Mechanistic study

figuration,[17b] therefore, the relative stereochemistry of the product of the reaction of boronic ester **7** will reveal the stereochemistry of the transmetalation step.

The known allylic boronic ester **7**[19] was prepared as an 83:17 mixture of *trans*/*cis* diastereoisomers and coupled with dimethyl malonate under our standard conditions (Scheme 5, b). The allylation product **9** was formed in a 19:81 mixture of *trans*/*cis* diastereoisomers showing that overall inversion had occurred. We can therefore conclude that the transmetalation must be occurring *syn* to the boronic ester, generating π-allyl intermediate **8** with retention of configuration, followed by inversion of configuration after nucleophilic addition of dimethyl malonate. It is proposed that the transmetalation occurs via intermediate **10** containing a B–O–Pd linkage which directs the transmetalation onto the same face as the boronic ester. This is consistent with Suzuki–Miyaura couplings of allylic boronic esters,[4g] and related reactions with allyl siloxanes,[16c] which have been shown to occur through a *syn* S_E' transmetalation process.

In summary, we have developed a method for inverting the normal mode of reactivity of allylic boronic esters from nucleophiles to electrophiles. This has been achieved through the application of oxidative palladium catalysis, which now allows for the coupling of (normally nucleophilic) allylic boronic esters with a range of carbon-, oxygen-, and nitrogen-based nucleophiles.[20] The process is highly regioselective, giving exclusively the linear isomers of the products with very high *E* selectivity. This process offers a new way to access synthetically useful π-allyl intermediates that is complementary to both the Tsuji–Trost reaction and allylic C–H activation methodologies.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380869.

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(12) The desired product was accompanied by ca. 10% of acetate **11** when $Pd(OAc)_2$ was used (Figure 1).

(13) 1,4-Diene **12** was the major product in the absence of phosphine ligands (Scheme 6).

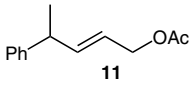

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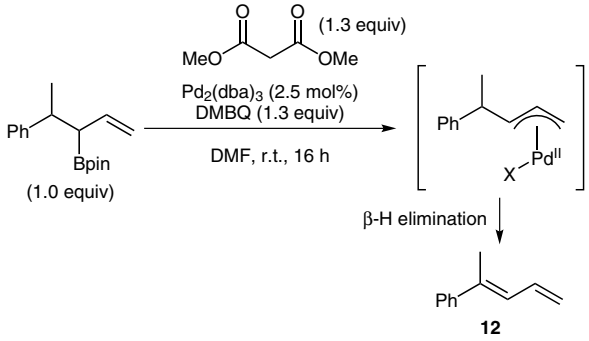
Figure 1



12

Scheme 6

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(20) **General Procedure**

Allylic boronic ester (0.50 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.50 mol%), tri(2-furyl) phosphine (2.0 mol%), and the nucleophile (1.3 equiv) were weighed into a dry flask and placed under argon [for reactions with nitrogen nucleophile **6**, $EtN(i\text{-}Pr)_2$ (5.0 mol%) was also added to the flask at this stage]. A solution of 2,6-dimethylbenzoquinone (1.3 equiv) in DMF (5.0 mL) was added in one portion, and the mixture was stirred at r.t for 16 h, or until the reaction was complete as determined by GC–MS analysis. 20% aq $NaHSO_3$ (10 mL) was added, and the mixture was stirred vigorously for 5 min. Et_2O (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (pentane–EtOAc) yielded the allylation product.

Dimethyl (*E*)-2-(4-Phenylpent-2-en-1-yl)malonate

Yield 53%; *E*/*Z* >95:5; linear to branched >95:5; R_f = 0.25 (pentane–EtOAc, 15:1); IR (neat): ν_{max} = 2958, 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (3 H, d, *J* = 7.0 Hz), 2.56–2.62 (2 H, m), 3.39 (1 H, app p, *J* = 7.0 Hz), 3.41 (1 H, t, *J* = 7.6 Hz), 3.65 (3 H, s), 3.68 (3 H, s), 5.40 (1 H, dtd, *J* = 15.3, 7.0, 1.3 Hz), 5.68 (1 H,

ddt, *J* = 15.3, 7.0, 1.3 Hz), 7.10–7.21 (3 H, m), 7.21–7.32 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 32.0, 42.3, 52.0, 52.5, 52.5, 124.1, 126.2, 127.3, 128.5, 138.8, 145.8, 169.5. HRMS (ESI$^+$): *m/z* calcd for $C_{16}H_{21}O_4Na$ [M + Na$^+$]: 299.1254; found: 299.1246.

(*E*)-4-Phenylpent-2-en-1-yl Benzoate

Yield 92%; *E*/*Z* >95:5; linear to branched >95:5; R_f = 0.30 (pentane–EtOAc, 30:1). IR (neat): ν_{max} = 2966, 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (3 H, d, *J* = 7.1 Hz), 3.53 (1 H, qd, *J* = 7.1, 6.6 Hz), 4.82 (2 H, m), 5.73 (1 H, dtd, *J* = 15.5, 6.2, 1.4 Hz), 6.05 (1 H, ddt, *J* = 15.5, 6.6, 1.3 Hz), 7.19–7.25 (3 H, m), 7.29–7.35 (2 H, m), 7.41–7.46 (2 H, m), 7.54 (1 H, m), 8.05-8.09 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 42.1, 65.6, 123.0, 126.4, 127.3, 128.4, 128.6, 129.7, 130.5, 133.0, 140.4, 145.2, 166.5. HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{18}O_2Na$ [M + Na$^+$]: 289.1199; found: 289.1186.

Methyl (*E*)-(4-Phenylpent-2-en-1-yl)(tosyl)carbamate

Yield 81%; *E*/*Z* >95:5; linear to branched >95:5; R_f = 0.30 (pentane–EtOAc, 6:1). IR (neat): ν_{max} = 2961, 1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (3 H, d, *J* = 7.0 Hz), 2.42 (3 H, s), 3.50 (1 H, app p, *J* = 6.8 Hz), 3.68 (3 H, s), 4.47 (2 H, app dt, *J* = 6.4, 1.2 Hz), 5.58 (1 H, dtd, *J* = 15.4, 6.4, 1.4 Hz), 5.98 (1 H, ddt, *J* = 15.4, 6.9, 1.2 Hz), 7.19–7.25 (5 H, m), 7.30–7.35 (2 H, m), 7.73–7.83 (2 H, m Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.7, 42.1, 48.5, 53.8, 123.3, 126.3, 127.2, 128.6, 128.6, 129.3, 136.5, 140.1, 144.5, 145.3, 152.7. HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{23}O_4NNaS$ [M + Na$^+$]: 396.1240; found: 396.12430.