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Rh^{I}-Catalyzed Bimolecular Cyclization between Two Different 1,5-Bisallenes: A Combinatorial One-Step Approach to Heterosteroids and Mechanistic Implications

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Abstract: In this paper, a bimolecular-cyclization reaction between two different bis(allene)s with at least one heteroatom as the tether under the catalysis of *trans*-[RhCl(CO)(PPh_3)$_2$] is described. This protocol provides an efficient entry to different heterocyclic 18,19-norsteroid-like scaffolds. The tricyclic product was formed highly selectively from the cyclization reaction of bis(2,3-butadienyl)sulfide with dimethyl 2-bis(2′,3′-butadienyl)malonate, which sheds light on the mechanism involving the metalla-[4.3.0]-bicyclic intermediate formed by the cyclometallation of the terminal and the internal C=C bonds of each of the two allene moieties in 2-bis(2′,3′-butadienyl)malonate.

Keywords: allenes · cyclization · rhodium · steroids · synthetic methods

Introduction

During the last decade, combinatorial chemistry[1–3] has been applied in chemical biology,[4–7] drug discovery,[8–14] and in the discovery of new catalysts[15–25] as well as materials.[26–30] Steroids, characterized by an all-carbon skeleton with four fused rings, have been identified in plants and animals.[31–32] Among the family of steroids, the chemical and biological properties of heterosteroids have made them the subjects of much scrutiny and the targets of numerous synthetic efforts.[33–34] The azasteroids have been among the most widely studied owing to their physiological activity.[35–38] Literature methods for the construction of the azasteroid skeleton usually entail the insertion of a nitrogen atom into the A ring of the steroid framework; these methods involve ring opening, transformation of functional groups, and ring closing by rearrangements.[35,37] Thus, efficient catalytic approaches to heterosteroid derivatives are of current interest. In our recent research, we have reported a one-step method for the efficient synthesis of steroid scaffolds with new structural and steric features from readily available 1,5-bisallenes under catalysis of *trans*-[RhCl(CO)(PPh_3)$_2$].[39] Herein we report our combinatorial one-step approach to heterosteroid scaffolds.

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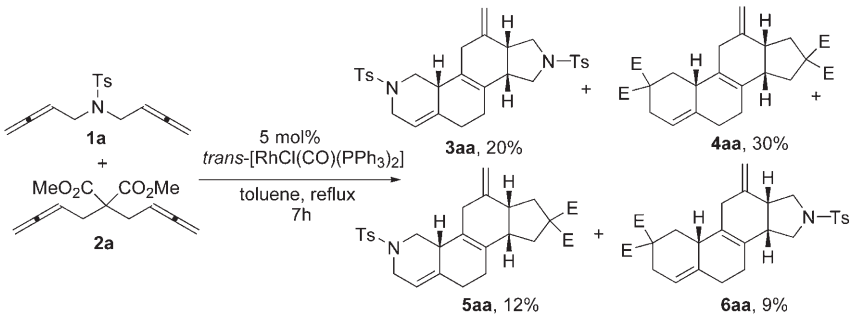
Results and Discussion

We initiated this study with the *trans*-[RhCl(CO)(PPh_3)$_2$]-catalyzed cross-cyclization between two different bisallene molecules **1a** and **2a** in toluene at reflux. We were pleased to find that the expected four steroid-like products **3aa**, **4aa**, **5aa**, and **6aa** were obtained in this one-step reaction (Scheme 1). Fortunately, all the products can be separated readily by column chromatography on silica gel, which allows convenient and efficient access to heterosteroids **5aa** and **6aa**.

Encouraged by the above results, we studied the scope of this combinatorial approach of bimolecular cross-cyclization of 1,5-bisallenes for the synthesis of other heteroatom-incorporated steroid derivatives. Typical results are summarized in Table 1. The reaction proceeded smoothly between two 1,5-bisallenes with different tethers (Table 1, entries 1–3). The heteroatom tether in bisallene **1** could be N, SO_2, or O (Table 1, entries 1–5). Cross-cyclization between two different heteroatom-tethered bisallenes was also possible and led to the formation of steroid derivatives with two heteroatoms (Table 1, entries 6 and 7). Notably, only two products were obtained when the heteroatom was oxygen (Table 1, en-



Scheme 1. Cyclization of bisallenes **1a** and **2a**.

tries 5 and 7), probably as a result of the large angle of the C–O–C bond in **1e**, which makes cyclometallation of its two allene moieties with *trans*-[RhCl(CO)(PPh_3)$_2$] more difficult. In fact, the reaction of bisallene **1e** itself under the catalysis of Rh^I failed to afford the corresponding steroid-scaffold product **3ee**. Furthermore, the reaction showed good stereoselectivity in all these cases, that is, although there are three stereogenic centers in the products, only one diastereoisomer with *cis* conjunction of the C/D rings was formed. The structures of the cross-cyclization products **5ae**, **6aa**, and **6ba** were determined by X-ray diffraction studies (Figure 1). The structures of other similarly structured **5** and **6** were tentatively assigned based on the analysis of ^{1}H NMR spectra by comparison with those of **5aa** and **6aa**. To the best of our knowledge, this is the most efficient synthetic route to heterosteroid scaffolds.

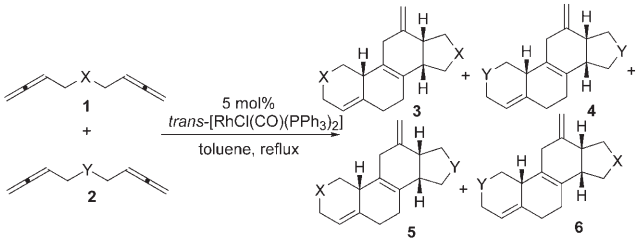
Interestingly, tricyclic product **7af** was formed when bis(2,3-butadienyl)sulfide **1f** and bisallene **2a** were used in the reaction (Table 2). The structure of **7af** was established by a single-crystal X-ray diffraction study (Figure 2). Under the conditions A and B, the **7af**/**4aa** selectivity was poor (Table 2, entries 1–4). However, when a solution of **2a**/**1f** (1:1.5) in toluene was injected into a solution of [RhCl(CO)(PPh_3)$_2$] in toluene (5 mol%) by a syringe pump, **7af** was formed in 44% yield with high selectivity (Table 2, entry 6).

On the basis of the highly selective formation of **7af**, a plausible mechanism for this transformation is proposed in Scheme 2. Initially, the cyclometallation of the bisallene **2** with Rh^I catalyst affords the intermediate **8**.[41–47] The rhodium atom in this intermediate coordinates with the sulfur atom in **1f**,[48–52] which leads to the formation of vinylic rhodium intermediate **9** through regioselective carbometallation.[53–55] The subsequent intramolecular carbometallation of **9** with the terminal C=C double bond of the allene moiety forms the intermediate **10** or **11**. Reductive elimination of **10** or **11** affords the tricyclic product **7** and regenerates the Rh^I catalyst. Notably, the formation of product **12** was not observed in the reaction of **2** and **1f** which would start from the cyclometallation of the two internal C=C double bonds of **2**. The carbometallation of **8** with the second molecule of **2** leads to intermediate **13**, which is followed by a reductive elimination and an intramolecular Diels–Alder reaction to form the product **4**.[39] Although it is too early to exclude completely the second pathway presented in our previous report,[39] intermediate **8** is surely the major intermediate in these reactions.

Conclusions

We have established an efficient one-step combinatorial protocol for the synthesis of heterosteroid scaffolds by the cross-cyclization reaction between two different 1,5-bisal-

Table 1. The Rh^I-catalyzed cross-cyclization of bisallenes for the synthesis of steroid and azasteroid skeletons.[a]



Entry	Substrate		Toluene	t	Yield[c] [%]			
	X	Y	[mL]	[h]	**3**	**4**	**5**	**6**
1	NTs (**1a**)	$C(CO_2Me)_2$ (**2a**)	72	7	20 (**3aa**)	30 (**4aa**)	12 (**5aa**)	9 (**6aa**)
2	NTs (**1a**)	$C(CN)_2$ (**2b**)	72	4	18 (**3aa**)	33 (**4bb**)	13 (**5ab**)	9 (**6ba**)
3	NTs (**1a**)	$C(SO_2Ph)_2$ (**2c**)	36	9.5	24 (**3aa**)	25 (**4cc**)	15 (**5ac**)	7 (**6ca**)
4	SO_2 (**1d**)	$C(CO_2Me)_2$ (**2a**)	48	4	17 (**3dd**)	23 (**4aa**)	8 (**5da**)	17 (**6ad**)
5[b]	O (**1e**)	$C(SO_2Ph)_2$ (**2c**)	36	21	–	38 (**4cc**)	–	13 (**6ce**)
6	NTs (**1a**)	SO_2 (**1d**)	48	19	15 (**3aa**)	19 (**3dd**)	10 (**5ad**)	9 (**6da**)
7[b]	NTs (**1a**)	O (**1e**)	72	24	19 (**3aa**)	–	5 (**5ae**)	–

[a] A solution of **1** (0.5–1.5 mmol), **2** (1 equiv), and *trans*-[RhCl(CO)(PPh_3)$_2$] (5 mol%) in toluene was stirred at reflux under an argon atmosphere for the time indicated in the table. [b] *trans*-[RhCl(CO)(PPh_3)$_2$] (10 mol%) was used and the reaction was conducted at 80°C. [c] Yields of isolated products.

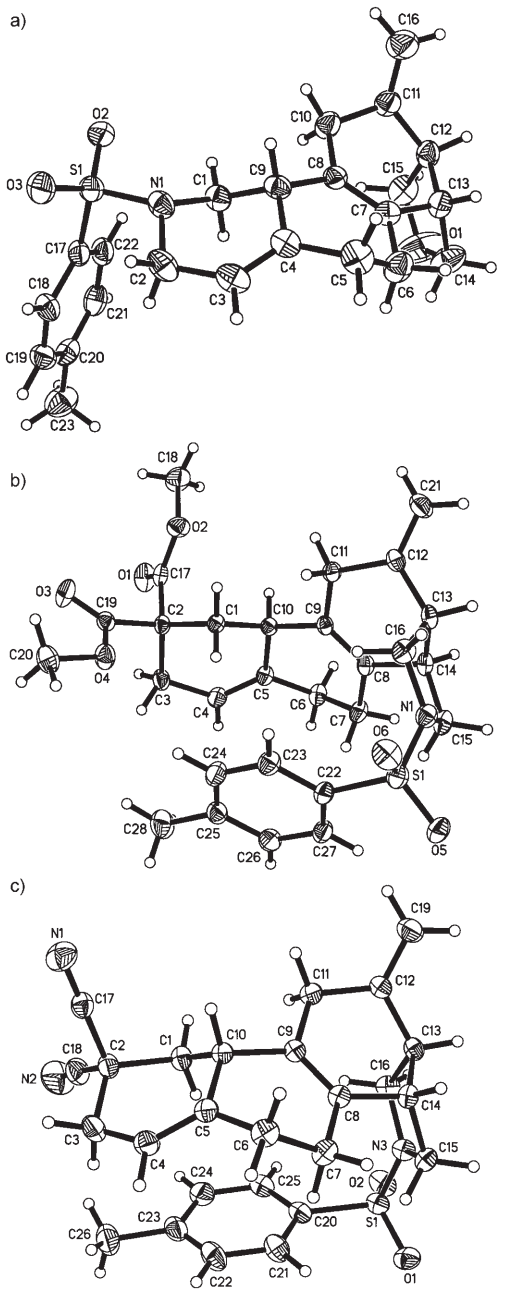
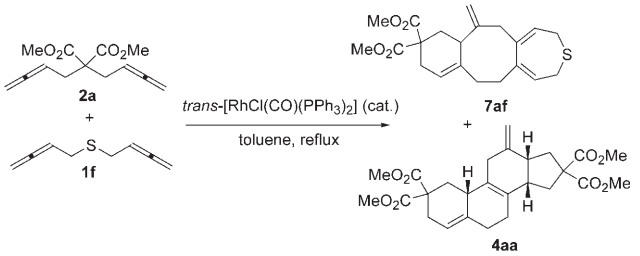


Figure 1. ORTEP representation of a) **5ae**, b) **6aa**, and c) **6ba**. Ellipsoids drawn at the 30% probability level.

lenes under the catalysis of *trans*-[RhCl(CO)(PPh_3)$_2$]. On the basis of the results of the reaction of dimethyl bis(2,3-butadienyl)malonate (**2a**) with bis(2,3-butadienyl) sulfide (**1f**), a plausible mechanism involving the metallo-[4.3.0]-bicyclic intermediate **8** was proposed. Owing to the importance of heterosteroid derivatives, this finding would be useful in medicinal chemistry. Further studies in this area are being pursued in our laboratory.

Table 2. The Rh^I-catalyzed cross-cyclization of **2a** and **1f**.



Entry	**2a**/**1f**	Cat. [mol%]	Conditions	*t* [h]	Yield[d] [%] **7af**	**4aa**
1	1:1		A[a]	12	29	19
2	1:2		A[a]	11	28	14
3	1:1	10	B[b]	25	30	20
4	1:2	10	B[b]	22	29	24
5	1:1	5	C[c]	24	36	11
6	1:1.5	5	C[c]	24	44	8

[a] Conditions A: A solution of **2a** (0.5 mmol), **1f** (amount shown in table), and *trans*-[RhCl(CO)(PPh_3)$_2$] (10 mol%) in toluene (24 mL) was stirred at reflux. [b] Conditions B: A solution of **2a** (0.25–0.5 mmol) in toluene (6–12 mL) was injected by means of a syringe pump into a mixture of **1f** (amount shown in table) and *trans*-[RhCl(CO)(PPh_3)$_2$] (10 mol%) in toluene (6–12 mL) at reflux. [c] Conditions C: A solution of **2a** (0.5 mmol) and **1f** (amount shown in table) in toluene (10 mL) was injected by means of a syringe pump into a solution of *trans*-[RhCl(CO)-(PPh_3)$_2$] (5 mol%) in toluene (2 mL) at reflux. [d] Yields of isolated products.

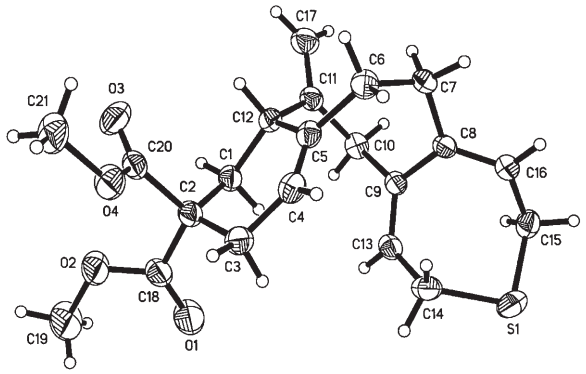


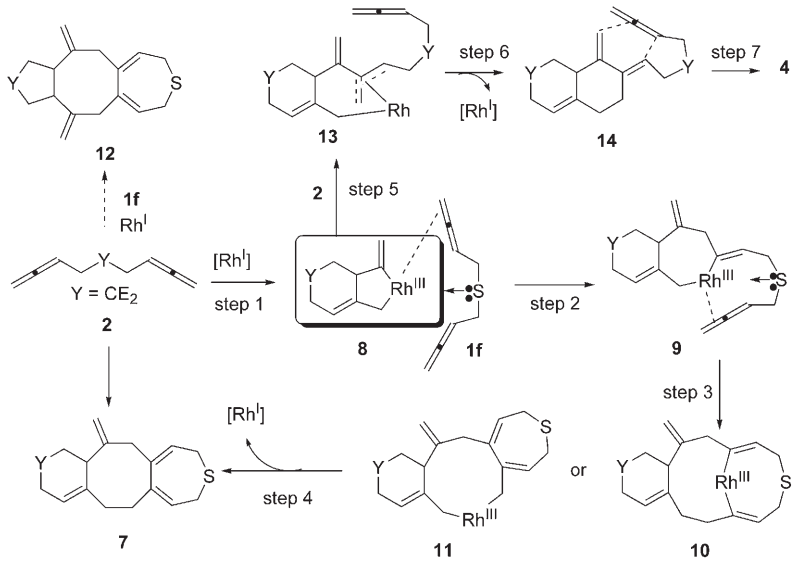
Figure 2. ORTEP representation of **7af**. Ellipsoids drawn at the 30% probability level.

Experimental Section

Typical Procedure for Rh^I-catalyzed Cross-Cyclization Reaction between Two Bisallenes

3aa, **4aa**, **5aa**, **6aa**: In a flame-dried argon-flushed flask, a solution of **1a** (413 mg, 1.5 mmol), **2a** (357 mg, 1.5 mmol), and *trans*-[RhCl(CO)(PPh_2)$_3$] (108 mg, 0.16 mmol) in dry toluene (72 mL) was stirred for 7 h at reflux. After the reaction was complete, as monitored by thin-layer chromatography (petroleum ether/ethyl acetate 5:1), the resulting mixture was concentrated by evaporation and purified by column chromatography (petroleum ether/ethyl acetate 10:1→7:1→5:1) on silica gel to afford **3aa** (82 mg, 20%), **4aa** (106 mg, 30%), **5aa** (88 mg, 12%), and **6aa** (68 mg, 9%).

5aa: Oil; IR (neat): $\tilde{\nu}$ = 1733, 1597, 1435, 1343, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.30–5.23 (m, 1H), 4.78 (s, 1H), 4.75 (s, 1H), 4.10–3.90 (m, 2H), 3.72 (s, 3H), 3.80–3.60 (m, 2H), 3.50 (s, 3H), 3.13–3.00 (m, 1H), 3.00–2.70 (m,



Scheme 2. Proposed mechanism for the formation of the steroid skeleton products and the tricyclic products. Step 1: cyclometallation, step 2: carbometallation, step 3: carbometallation, step 4: reductive elimination, step 5: carbometallation, step 6: reductive elimination, step 7: Diels–Alder reaction.

2H), 2.70–2.30 (m, 4H), 2.40 (s, 3H), 2.30–1.90 (m, 5H), 1.84–1.73 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.6, 172.1, 144.6, 143.5, 137.5, 133.3, 132.4, 129.7, 127.6, 126.4, 114.9, 109.2, 59.6, 52.9, 52.4, 46.5, 46.4, 44.9, 44.9, 40.3, 38.9, 37.9, 32.4, 30.4, 30.1, 21.5 ppm; MS (ESI): *m/z*: 529 $[M+NH_4]^+$, 512 $[M+H]^+$; HRMS: calcd for $C_{28}H_{33}NO_6SNa^+$ (MNa^+): 534.1921; found: 534.1923.

6aa: Solid; m.p.: 157–160 °C (ethyl acetate/hexane); IR (neat) $\tilde{\nu}$ = 1760, 1728, 1654, 1597, 1346, 1250, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.37–5.30 (m, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.40–3.20 (m, 3H), 3.11 (t, J = 9.3 Hz, 1H), 3.00–2.75 (m, 3H), 2.65–2.45 (m, 3H), 2.45–2.35 (m, 1H), 2.44 (s, 3H), 2.35–2.25 (m, 1H), 2.20–2.10 (m, 1H), 2.07–1.90 (m, 1H), 1.85–1.63 (m, 2H), 1.30 ppm (t, J = 13.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.4, 171.2, 143.3, 141.7, 136.9, 133.7, 130.2, 129.5, 127.7, 127.5, 116.6, 110.4, 53.5, 52.8, 52.7, 50.7, 49.6, 46.5, 45.0, 37.3, 32.4, 32.3, 31.2, 30.4, 30.3, 21.5 ppm; MS (ESI): *m/z*: 550 $[M+K]^+$, 529 $[M+NH_4]^+$, 512 $[M+H]^+$; elemental analysis: calcd for $C_{28}H_{33}NO_6S$: C 65.73, H 6.50, N 2.74; found: C 65.69, H 6.42, N 2.69; X-ray data ($C_{28}H_{33}NO_6S$): M_r = 511.61, triclinic, space group P-1, $Mo_{K\alpha}$, final R indices $[I>2\sigma(I)]$, $R1$ = 0.0507, $wR2$ = 0.1108, R indices (all data) $R1$ = 0.0704, $wR2$ = 0.1208, a = 10.1625(10) Å, b = 10.5692(10) Å, c = 13.3355(13) Å, α = 80.208(2)°, β = 77.046(2)°, γ = 64.446(2)°, V = 1255.0(2) Å^3, T = 293(2) K, Z = 2, reflections collected/unique: 7411/5329 (R_{int} = 0.0338), parameters 421.[56]

3aa, **4bb**, **5ab**, and **6ba**: The reaction of **1a** (413 mg, 1.5 mmol), **2b** (255 mg, 1.5 mmol), and *trans*-$[RhCl(CO)(PPh_2)_3]$ (109 mg, 0.16 mmol) in dry toluene (72 mL) afforded **3aa** (76 mg, 18%), **4bb** (84 mg, 33%), **5ab** (88 mg, 13%), and **6ba** (57 mg, 9%).

5ab: Oil; IR (neat): $\tilde{\nu}$ = 2250, 1653, 1598, 1345, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.45–5.35 (m, 1H), 4.97–4.87 (m, 2H), 4.13–3.93 (m, 2H), 3.22–2.93 (m, 3H), 2.93–2.50 (m, 6H), 2.41 (s, 3H), 2.35–1.90 (m, 5H), 1.87–1.75 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 143.6, 141.1, 136.3, 133.2, 130.5, 129.7, 127.9, 127.4, 116.4, 116.2, 115.7, 111.7, 46.2, 45.6, 44.8, 44.5, 43.1, 41.8, 40.4, 32.3, 32.0, 30.2, 29.9, 21.5; MS (ESI): *m/z*: 446 $[M+H]^+$; HRMS: calcd for $C_{26}H_{27}N_3O_2SNa^+$ (MNa^+): 468.1716; found: 468.1714.

6ba: Solid; m.p.: 213–216 °C (ethyl acetate/hexane); IR (neat) $\tilde{\nu}$ = 2252, 1651, 1595, 1344, 1159 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.42–5.36 (m, 1H), 4.81 (s, 1H), 4.79 (s, 1H), 3.40–3.10 (m, 4H), 3.10–2.47 (m, 8H), 2.44 (s, 3H), 2.35–1.97 (m, 3H), 1.90–1.80 (m, 1H), 1.60 ppm (t, J = 12.3 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 143.3, 140.8, 138.6, 133.6, 129.7, 129.5, 128.1, 127.5, 116.2, 115.1, 113.0, 111.0, 50.8, 49.3, 46.3, 44.6, 36.9, 34.8, 33.8, 32.0, 31.1, 30.33, 30.29, 21.5 ppm; MS (ESI): *m/z*: 446 $[M+H]^+$; elemental analysis: calcd for $C_{26}H_{27}N_3O_2S$: C 70.08, H 6.11, N 9.43; found: C 70.11, H 6.04, N 9.38; X-ray data ($C_{26}H_{27}N_3O_2S$): M_r = 445.57, monoclinic, space group $P21/n$, $Mo_{K\alpha}$, final R indices $[I>2\sigma(I)]$, $R1$ = 0.0580, $wR2$ = 0.1444, R indices (all data) $R1$ = 0.0773, $wR2$ = 0.1539, a = 9.7873(10) Å, b = 22.918(2) Å, c = 10.1220(10) Å, α = 90°, β = 98.692(2)°, γ = 90°, V = 2244.3(4) Å^3, T = 293(2) K, Z = 4, reflections collected/unique: 13155/4897 (R_{int} = 0.1284), parameters 359.[56]

3aa, **4cc**, **5ac**, and **6ca**: The reaction of **1a** (207 mg, 0.75 mmol), **2c** (300 mg, 0.75 mmol), and *trans*-$[RhCl(CO)(PPh_2)_3]$ (54 mg, 0.078 mmol) in dry toluene (36 mL) afforded **3aa** (49 mg, 24%), **4cc** (74 mg, 25%), **5ac** (74 mg, 15%), and **6ca** (37 mg, 7%). The structures of **5ac** and **6ca** were tentatively assigned based on the analysis of ^{1}H NMR spectra by the comparison with those of **5aa** and **6aa**.

5ac: Oil; IR (neat): $\tilde{\nu}$ = 1597, 1583, 1447, 1330, 1310, 1155, 1144 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 7.5 Hz, 2H), 7.80–7.40 (m, 8H), 7.30 (d, J = 7.8 Hz, 2H), 5.34 (br s, 1H), 4.82 (s, 2H), 4.20–3.90 (m, 2H), 3.23–3.00 (m, 2H), 3.00–2.67 (m, 4H), 2.67–2.27 (m, 4H), 2.37 (s, 3H), 2.37–2.00 (m, 4H), 1.85–1.70 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 143.5, 142.4, 137.1, 136.8, 136.0, 134.7, 134.4, 133.7, 131.7, 131.3, 130.9, 129.7, 128.8, 128.6, 127.5, 125.7, 115.1, 110.8, 93.6, 47.0, 46.3, 45.8, 44.8, 40.6, 36.0, 34.9, 31.8, 30.4, 30.0, 21.5 ppm; MS (ESI): *m/z*: 698 $[M+Na]^+$, 676 $[M+H]^+$; HRMS: calcd for $C_{36}H_{37}NO_6S_3Na^+$ (MNa^+): 698.1675; found: 698.1673.

6ca: Oil; IR (neat): $\tilde{\nu}$ = 1647, 1447, 1332, 1309, 1146 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 7.2 Hz, 2H), 7.75–7.50 (m, 8H), 7.30 (d, J = 8.4 Hz, 2H), 5.20 (br s, 1H), 4.73 (s, 2H), 3.41–3.23 (m, 2H), 3.18–2.58 (m, 10H), 2.42 (s, 3H), 2.40–2.25 (m, 2H), 2.10–1.95 (m, 2H), 1.82 ppm (dd, J = 13.8, 12.3 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 143.4, 141.3, 137.7, 136.8, 135.9, 134.73, 134.67, 133.6, 131.5, 131.1, 129.7, 129.3, 128.9, 128.8, 128.6, 127.4, 114.4, 110.6, 87.9, 50.6, 49.6, 46.5, 44.6, 36.7, 32.5, 30.7, 29.7, 28.9, 26.3, 21.5 ppm; MS (ESI): *m/z*: 698 $[M+Na]^+$, 693 $[M+NH_4]^+$, 676 $[M+H]^+$; HRMS: calcd for $C_{36}H_{37}NO_6S_3Na^+$ (MNa^+): 698.1675; found: 698.1675.

3dd, **4aa**, **5da**, and **6ad**: The reaction of **1d** (174 mg, 1 mmol), **2a** (238 mg, 1 mmol), and *trans*-$[RhCl(CO)(PPh_2)_3]$ (69 mg, 0.1 mmol) in dry toluene (48 mL) afforded **3dd** (29 mg, 17%), **4aa** (54 mg, 23%), **5da** (33 mg, 8%), and **6ad** (68 mg, 17%). The structures of **5da** and **6ad** were tentatively assigned based on the analysis of ^{1}H NMR spectra by the comparison with those of **5aa** and **6aa**.

3dd: solid; m.p.: 240–243 °C (ethyl acetate/petroleum ether); IR (neat): $\tilde{\nu}$ = 1655, 1322, 1299, 1280, 1133, 1115 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ = 5.47–5.40 (m, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 3.90–3.78 (m, 1H), 3.63–3.50 (m, 1H), 3.45–3.20 (m, 4H), 3.20–2.80 (m, 6H), 2.63–2.50 (m, 1H), 2.40–2.30 (m, 2H), 2.20–1.95 (m, 1H), 1.95–1.85 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 139.3, 137.9, 130.1, 128.2, 112.6, 112.5, 53.7, 52.6, 50.6, 50.5, 43.5, 42.2, 41.2, 31.9, 31.8, 29.9 ppm; MS (ESI): *m/z*: 358 $[M+NH_4]^+$, 341 $[M+H]^+$; HRMS: calcd for $C_{16}H_{20}O_4S_2Na^+$ (MNa^+): 363.0695; found: 363.0693.

5da: oil; IR (neat): $\tilde{\nu}$ = 1731, 1435, 1321, 1297, 1278, 1125 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42 (br s, 1H), 4.84 (s, 1H), 4.78 (s, 1H), 3.80–

3.65 (m, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 3.60–3.35 (m, 2H), 3.24 (dt, J= 13.8, 3.3 Hz, 1H), 3.00–2.05 (m, 11H), 1.95–1.85 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=172.6, 172.2, 143.9, 139.5, 133.3, 126.1, 111.5, 109.6, 59.5, 52.9, 52.6, 50.7, 50.5, 46.9, 45.2, 41.5, 38.4, 37.5, 32.0, 31.9, 30.0 ppm; MS (EI): *m/z* (%): 406 [M^+] (21.87), 385 (100); HRMS: calcd for $C_{21}H_{26}O_6SNa^+$ (MNa^+): 429.1342; found: 429.1358.

6ad: oil; IR (neat): $\tilde{\nu}$=1732, 1651, 1434, 1303, 1253, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.41 (br s, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.40–3.30 (m, 1H), 3.25–2.90 (m, 6H), 2.90–2.50 (m, 4H), 2.40–2.05 (m, 4H), 1.90–1.73 (m, 1H), 1.63–1.50 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=172.3, 171.2, 140.6, 136.2, 131.4, 127.1, 117.6, 111.4, 54.0, 53.5, 52.9, 52.8, 52.7, 43.6, 42.3, 37.1, 32.7, 32.4, 31.2, 30.7, 30.3 ppm; MS (EI): *m/z* (%): 406 [M^+] (2.63), 314 (100); HRMS: calcd for $C_{21}H_{26}O_6SNa^+$ (MNa^+): 429.1342; found: 429.1342.

4cc and **6ce**: The reaction of **1e** (184 mg, 1.5 mmol), **2c** (301 mg, 0.75 mmol), and *trans*-[RhCl(CO)(PPh_2)$_3$] (52 mg, 0.075 mmol) in dry toluene (36 mL) afforded **4cc** (115 mg, 38%) and **6ce** (50 mg, 13%). The structure of **6ce** was tentatively assigned based on the analysis of its ^{1}H NMR spectrum by the comparison with that of **5ae**.

6ce: Oil; IR (neat): $\tilde{\nu}$=1650, 1583, 1447, 1330, 1310, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.14 (d, J=8.1 Hz, 2H), 8.00 (d, J=8.1 Hz, 2H), 7.75–7.50 (m, 6H), 5.25–5.20 (m, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 3.95–3.80 (m, 2H), 3.60–3.45 (m, 2H), 3.20–2.57 (m, 7H), 2.30–1.70 (m, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=143.0, 137.8, 136.7, 136.1, 134.6, 134.6, 131.5, 131.0, 130.3, 128.6, 128.6, 128.5, 114.4, 110.1, 88.0, 72.5, 70.8, 47.5, 45.8, 36.7, 32.4, 30.8, 30.2, 28.7, 26.3 ppm; MS (ESI): *m/z*: 545 [M+Na]$^+$, 540 [M+NH_4]$^+$, 523 [M+H]$^+$; HRMS: calcd for $C_{29}H_{30}O_5S_2Na^+$ (M+Na^+): 545.1427; found: 545.1437.

3aa, **4dd**, **5ad**, **6da**: The reaction of **1a** (276 mg, 1 mmol), **1d** (172 mg, 1 mmol), and *trans*-[RhCl(CO)(PPh_2)$_3$] (69 mg, 0.1 mmol) in dry toluene (48 mL) afforded **3aa** (41 mg, 15%), **4dd** (32 mg, 19%), **5ad** (45 mg, 10%), and **6da** (38 mg, 9%). The structures of **5ad** and **6da** were tentatively assigned based on the analysis of ^{1}H NMR spectra by the comparison with those of **5aa** and **6aa**.

5ad: Oil; IR (neat): $\tilde{\nu}$=1598, 1344, 1303, 1162, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65 (d, J=8.1 Hz, 2H), 7.72 (d, J=8.1 Hz, 2H), 5.40–5.35 (m, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.25–3.93 (m, 2H), 3.43–3.30 (m, 1H), 3.25–2.95 (m, 7H), 2.90–2.60 (m, 2H), 3.42 (s, 3H), 2.35–1.97 (m, 4H), 1.95–1.85 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ= 143.7, 139.8, 136.1, 133.0, 129.8, 128.8, 128.7, 127.5, 115.9, 112.0, 53.9, 52.8, 46.5, 44.8, 43.5, 42.3, 40.1, 32.6, 30.4, 30.1, 21.5 ppm; MS (ESI): *m/z*: 463 [M+NH_4]$^+$, 446 [M+H]$^+$; HRMS: calcd for $C_{23}H_{27}NO_4S_2Na^+$ (MNa^+): 468.1274; found: 468.1288.

6da: Oil; IR (neat): $\tilde{\nu}$=1597, 1458, 1344, 1302, 1161, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67 (d, J=8.4 Hz, 2H) 7.30 (d, J=8.4 Hz, 2H), 5.43–5.37 (m, 1H), 4.80 (s, 2H), 3.80–3.70 (m, 1H), 3.60–3.45 (m, 1H), 3.40–3.03 (m, 5H), 3.00–2.90 (m, 1H), 2.80–2.60 (m, 2H), 2.53–1.80 ppm (m, 10H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=143.5, 140.6, 138.7, 133.8, 130.9, 129.6, 127.6, 127.5, 112.0, 111.4, 53.7, 50.9, 50.8, 50.7, 49.4, 44.7, 41.4, 31.9, 29.9, 29.2, 21.6 ppm; MS (ESI): *m/z*: 468 [M+Na]$^+$, 463 [M+NH_4]$^+$, 446 [M+H]$^+$; HRMS: calcd for $C_{23}H_{27}NO_4S_2Na^+$ (MNa^+): 468.1274; found: 468.1281.

3aa and **5ae**: The reaction of **1a** (413 mg, 1.5 mmol), **1e** (365 mg, 3 mmol), and *trans*-RhCl(CO)(PPh_2)$_3$ (104 mg, 0.15 mmol) in dry toluene (72 mL) afforded **3aa** (77 mg, 19%) and **5ae** (28 mg, 5%).

5ae: Solid; M.p.: 156–158°C (ethyl acetate/petroleum ether); IR (neat): $\tilde{\nu}$=1651, 1597, 1347, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65 (d, J=7.9 Hz, 2H), 7.31 (d, J=7.9 Hz, 2H), 5.33 (brs, 1H), 4.86 (s, 1H), 4.83 (s, 1H), 4.10–3.95 (m, 2H), 3.87–3.78 (m, 2H), 3.63–3.47 (m, 2H), 3.18–2.50 (m, 6H), 2.42 (s, 3H), 2.30–1.65 ppm (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=143.6, 142.8, 137.1, 133.1, 130.9, 129.7, 127.5, 127.3, 115.1, 110.3, 72.4, 70.9, 47.6, 46.8, 45.8, 44.9, 40.4, 32.4, 30.5, 30.4, 21.5 ppm; MS (ESI): *m/z*: 420 [M+Na]$^+$, 415 [M+NH_4]$^+$, 398 [M+H]$^+$; HRMS: calcd for $C_{23}H_{27}NO_3SNa^+$ (MNa^+): 420.1604; found: 420.1605; X-ray data ($C_{23}H_{27}NO_3S$): M_r=397.52, monoclinic, space group $C2/c$, final R indices [$I>2\sigma(I)$], $R1$=0.0680, $wR2$=0.1578, R indices (all data) $R1$=0.1095, $wR2$=0.1784, a=20.913(8) Å, b=8.253(3) Å, c=25.233(10) Å, α=90°, β=105.340(8)°, γ=90°, V=4200(3) Å^3, T=293(2) K, Z=8, reflections collected/unique: 11790/4562 (R_{int}=0.1115), parameters: 274.[56]

Cross-Cyclization Reaction of **1f** *with* **2a**

7af: A solution of **2a** (119 mg, 0.5 mmol) and **1f** (105 mg, 0.75 mmol) in toluene (10 mL) was added over 10 h by means of a syringe pump to a two-necked flask (equipped with a condenser and an argon inlet) containing *trans*-[RhCl(CO)(PPh_3)$_2$] (17 mg, 0.025 mmol) and toluene (2 mL) at reflux. The solution was stirred at reflux until the reaction was complete as monitored by thin-layer chromatography. After removal of the solvent, the residue was purified by column chromatography on silica gel to afforded the tricyclic product **7af** (83 mg, 44%) and **4aa** (9 mg, 8%) as a solid. M.p.: 116–119°C (CH_2Cl_2/hexane); IR (neat) $\tilde{\nu}$=1735, 1432, 1256, 1196, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.90 (t, J= 7.2 Hz, 1H), 5.79 (t, J=7.5 Hz, 1H), 5.41 (d, J=5.7, 1H), 5.00 (s, 1H), 4.89 (s, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 3.13–2.80 (m, 6H), 2.75–2.60 (m, 1H), 2.60–2.45 (m, 2H), 2.35–1.97 (m, 5H), 1.91 ppm (t, J=10.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ=172.4, 171.2, 150.1, 146.4, 144.6, 138.8, 123.8, 123.6, 121.0, 114.8, 53.3, 52.8, 52.6, 46.2, 39.5, 37.7, 35.4, 33.9, 30.7, 25.8, 25.7 ppm; MS (EI): *m/z* (%): 374 [M^+], (21.86), 59 (100); HRMS: calcd for $C_{21}H_{26}O_4S$: 374.1552; found: 374.1561; X-ray data ($C_{21}H_{26}O_4S$): M_r=374.48, triclinic, space group P-1, final R indices [$I>2\sigma(I)$], $R1$=0.0505, $wR2$=0.1296, R indices (all data) $R1$=0.0674, $wR2$=0.1391, a=7.2647(7) Å, b=7.8867(8) Å, c=17.1574(16) Å, α=87.456(2)°, β=79.079(2)°, γ=84.190(2)°, V=959.94(16) Å^3, T=293(2) K, Z=2, reflections collected/unique: 5691/4057 (R_{int}=0.0343), parameters: 237.[56]

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