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Reductive Cyclization of Bromoenynamides with Alcohols as Hydride Source: Synthesis and Reactions of 2-Amidodienes

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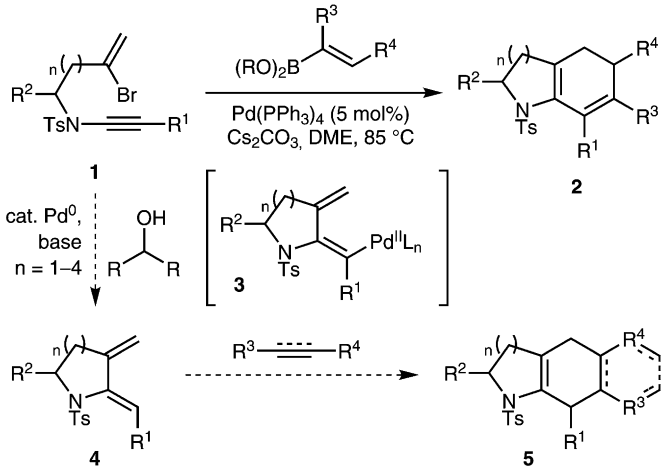
Abstract: Under basic conditions in alcoholic solvents, bromoenynamides undergo palladium-catalyzed cyclization to cyclic 2-amidodienes in good to excellent yields. This process represents the first use of an alcohol as a hydride source in an alkyne carbopalladation/termination sequence, with the site selectivity of the reduction showing a strong dependence on the tethering ring size (5–8), and the nature of the alcohol and base. Reaction of the dienes with a range of dienophiles (including alkenes, alkynes and arynes) under various conditions gives bi- and tricyclic azacycles, which can be further oxidized to the aromatic azacycles.

Keywords: carbopalladation; homogeneous catalysis; nitrogen heterocycles; reduction; ynamides

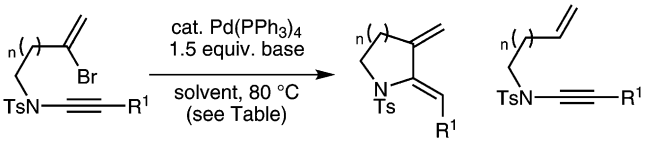
Alkyne carbopalladation is a powerful tool for cascade C–C bond formation, owing to its broad substrate scope and functional group tolerance, and ability to be coupled with a range of other palladium-mediated processes.[1] One notable absence from this field is ynamide carbopalladation, where few studies have been described,[2] despite the recognized value of ynamides in organic synthesis.[3] In previous work, we showed that bromoenynamides **1** undergo efficient carbopalladative cyclization to azabicycles **2** *via* cross-coupling of dienylpalladium(II) complex **3** (Scheme 1).[2a] We recognized that a reductive termination step from **3** would afford monocyclic amidodienes **4**, which could engage in Diels–Alder cycloaddition reactions to afford complementary aza-bicyclic or tricyclic products. Here we describe the application of this process and its application to a wide range of bromoenynamides using ethanol as a hydride source, which represents the first use of an alcohol as a convenient reductant in an alkyne carbopalladation sequence.[4] Cycloadditions of the resultant cyclic dienes lead to bi- or tricyclic products **5** that are difficult to access using other methods.

We began our studies with bromoenynamide **1a** (Table 1).[5] Our selection of ethanol as a cheap stoichiometric reductant arose from observations made in our previous work, where variable amounts of diene **4a** had been isolated from attempted carbopalladation/Suzuki cross-coupling reactions in hydroxylic solvents.[2a] Initial investigations using ethanol as solvent, Cs_2CO_3 as base, and 2.5 mol% $Pd(PPh_3)_4$ as catalyst, delivered **4a** in excellent yield as a single stereoisomer, as evidenced by ^{1}H NMR nOe experiments (83%).[6] These conditions were superior to the use of other catalysts [e.g., $PdCl_2(PPh_3)_2$, $PdCl_2$dppf, $Pd(OAc)_2$/2 PPh_3], or triethylsilane as reducing agent, and indeed on larger scales a lower catalyst loading of 1 mol% proved viable (entry 2). Although other inorganic bases were less effective (entries 3–5), increas-



Scheme 1. Cyclization by carbopalladation/reduction: planned synthesis of nitrogen heterocycles from ynamides.

Table 1. Reductive cyclization of bromoenynamides **1a–c**.



1a (n = 1, R^1 = *n*-Hex)
1b (n = 2, R^1 = Ph)
1c (n = 3, R^1 = *n*-Hex)

4a (n = 1)
4b (n = 2)
4c (n = 3)

6a (n = 1)
6b (n = 2)
6c (n = 3)

Entry	SM	Cat. mol%	Base	Solvent,[a] time [h]	**4**:**6**	Yield [%][b]
1	**1a**	2.5	Cs_2CO_3	EtOH, 0.5	1:0	83
2	**1a**	1	Cs_2CO_3	EtOH, 1	1:0	84[c]
3	**1a**	2.5	NaOH	EtOH, 1	1:0	62
4	**1a**	2.5	K_3PO_4	EtOH, 18	1:0	62
5	**1a**	2.5	K_2CO_3	EtOH, 1	1:0	62
6	**1a**	2.5	Cs_2CO_3	EtOH, 0.25	1:0	84
7	**1b**	2.5	Cs_2CO_3	EtOH, 0.5	6:1	71
8	**1c**	2.5	Cs_2CO_3	EtOH, 1	1:3.3	59
9	**1c**	10	Cs_2CO_3	PhMe/EtOH (10:1), 2	1:0.4	45
10	**1c**	10	Cs_2CO_3	PhMe/*i*PrOH (10:1), 2	1:0.2	68
11	**1c**	10	Cs_2CO_3	PhMe/MeOH (10:1), 1	1:1	52
12	**1c**	10	K_2CO_3	EtOH, 1.75	1:0.15	68
13	**1c**	10	$NaHCO_3$	EtOH, 4	1:0	40[d]
14	**1c**	2.5	K_2CO_3	PhMe/EtOH (1:1), 3.5	1:0	69

[a] Entries 1–5 at 0.02 M, entries 6–14 at 0.045 M.
[b] Isolated yield.
[c] Performed on a 2.42 mmol (1 g) scale.
[d] Conversion as monitored by ^{1}H NMR spectroscopy.

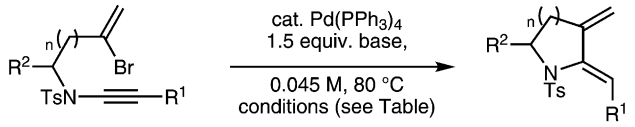
ing the reaction concentration enabled the isolation of **4a** in an optimized 84% yield (entry 6). Notably, in none of the reactions of **1a** did we observe direct reduction of the bromoalkene to alkene **6a**, which reflects the rapid nature of 5-*exo*-*dig* carbopalladation.

In contrast, application of these conditions to the homologous substrates **1b** and **1c** led to significant, or even predominant, reduction of the bromoalkene to **6b** and **6c** (entries 7 and 8). Attempts to retard the rate of hydride transfer through the use of mixed solvent systems (entries 9–11) revealed a dependence on the nature of the alcohol cosolvent, but did not eliminate the problem. Pleasingly, the use of different bases led to greater success, with K_2CO_3 reducing the extent of direct reduction, and $NaHCO_3$ effecting exclusive carbopalladation, albeit with incomplete reaction (entries 12 and 13). A compromise to these conditions was found using K_2CO_3 in 1:1 toluene/ethanol (entry 14), which gave full conversion of **1c** to azepane diene **4c** with no undesired direct reduction (69%).

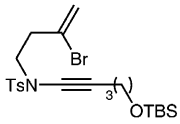
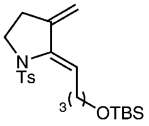
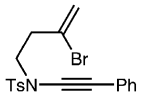
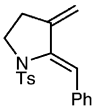
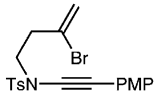
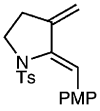
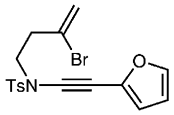
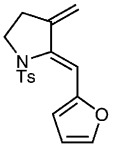
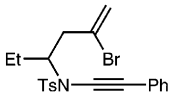
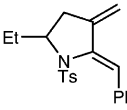
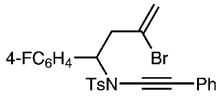
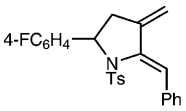
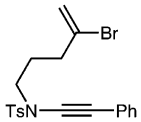
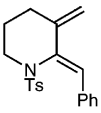
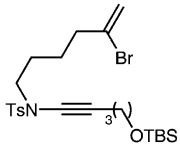
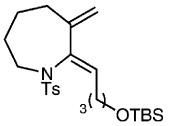
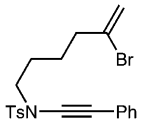
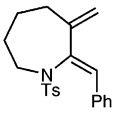
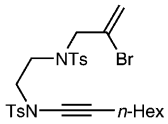
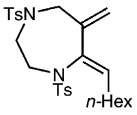
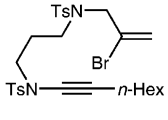
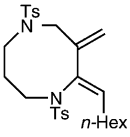
With optimized sets of conditions in hand, we explored the scope of the cyclization (Table 2). The influence of the substituent at the ynamide terminus was first investigated (entries 1–4), with alkyl and aryl substituents both affording the corresponding amidodienes **4d–g** in good yields, although electron-rich dienes **4f** and **4g** were prone to isomerization during purification, or on standing in $CDCl_3$. The introduction of a substituent adjacent to the sulfonamide enabled the synthesis of α-branched cyclic dienamides **4h** and **4i** (entries 5 and 6). The synthesis of larger rings could also be demonstrated using the modified (K_2CO_3) cyclization conditions, which gave piperidine **4b** and azepanes **4j** and **4k** (entries 7–9). Excitingly, ynamide **1l** (entry 10), which features two heteroatoms in the ynamide/bromoalkene tether, delivered diazepane **4l** in high yield (85%). Given the particular challenge of alkyne carbopalladation to form 8-membered rings,[7] competing direct reduction (~20%) in the cyclization of bromoenynamide **1m** was not unexpected (using K_2CO_3 as base). However, by employing $NaHCO_3$ in EtOH we were delighted to be able to effect the desired 8-membered ring formation to diazocane **4m** (73%, entry 12), albeit with increased catalyst loading and reaction time.[8]

The formation of these exocyclic amidodienes can be rationalized mechanistically (Scheme 2) by initial oxidative addition of the bromoalkene, followed by *syn*-carbopalladation of the ynamide to give dienylpalladium intermediate **7**. Coordination of ethoxide to palladium enables hydride transfer *via* β-hydride elimination, with subsequent reductive elimination affording diene product and regenerating Pd(0) cata-

Table 2. Reductive cyclization of bromoenynamides to cyclic dienamides.



1b–l **4b–l**

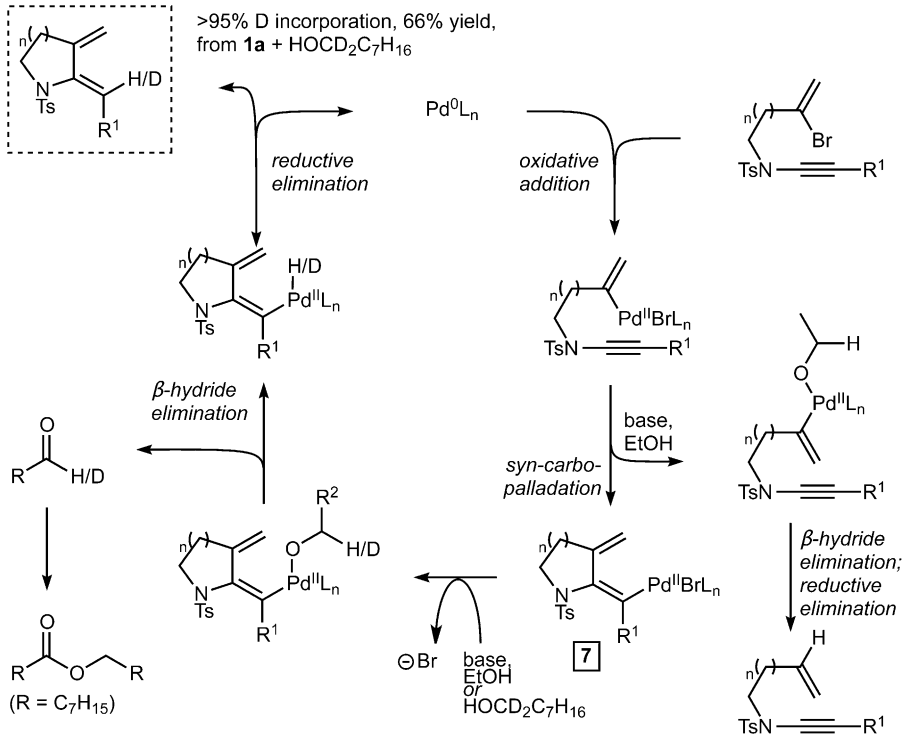
Entry		Substrate	Conditions[a]	Product		Yield [%][b]
1	**1d**		A	**4d**		83
2	**1e**		A	**4e**		65, 65[c]
3	**1f**		A	**4f**		61
4	**1g**		A	**4g**		66[d]
5	**1h**		A	**4h**		68
6	**1i**		A	**4i**		75
7	**1b**		B	**4b**		73
8	**1j**		B	**4j**		65
9	**1k**		C	**4k**		61
10	**1l**		B	**4l**		85
11	**1m**		D	**4m**		73

[a] *Conditions A:* 2.5 mol% $Pd(PPh_3)_4$, Cs_2CO_3, EtOH. *Conditions B:* 2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH (1:1). *Conditions C:* 10 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH (10:1). *Conditions D:* 10 mol% $Pd(PPh_3)_4$, $NaHCO_3$, EtOH.

[b] Isolated yield.

[c] Performed on 1.24 mmol (0.5 g) scale with 1 mol% catalyst.

[d] Isolated as a 1:4.2 *E*:*Z* mixture.



Scheme 2. Proposed mechanism for the reductive cyclization, and deuterium-labelling studies.

lyst.[4f,9] This mechanism is supported by the use of octanol as hydride source, which led to the formation of octanal and octyl octanoate (implying the hemiacetal to be a superior hydride donor),[10] and deuterium labelling studies, in which >95% deuterium incorporation was observed using d_2-octanol. The variation in product ratio with inorganic base and alcohol presumably relates to the rate of hydride transfer to palladium, which itself likely depends on both the extent of dissociation of the metal cation from the alkoxide (and the resulting effect on alkoxide nucleophilicity), and the influence of the degree of branching of the alcohol on its propensity to undergo β-hydride elimination.[9d]

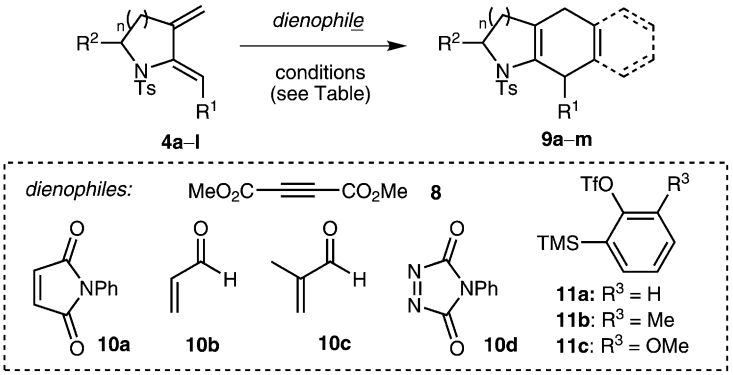
With access to a range of cyclic dienamides now secured, we chose to demonstrate their utility in a variety of cycloaddition processes (Table 3).[11] The Diels–Alder reaction of dienes **4a–c** with dimethylacetylene dicarboxylate **8** (DMAD, entry 1) revealed the reactivity of the diene to be highly dependent on the tethering ring size: all three dienes successfully gave the corresponding bicyclic cycloadducts **9a–c**, but with varying reaction times. This reactivity difference likely reflects the influence of ring flexibility on the diene torsion angle, and of ring size on the bond angles of the diene. *N*-Phenylmaleimide **10a** also performed well under thermal conditions,[11a,b,12] as did acrolein **10b**, which provided cycloadduct **9e** as a single regio- and diastereoisomer (entries 2 and 3).[6] The equivalent reaction of methacrolein **10c** with **4a** was not successful, but could be realized using $BF_3{\cdot}OEt_2$ as a Lewis acid catalyst,[13] which also gave cycloadduct **9f** as a single isomer (entry 4).[6] Interestingly, the regioselectivity of these processes implies the sulfonamide nitrogen atom to have a negligible electronic directing effect, with the diene alkyl groups, or steric effects, playing a more important role. PTAD (**10d**) proved a particularly good dienophile, affording the diazepane tricycle **9g** in excellent yield at room temperature (84%, entry 5).

To extend these Diels–Alder processes, we were attracted to the idea of using arynes, as these would deliver tricyclic products which would not be readily accessible through other means, including our own previous work. We found that the benzyne precursor **11a** underwent smooth reaction with **4a** in 2 h at 60 °C (entry 6, Conditions D), conditions which are typical for aryne formation,[14] but also that this reaction proceeded with equal efficiency but extended reaction time at room temperature (entry 6, Conditions E).[15] Evaluation of other arynes supported our view that the sulfonamide nitrogen does not act as a significant activator, due to the mixture of regioisomers observed with arynes derived from **11b** and **11c** (entries 7 and 8).[16] The complementary regioselectivity of these two reactions likely reflects a balance of steric and electronic factors; addition of **11b** positions the methyl substituent distal to the hexyl sidechain of the diene to minimize steric interactions, whereas the electronic influence of the methoxy group in **11c** favors ad-

vanced bond formation at the *exo*-methylene terminus of the diene in the transition state, mirroring the cycloadditions with acrolein and methacrolein. The reaction of diene **4h** delivered cycloadduct **9l** as a single diastereomer (entry 9),[17] reflecting the conformational effect of the sulfonamide and arene substituents in controlling the facial selectivity of the cycloaddition. To our delight, diazepane diene **4l** also underwent smooth cycloaddition with benzyne, delivering dihydrobenzodiazepine **9m** in excellent yield (80%, entry 10).

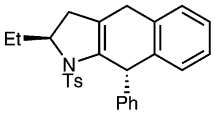
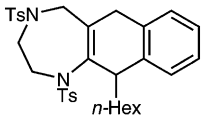
Finally, we recognized that the products of cycloaddition with alkynes and arynes could represent precursors to useful bi- and tricyclic heteroaromatic scaf-

Table 3. Diels–Alder reactions of cyclic dienamides.



Entry	Diene	Dienophile	Conditions, time [h][a]	Product	Yield [%][b]	*dr*/*rr*[c]
1	**4a** **4b** **4c**	**8**		**9a** **9b** **9c**	78 60 61	–
2	**4a**	**10a**	A (1)	**9d**	72	1:0
3	**4a**	**10b**	A (5) B (1)	**9e**	69 65	1:0
4	**4a**	**10c**	B (2)	**9f**	71	1:0
5	**4l**	**10d**	C (2)	**9g**	84	–
6	**4a** **4a** **4c**	**11a**	D (2) E (19) D (16)	**9h** **9h** **9i**	63 81 85	–
7	**4a**	**11b**	E (21)	**9j**	65	2:1
8	**4a**	**11c**	D (2) E (23)	**9k**	71 76	4.4:1 3.1:1

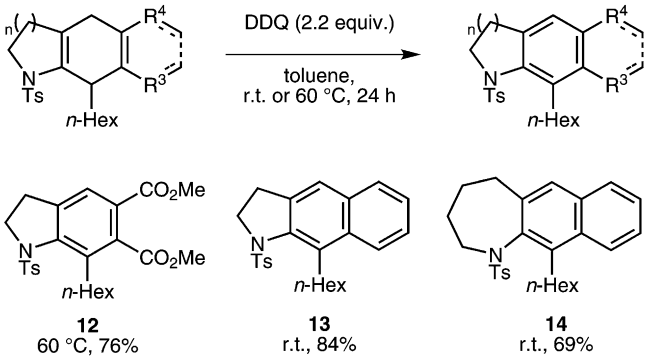
Table 3. (Continued)

Entry	Diene	Dienophile	Conditions, time [h][a]	Product	Yield [%][b]	*dr*/*rr*[c]
9	**4h**	**11a**	D (1.5)	**9l** 	72	1:0
10	**4l**	**11a**	D (16)	**9m** 	80	–

[a] *Conditions A:* PhMe, 80 °C. *Conditions B:* $BF_3{\cdot}OEt_2$ (0.55 equiv.), CH_2Cl_2, –78 °C. *Conditions C:* CH_2Cl_2, room temperature. *Conditions D:* CsF (4.0 equiv), MeCN/PhMe (1:1), 60 °C. *Conditions E:* CsF (4.0 equiv), MeCN/PhMe (1:1), room temperature.

[b] Isolated yield.

[c] Ratio indicates ratio of diastereomers (*dr*) or regioisomers (*rr*) in the crude reaction mixture as determined by ^{1}H NMR spectroscopic analysis; major isomer shown.



Scheme 3. Oxidation of Diels–Alder products.

folds. Pleasingly, we found that a number of cycloadducts could be oxidized to the corresponding arenes in a straightforward manner using DDQ (Scheme 3), providing indoline **12**, benzoindoline **13**, and naphthoazepine **14** in good yields (69–84%).

In conclusion, we have developed the first example of a carbopalladation/reduction cyclization process which employs a simple alcohol as a hydride source, *via* β-hydride elimination from a palladium alkoxide. The reaction converts a wide range of bromoenynamides to cyclic 2-amidodienes, which are substrates for Diels–Alder reactions with electron-deficient alkenes and alkynes including arynes, and as such offer a straightforward route into bi- and tricyclic azacycles.

Experimental Section

Typical Procedure for the Reductive Cyclization of 1 [Table 1, entry 2 (4a)]

To a solution of ynamide **1a** (1.00 g, 2.42 mmol, 1.0 equiv.) in EtOH (54 mL, 0.045 M) was added $Pd(PPh_3)_4$ (28 mg, 24.2 μmol, 1 mol%) and Cs_2CO_3 (1.18 g, 3.63 mmol, 1.5 equiv.). The reaction mixture was heated to 80 °C for 1 h (until judged complete by TLC), then it was cooled to room temperature and filtered through a Celite® plug (EtOAc eluent). The filtrate was concentrated under vacuum, and the residue purified *via* flash chromatography (SiO_2, petroleum ether→petroleum ether/EtOAc, 95:5) to give diene **4a** as a yellow oil; yield: 673 mg (2.02 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.68$ (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 5.87 (t, $J = 7.5$ Hz, 1H), 5.20 (t, $J = 2.0$ Hz, 1H), 4.64 (t, $J = 2.0$ Hz, 1H), 3.53 (t, $J = 7.5$ Hz, 2H), 2.53 (q, $J = 7.5$ Hz, 2H), 2.41 (s, 3H), 1.84 (tt, $J = 7.5$, 2.0 Hz, 2H), 1.45 (app. quintet, $J = 7.5$ Hz, 2H), 1.39–1.29 (m, 6H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 143.8$, 143.3, 136.5, 136.0, 129.5, 127.8, 122.1, 103.5, 48.5, 31.8, 29.7, 29.5, 29.1, 29.0, 22.7, 21.6, 14.1; IR (thin film): $\nu = 2925$, 1166, 1091, 801, 415 cm^{-1}; HR-MS: $m/z = 356.1656$, calcd. for $C_{19}H_{27}NO_2S$ $[M+Na]^+$: 356.1660; $R_f = 0.33$ (petroleum ether/EtOAc, 10:1).

Typical Procedure for Cycloaddition of 4 with Benzyne [Table 3, Entry 6 (9i)]

To CsF (50 mg, 0.33 mmol, 4.0 equiv., weighed in a glovebox) in an oven-dried vial sealed with a rubber septum under an argon atmosphere was added a solution of **4c** (30 mg, 0.083 mmol, 1.0 equiv.) in anhydrous toluene (0.33 mL), anhydrous acetonitrile (0.33 mL), and **11a** (40 μL, 0.165 mmol, 2.0 equiv.). The reaction mixture was heated to 60 °C for 16 h (until judged complete by TLC), then it was cooled to room temperature and concentrated under vacuum. Purification of the residue by flash chromatography (petroleum ether→petroleum ether/EtOAc, 20:1) gave **9i** as a colourless oil; yield: 31 mg (0.0708 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.5$ Hz, 2H), 7.25 (d, $J = 7.0$ Hz, 2H), 7.20–7.05 (m, 4H), 4.20 (d, $J = 14.5$ Hz, 1H), 3.97 (br s, 1H), 3.65 (dd, $J = 21.0$, 4.0 Hz, 1H), 3.21 (dd, $J = 21.0$, 2.0 Hz, 1H), 2.88 (t, $J = 12.5$ Hz, 1H), 2.42 (s, 3H), 1.98 (t, $J = 13.5$ Hz, 1H), 1.84–1.75 (m, 2H), 1.73–1.61 (m, 4H), 1.61–1.54 (m, 1H), 1.31–1.07 (m, 7H), 0.91–0.86 (m, 1H), 0.81 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 143.1$, 139.1, 138.6, 137.1, 135.2, 134.0, 129.6, 128.1, 127.4, 127.3, 126.1, 125.9, 50.65, 44.52, 37.81, 35.02, 33.21, 31.93, 29.81, 29.61, 25.01, 23.93, 22.74, 21.66, 14.16; IR (thin film): $\nu =$

2928, 2856, 1598, 1494, 1454, 1341, 1156, 1091, 1026, 909 cm^{-1}; HR-MS: $m/z = 460.2264$, calcd. for $C_{27}H_{35}NNaO_2S$ $[M+Na]^+$ 460.2281; $R_f = 0.56$ (petroleum ether/EtOAc, 4:1).

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