Cycloaddition Reactions

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# Pericyclic Cascade Reactions of (Bicyclo-[1.1.0]butylmethyl)amines**

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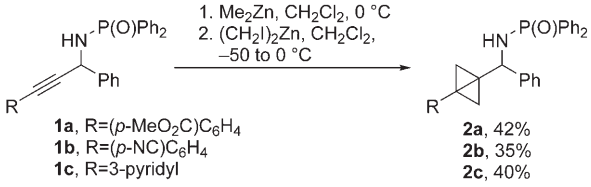
*Dedicated to Professor Heinz Heimgartner*

Cyclopropanes and cyclobutanes are often used as scaffolds in selective functionalizations and in the expansion of molecular complexity.[1,2] In contrast, applications of bicyclo-[1.1.0]butanes[3] in organic synthesis have been much more limited.[4] Because of their impressive strain energy of 64 kcal mol$^{-1}$,[5] the latter compounds readily undergo electrophilic, nucleophilic, and radical additions as well as cycloaddition reactions.[3] Of special interest for bicyclobutane chemistry is the high $\pi$ character of the central C–C bond, which can be utilized for the synthesis of cyclobutene derivatives.[6]

We recently described a cascade reaction initiated by the hydrozirconation of alkynes followed by transmetalation to dimethylzinc and addition to alkynyl imines.[7] Exposure of the resulting *N*-metalated intermediates to the cyclopropanation conditions developed by Furukawa et al.[8] resulted in an unprecedented series of C–C bond-formation and -cleavage processes, thus leading to bicyclo[1.1.0]butanes and (dicyclopropylmethyl)amines.[7a]

Bicyclo[1.1.0]butanes can also be obtained by direct cyclopropanation of propargyl phosphinylamides[9] (Scheme 1). Treatment of **1a–c** with $Me_2Zn$ followed by addition of $(CH_2I)_2Zn$ at −50 °C provided **2a–c**.[10] Conjugated propargylamides with electron-withdrawing substitu-




***Scheme 1.*** Synthesis of bicyclobutanes by a directed Simmons–Smith reaction.

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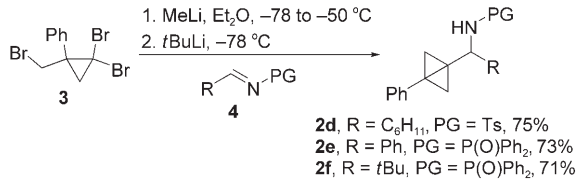
ents in the aryl group provide higher yields in this transformation. Alternatively, bicyclobutanes **2** can be accessed by addition of bicyclo[1.1.0]butyllithium to the activated imines (Scheme 2).[11] Treatment of **3** with MeLi followed by transmetallation with *t*BuLi and addition to imines **4** furnished bicyclobutanes **2d–f** in high yields.



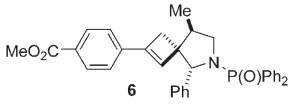
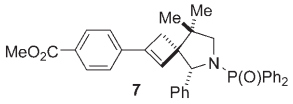
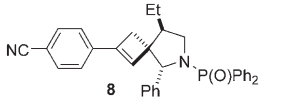
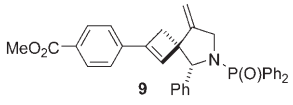
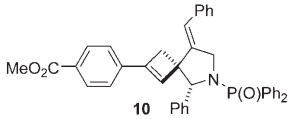
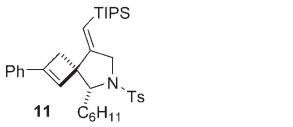

***Scheme 2.*** Synthesis of bicyclobutanes by addition of bicyclo-[1.1.0]butyllithium. PG = protecting group, Ts = *p*-toluenesulfonyl.

Based on the ease of insertion of zinc carbenoids into the bicyclobutane scaffold,[7] we decided to explore the intramolecular cycloadditions with alkenes and alkynes.[12] Under modified phase-transfer conditions[13] (allyl bromide, $Bu_4NHSO_4$, 50% aq. NaOH, toluene), *N*-allylation of **2e** proceeded efficiently; however, instead of the expected product, we found that the initial product underwent a spontaneous formal ene reaction[14] to give spirocycle **5** in 63% yield as the only detectable diastereomer based on the $^1$H NMR spectroscopic analysis of the crude reaction mixture (Scheme 3).[15]


***Scheme 3.*** Cascade *N*-allylation—an Alder ene reaction.

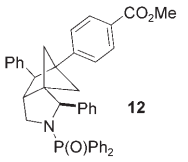
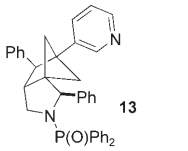
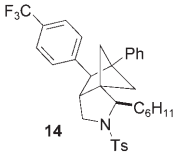
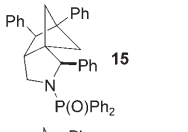
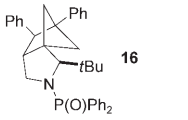
For a further investigation of the scope of this novel cascade process (Table 1), various bicyclobutane derivatives were reacted with allyl, 2-methylallyl, crotyl, propargyl, 3-phenylpropargyl, and 3-triisopropylsilylpropargyl bromides (entries 1–6, respectively). The course of the reaction was dependent on the substitution of the allyl moiety and the electronic environment at the bicyclobutane ring. For example, reaction of **2a** with 3-bromo-2-methylbutene led to the *N*-allylated intermediate (90% yield), which underwent conversion into **7** in 80% yield under reflux conditions in toluene. To directly convert **2a** into **7**, our initial conditions had to be modified—the reaction was carried out at elevated temperatures in the presence of a mixture of powdered NaOH and $K_2CO_3$ (entry 2).[12] Interestingly, when bicyclobutanes **2** were treated with cinnamyl bromides, the pathway changed from an Alder ene reaction to a formal [2+2] cycloaddition, thus leading to the first synthesis of 3-azatricyclo[5.1.1.0$^{1,5}$]nonanes (Table 2).[16,17] Yields in this remarkable conversion ranged from modest (32% with the pyridine-substituted **2c**; entry 2) to excellent (93%; entry 1), and both aromatic and aliphatic groups α to the pyrrolidine nitrogen atoms were well tolerated. It is, however, important to note that with our current experimental protocol only bicyclobutanes conju-

***Table 1:*** Reactions of bicyclobutanes with allyl and propargyl bromides.

| Entry | Substrates | Product | Yield [%] |
|---|---|---|---|
| 1 | **2a**, allyl bromide |  **6** | 82 |
| 2 | **2a**, 3-bromo-2-methyl-propene |  **7** | 66[a,b] |
| 3 | **2b**, (*E*)-crotyl bromide |  **8** | 51[a] |
| 4 | **2a**, propargyl bromide |  **9** | 87 |
| 5 | **2a**, 3-phenylpropargyl bromide |  **10** | 49 |
| 6 | **2d**, 3-triisopropylsilyl-propargyl bromide |  **11** | 62 |

[a] The reaction was carried out in the presence of a mixture of powdered NaOH and $K_2CO_3$. [b] Obtained as a 2.9:1 mixture of diastereoisomers; only the major isomer is shown.

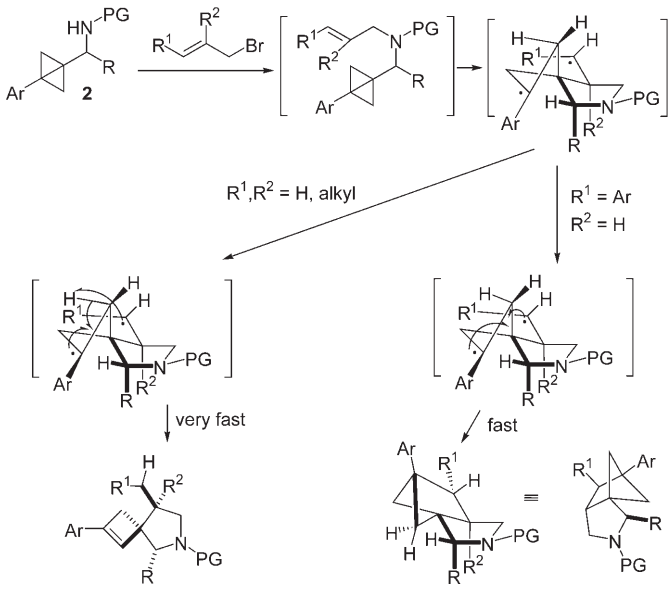
***Table 2:*** Reactions of bicyclobutanes with cinnamyl bromides.

| Entry | Substrates | Product | Yield [%] |
|---|---|---|---|
| 1 | **2a**, (*E*)-cinnamyl bromide |  **12** | 93 |
| 2 | **2c**, (*E*)-cinnamyl bromide |  **13** | 32 |
| 3 | **2d**, 1-((*E*)-3-bromoprop-1-enyl)-4-(trifluoro-methyl)benzene |  **14** | 68 |
| 4 | **2e**, (*E*)-cinnamyl bromide |  **15** | 59 |
| 5 | **2f**, (*E*)-cinnamyl bromide |  **16** | 54 |

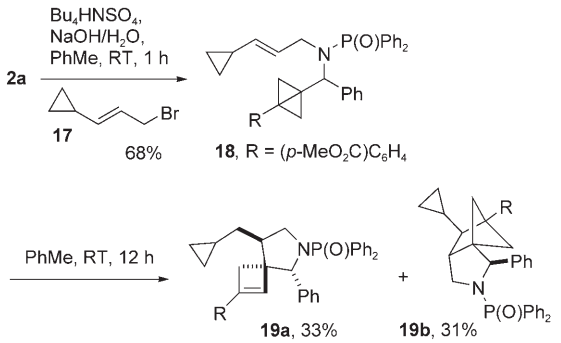
gated to aromatic rings were found to undergo either the intramolecular ene or the [2+2] reaction.[18]

Scheme 4 summarizes our mechanistic model of the two competing reaction pathways for the reactions of bicyclobutanes with allyl bromides. A stepwise addition of the π system across the central bicyclobutane C–C σ bond leads to a putative biradical species,[12b,c,d,e,19] which in case of alkyl substituents at $R^1$ rapidly abstracts the inside hydrogen atom to form the spirocyclic butene.[12c] If the biradical species is stabilized by an aromatic group at $R^1$, its prolonged lifetime allows for a ring inversion of the cyclobutane and radical recombination in a formal [2+2] cycloaddition process, thus yielding the tricyclic pyrrolidine system.




***Scheme 4.*** A mechanistic hypothesis that involves ene and [2+2] reaction pathways of bicyclobutanes **2**.

To probe the lifetime of the proposed biradical intermediates[12b,c,d,e,19] in the conversion of **2a** into **6** and **12**, we introduced a cyclopropylallyl substituent (Scheme 5).[20] Bicyclobutane **2a** was allowed to react with freshly prepared bromide **17** and the unstable amide **18** was obtained in 68% yield. Compound **18** underwent spontaneous conversion into equimolar amounts of **19a** and **19b** upon standing at room temperature. The lack of cyclopropane ring-opened products is not unusual for short-lived biradical intermediates,[21a] and the bifurcation in the reaction pathway with the cyclopropane substituent at $R^1$ supports our hypothesis of a common intermediate for both spirocycle and tricycle formation. A nonconcerted pathway for the formal [2+2] process was further supported by the reaction of **2a** with (*Z*)-cinnamyl bromide, which afforded **12** in 52% yield under our standard conditions instead of the diastereomeric product derived from a stereospecific process.[21b] Thus, the lifetime of the intermediate biradical is sufficiently long to allow σ-bond rotation at $R_1$ to give the more stable *anti* conformer.




***Scheme 5.*** A mechanistic study with cyclopropane as a radical trap.

In summary, we have established a direct synthetic access to (bicyclo[1.1.0]butylmethyl)amines from propargyl phosphinamides through a Simmons–Smith reaction with $Et_2Zn/CH_2I_2$ or by addition of bicyclo[1.1.0]butyllithium to activated imines. Phase-transfer conditions proved optimal for the introduction of *N*-allyl or *N*-propargyl substituents, and the resulting amides underwent highly diastereoselective cascade rearrangements by formal ene or [2+2] pathways to yield novel spirocyclic and tricyclic pyrrolidine heterocycles.

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**Keywords:** bicyclobutanes · cascade reactions · pericyclic reactions · pyrrolidines · spirocycles

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[15] The structure of **5** was assigned based on the X-ray analysis of the ketoaldehyde derived from cleavage of the cyclobutene ring.
[16] The relative stereochemistry of **12** was assigned based on NOESY analysis.
[17] A steric argument was used to rationalize the selectivity of the ene versus [2+2] pathway for simple bicyclo[1.1.0]butanes (see reference [12]); prior pericyclic reactions of bicyclo-[1.1.0]butanes were limited to structurally simple substrates, and no further synthetic applications were reported.
[18] Reaction of 3-phenylbicyclo[1.1.0]butyllithium with acetaldehyde or benzaldehyde followed by phase-transfer alkylation resulted in a low yield of the alkylated product.
[19] For a demonstration of the radical nature of reactions of bicyclo[2.1.0]pentane with alkenes, see: a) P. G. Gassman, K. T. Mansfield, T. J. Murphy, *J. Am. Chem. Soc.* **1969**, *91*, 1684 – 1689; b) P. G. Gassman, K. T. Mansfield, *J. Am. Chem. Soc.* **1968**, *90*, 1524 – 1526.
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[21] a) T. Linker, *Angew. Chem.* **1997**, *109*, 2150 – 2152; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2060 – 2062; b) alkene *Z*/*E* isomerization during *N*-alkylation was not responsible for the lack of stereospecificity; (*Z*)-cinnamyl bromide when treated with *N*-(3-*p*henylprop-2-ynyl)diphenylphosphinylamide gives an alkylated product with an intact *Z* double-bond configuration in 67% yield.

  