

A platinum-catalyzed annulation reaction leading to medium-sized rings†

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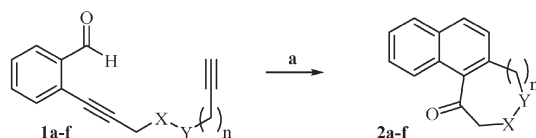
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A platinum-catalyzed domino process with intermediate benzopyrylium cations reaches its optimum utility in the formation of 7- and 8-membered rings. With iron(III) chloride, a tetracyclic product is isolated, derived from an oxidative transformation of a metal-carbene intermediate.

Whereas synthetic methods for the construction of five- and six-membered rings are numerous, the development of novel and efficient cyclization reactions leading to medium-sized carbocycles and heterocycles is still challenging because of the disadvantageous influence of both entropic and enthalpic factors.¹ In the course of our studies on gold- and platinum-catalyzed annulation reactions with *ortho*-alkynyl-substituted benzaldehydes,² we intended to test the generality of the transformation depicted in Scheme 1. The formation of five- and six-membered naphthalena-carbocycles of type **2**, catalyzed by gold salts, has recently been described.³ In the case of our total synthesis of heliophenanthrone,^{2c} which resembles a substituted derivative of **2** (with $n = 0$), we found PtCl₂ to be the superior catalyst compared to gold chloride.⁴ Therefore, we have concentrated on PtCl₂ as the catalyst for the reactions in Scheme 1, testing its scope and limitations with respect to ring size and the presence of heteroatoms.

For the synthesis of model compounds **1a–f**, we started from 2-bromobenzaldehyde (**3**), as illustrated in Scheme 2. The bis-alkyne side chain⁵ was either introduced directly in a one-step procedure by a Sonogashira coupling reaction⁶ (for **1c–f**), or *via* the corresponding cyclic acetal⁷ and intermediate alcohols **4a** and **4b**. In the latter case, the ether functionalities were prepared with propargyl bromide, using NaH as the base,⁸ and the aldehyde was finally deprotected with dilute hydrochloric acid to give **1a** and **1b**.⁹ Surprisingly, another established method of deprotection—FeCl₃

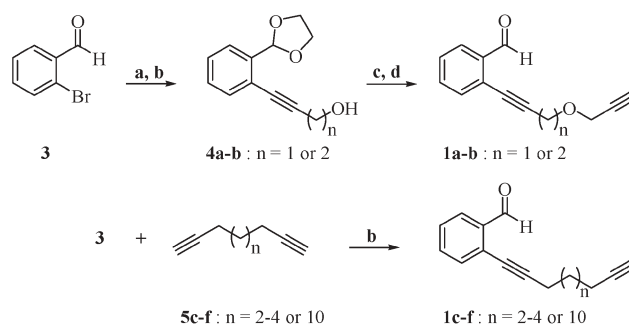


1a: X = O, Y = CH₂, $n = 0$
1b: X = CH₂, Y = O, $n = 1$
1c–f: X = CH₂, Y = CH₂, $n = 1–3$ or 9

Scheme 1 PtCl₂-catalysed annulations. **a**: PtCl₂ (3 mol%), toluene, reflux.

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Scheme 2 Synthesis of the precursors **1a–f**. **a**: ethylene glycol, TMSCl, DCM, reflux; **b**: Pt(PPh₃)₂Cl₂ (2 mol%), CuI (2 mol%), TEA, reflux; **c**: NaH, propargyl bromide, THF, 20 °C; **d**: 5% HCl, THF, 20 °C.

in dichloromethane at room temperature¹⁰—led to the formation of annulation product **6b** in 10% isolated yield, identified by NMR and X-ray crystal structure analysis (Fig. 1).¹¹ In the control experiment, substrate **1b** reacted under the same conditions to give the [3 + 2] cycloadduct **6b** in 13% yield; a related product being recently observed by Gupta *et al.* in a similar gold-catalyzed process with a participating allenyl unit.¹²

We generally performed the platinum-catalyzed domino process on a 0.5 mmol scale: substrates **1a–f** were heated in 20 ml toluene and a catalytic amount of PtCl₂ (3 mol%) in a screw-capped flask at 140 °C. The results are summarized in Table 1. Substrates **1a–c** were consumed in 3 h, and the corresponding annulation products **2a–c** were obtained in isolated yields of 67, 89 and 95%, respectively (Table 1, entries 1–3). Formation of an eight-membered ring occurred smoothly to give product **2d** in a very satisfactory 80% yield (Table 1, entry 4), although a somewhat enhanced reaction time was necessary. Consequently, for the generation of a nine-membered carbocycle in product **2e**, the time for the consumption of **1e** rose to 24 h (Table 1, entry 5). In

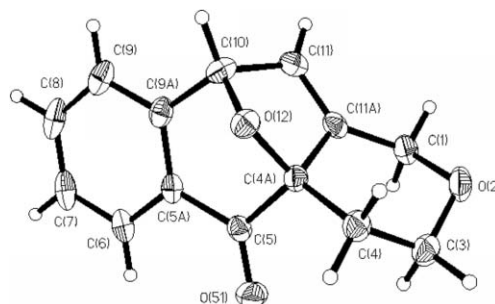
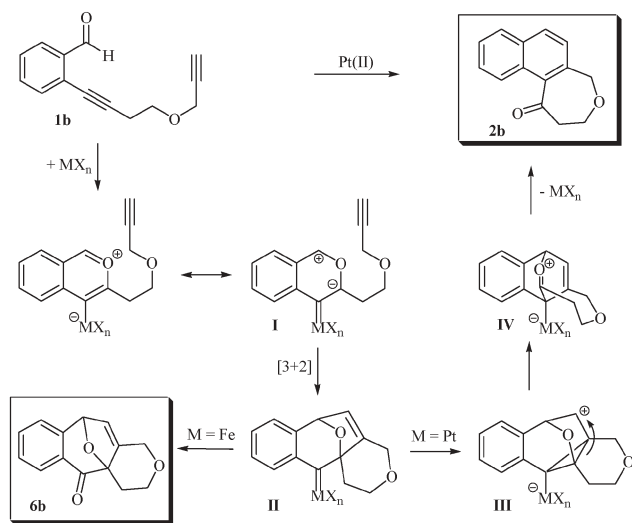


Fig. 1 Crystal structure of **6b**.

Table 1 PtCl₂-catalyzed cyclization of bis-alkynes

Entry	Substrate	Reaction time/h	Product	Ring size	Yield (%)
1	1a	3	2a	6	67 ^a
2	1b	3	2b	7	89
3	1c	3	2c	7	95
4	1d	12	2d	8	80
5	1e	24	2e	9	13
6	1f	24	2f	15	<5 ^b

^a 0.2 mmol scale. ^b Slightly impure, not fully characterized.

**Scheme 3** Plausible mechanism for annulation reaction.

addition, the yield of annulation product **2e** dropped to only 13%, indicating a limitation of this process. Since the ring strain of carbocycles generally reaches its maximum in nine-membered rings, we hoped for higher yields in the cases of macrocycles. However, an attempt to produce a 15-membered ring from substrate **1f** resulted in a very low yield (Table 1, entry 6).

For comparison, we also tried AuCl₃ (5 mol%, 80 °C in acetonitrile) as a catalyst for the annulation reaction. With **1a** and **1e** as substrates, we achieved yields of less than 10%, confirming that PtCl₂ is superior.

A plausible mechanism for the platinum(II)-catalyzed annulation reaction is depicted in Scheme 3. The double annulation process most probably proceeds through the benzopyrylium cation **I**, which results from the nucleophilic attack of the carbonyl oxygen at the alkyne, activated by the Lewis-acidic platinum salt. A subsequent intramolecular Huisgen-type [3 + 2] cycloaddition of the second alkyne is assumed to generate intermediate **II**.¹³ Rearrangement to **III** and the formal [4 + 2] cycloaddition product **IV** leads to the aromatized final **2b**, liberating the active catalyst, in analogy to the calculations of Straub.¹³ In the case of FeCl₃ as the Lewis acid, we assume that intermediate **II** is oxidatively transformed to **6b**.¹⁴

The platinum-catalyzed intramolecular domino annulation reaction of *ortho*-alkynyl benzaldehydes described herein represents a versatile approach to naphthalenes with annulated

carbocycles or heterocycles of various ring sizes. The easily accessible starting materials, simple reaction procedure and mild conditions make this method attractive for the production of common- and medium-sized rings.

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