Facile formation of iodocyclobutenes by a ruthenium-catalyzed enyne cycloisomerization†

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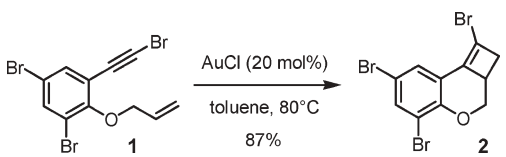
Enynes bearing an iodide (bromide) at their alkyne terminus react with catalytic amounts of [Cp*Ru(MeCN)$_3$]PF$_6$ in DMF to give strained iodo(bromo)cyclobutene derivatives in good to excellent yields.

During our ongoing investigations on noble metal catalyzed skeletal rearrangement reactions,[1,2] we noticed that the brominated enyne **1**, on treatment with catalytic amounts of AuCl in toluene at 80 °C, furnished the tricyclic bromocyclobutene derivative **2** in 87% yield (Scheme 1). However, this particular outcome remained unique and analogous cyclizations of related substrates could not be achieved under the chosen conditions.[3,4]

Despite the many impressive advances in the field of gold and platinum catalysis, a mechanistic analysis shows that such transformations usually exploit the pronounced carbophilicity of these noble metals but do not involve conventional redox cycles.[5] Cyclobutene **2**, however, likely originates from an oxidative cyclization of the enyne followed by reductive elimination of the resulting metallacycle. Therefore it seemed reasonable to focus on more redox active transition metals in the quest for a catalyst system that allows the scope of this novel mode of cycloisomerization to be extended.

Metallacyclic intermediates are believed to dominate the behavior of CpRu(II) and Cp*Ru(II) templates.[6,7] In line with this notion, [Cp*Ru(MeCN)$_3$]PF$_6$ (**4**), a readily prepared and also commercially available complex with a truly remarkable track record in catalysis,[6–10] turned out to effect cycloisomerizations of this kind with exceptional ease. As shown in Scheme 2, the model substrate **3** converts within minutes at ambient temperature into the desired iodocyclobutene **5** when exposed to catalytic amounts of **4** in THF or DMF as the preferred solvents, presumably *via* a metallacycle of type **A** as the key reactive intermediate. Product **5** was isolated in excellent yield, provided that either neutral alumina or Florisil® were used as stationary phase for flash



Scheme 1 Lead finding on a novel mode of enyne cycloisomerization.

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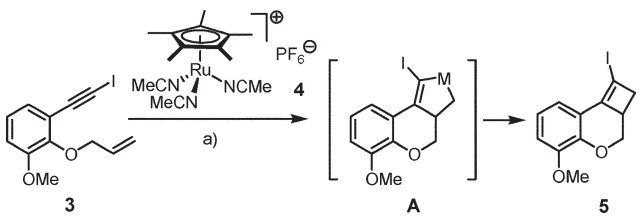


Scheme 2 *Reagents and conditions*: (a) complex **4** (5 mol%), RT, 94% (DMF), 75% (THF).

chromatography; in pure form, the compound is stable for weeks when kept cold (−18 °C). The constitution of this and related products was unambiguously proven by extensive NMR investigations (see ESI†). The structure of the amide analogue **16** in the solid state‡ is depicted in Fig. 1, which represents the first example of a tricyclic skeleton of this type.

The selected examples compiled in Tables 1 and 2 illustrate the scope of the method. Specifically, enynes incorporating an ether or an amido group in the tether between the olefin and the haloalkyne unit are converted with high efficiency into the corresponding cyclobutenes, irrespective of whether the backbone of the substrates is aromatic or aliphatic; purely carbocyclic products form equally well (entry 10, Table 1). The fact that not only the produced alkenyl iodide but also a pre-existing aryl bromide entity (entries 7 and 8, Table 1) is compatible with the reaction conditions shows that oxidative insertion of the catalyst into such reactive C–X bonds does not compete with the proposed

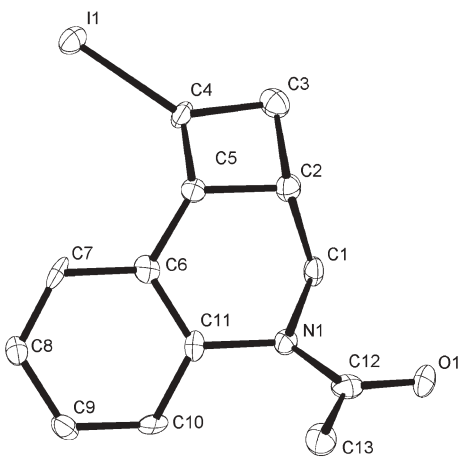
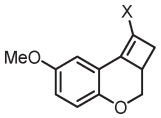
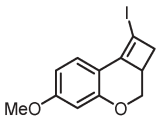
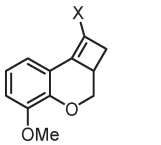
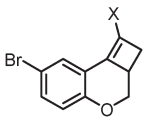
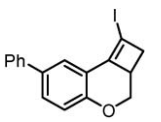
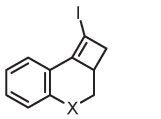
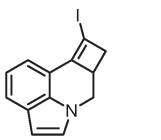


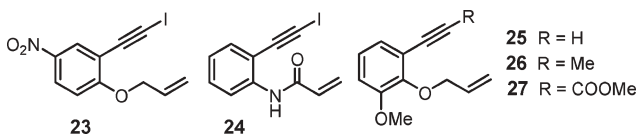
Fig. 1 Molecular structure of **16** from single-crystal X-ray structure determination. Anisotropic displacement parameter ellipsoids are shown at 50% probability and hydrogen atoms have been omitted.

Table 1 Cycloisomerization of 1-haloenynes with aromatic backbones into iodo(bromo)cyclobutene derivatives catalyzed by complex **4**[a]

Entry	Product		Yield (%)
1		**6**	81 (X = I)
2		**7**	78 (X = Br)[c]
3		**8**	0 (X = Cl)
4		**9**	45
5		**5**	94 (X = I)
6		**10**	43 (X = Br)
7		**11**	90 (X = I)
8		**12**	89 (X = Br)[c]
9		**13**	86
10		**14**	82 (X = CH_2)[b,c]
11		**15**	88 (X = NTs)
12		**16**	74 (X = NAc)
13		**17**	63

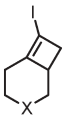
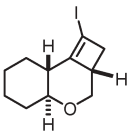
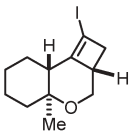
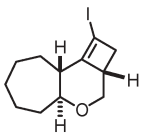
[a] Unless stated otherwise, all reactions were carried out with 5 mol% of **4** in DMF at ambient temperature. [b] In THF. [c] **4** (10 mol%).

oxidative cyclization pathway thought to be responsible for the formation of the cyclobutene ring.



A comparison of entries 1, 4 and 5 in Table 1, however, indicates a subtle effect of the substrate's electronic properties on the efficiency of cyclization. The view that more electron rich substrates seem to be preferred is supported by the fact that enyne **23** carrying an electron withdrawing nitro group essentially failed to afford the corresponding cyclobutene, whereas acrylate **24** was decomposed. It is also important to note that the substituent on the alkyne plays a pre-eminent role in the cyclization process. Thus, alkynyl bromides tend to react less readily than the corresponding iodides and require a higher catalyst loading to reach full conversion (entries 2, 6 and 8, Table 1). Even more striking is the difference between alkynyl iodides and alkynyl

Table 2 Cycloisomerization of 1-iodoenynes with aliphatic backbones into the corresponding iodocyclobutene derivatives catalyzed by complex **4**[a]

Entry	Product		Yield (%)
1		**18**	63 (X = O)
2		**19**	63 (X = NTs)
3		**20**	70
4		**21**	79
5		**22**	60 + 20[b]

[a] All reactions were carried out with 5 mol% of **4** in DMF at ambient temperature. [b] 60% of major isomer (depicted) + 20% of diastereomer.

chlorides, as evident from a comparison of entries 1 and 3 in Table 1. While cyclobutenyl iodide **6** was obtained in excellent yield, the analogous chloride **8** would not form under the standard conditions. Likewise, enynes **25–27** featuring either a terminal or an internal alkyne unit remained unchanged. The exact role exerted by the iodine moiety, however, which is obviously not merely electronic in nature, remains to be elucidated.

Even though the cyclobutenyl iodides produced by this novel route are fairly labile due to the strain inherent to their polycyclic frames,[11] they are amenable to further functionalization (Scheme 3). This includes conventional palladium catalyzed cross couplings as exemplified by the Sonogashira reaction[12] affording compound **28** and the Suzuki coupling[13] leading to **29**, which was performed according to the "9-MeO-9-BBN-variant"[14] of this venerable transformation. Gratifyingly, iodides **6** and **15** also react with Grignard reagents under iron catalysis as a benign alternative to the established methods for cross coupling.[15–18] BuLi alkylates substrates of this type even without any further additive, although the yield was low in the case of product **32** (n = 1). Subsequent electrocyclic ring opening afforded diene **33** that is amenable to further manipulation, suggesting that the novel mode of enyne cycloisomerization described herein may pave the way to a host of valuable product structures and should therefore qualify for (diversity oriented) synthetic endeavours. Some possibilities along these lines are presently pursued in this laboratory and will be reported in due course.

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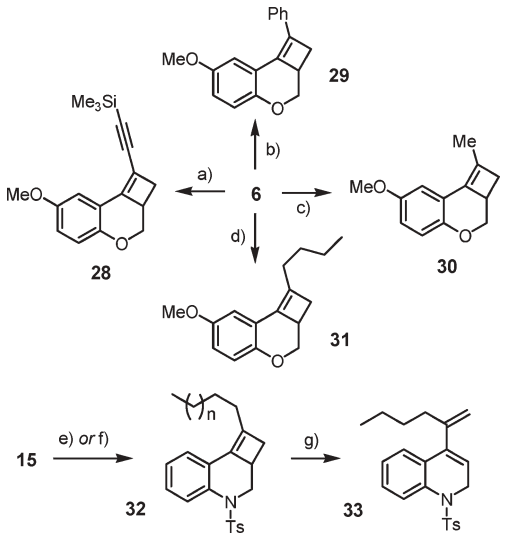

Scheme 3 *Reagents and conditions*: (a) $Me_3SiC{\equiv}CH$, CuI (20 mol%), $(Ph_3P)_2PdCl_2$ (10 mol%), Et_3N, 77%; (b) PhMgBr, 9-MeO-9-BBN, (dppf)$PdCl_2$ (5 mol%), Ph_3As (10 mol%), THF, 60–80 °C, 56%; (c) MeMgBr, $[(C_2H_4)_4Fe][Li(tmeda)]_2$ (10 mol%), THF, −20 °C, 55%; (d) *n*BuLi, THF–Et_2O, −78 °C → RT, 72%; (e) hexylmagnesium bromide, $[(C_2H_4)_4Fe][Li(tmeda)]_2$ (10 mol%), THF, −20 °C, 51% (*n* = 3); (f) *n*BuLi, THF–Et_2O, −78 °C → RT, 31% (*n* = 1); (g) toluene, reflux, 88%.

Notes and references

‡ *Crystal data* for **16**: $[C_{13}H_{12}INO]$, M_r = 325.14, colourless, crystal size: 0.03 × 0.05 × 0.07 mm; monoclinic, space group *Cc* (no. 9), a = 24.4838(8), b = 8.0709(3), c = 12.1166(4) Å, β = 104.469(2)°, U = 2318.4(1) Å^3, T = 100 K, Z = 8, D_c = 1.86 g cm^{-3}, $F(000)$ = 1264, Bruker-AXS X8-Proteum diffractometer, λ(Cu-Kα) = 1.54178 Å, μ = 21.52 mm^{-1}, 9921 measured and 2821 independent reflections (R_{int} = 0.037), 2474 with $I > 2\sigma(I)$, θ_{max} = 63.26°, apparent $T_{min/max}$ = 0.4362 (SADABS), direct methods (SHELXS-97) and least-squares refinement (SHELXL-97) on F_o^2, programs from G. Sheldrick, University of Göttingen, 1997. Two crystallographically independent molecules. Chebyshev type weights, 290 parameters, R_1 = 0.032 ($I > 2\sigma(I)$), wR_2 = 0.081 (all data), $\Delta\rho_{max/min}$ = 1.5/−0.7 e Å^{-3} (1.0 Å from I2/0.95 Å from I1). CCDC 650426. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708903a

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