Isoindoles and dihydroisoquinolines by gold-catalyzed intramolecular hydroamination of alkynes

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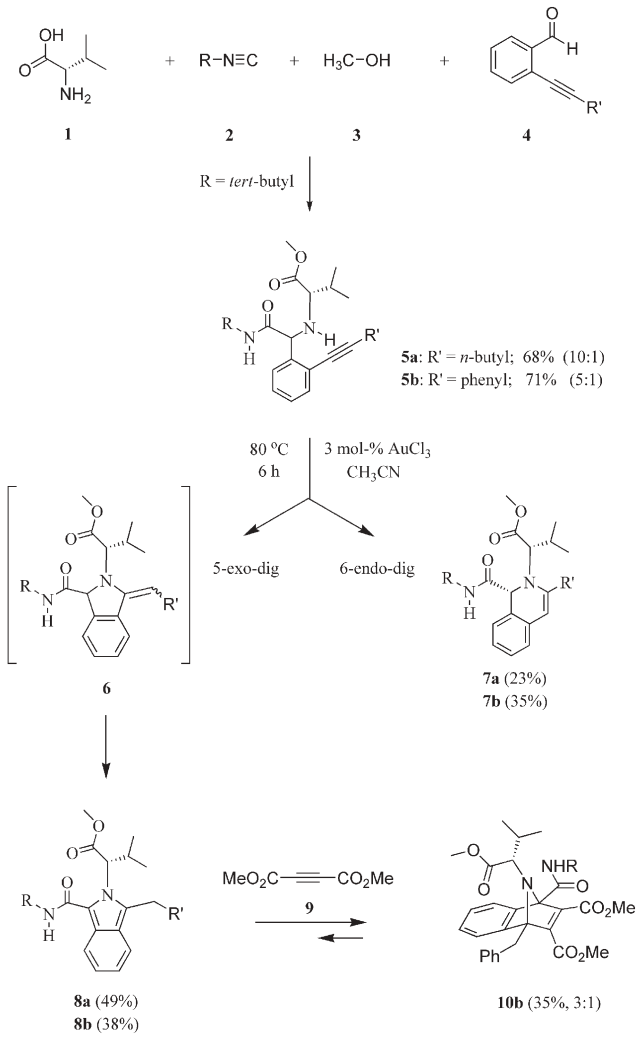
The title compounds are enantioselectively synthesized in just two prepararative steps, making use of the Ugi-four-component reaction with an amino acid as chiral component, followed by a gold-catalyzed hydroamination.

Gold-catalyzed reactions have emerged as powerful and highly selective tools for organic synthesis in recent years:[1] obviously gold complexes exhibit a high reactivity as rather soft Lewis-acids, especially in terms of alkyne activation for nucleophilic attacks,[2] enabling these processes to proceed under very moderate reaction conditions. As part of our ongoing studies on gold-catalyzed annelation reactions[3] we envisioned that a two step sequence of the Ugi-four-component reaction[4] with a gold-catalyzed cyclization should offer a fascinating opportunity to build up chiral heterocycles with a high degree of complexity.



Scheme 1 Combination of Ugi reaction, hydroamination and Diels–Alder reaction.

According to this general idea we applied L-valine (**1**) as chiral amine component and benzaldehydes **4**[5] as source of the alkyne moiety. The condensation process of the four reaction components **1–4** proceeds somewhat sluggishly at room temperature within 6 to 9 days, building up the highly functionalized amines **5**, finally with satisfactory yield and diastereoselectivity (Scheme 1).

The hydroamination[6] succeeded with just 3 mol-% gold chloride as catalyst in acetonitrile at 80 °C with overall yields above 70%: the dihydroisoquinolines **7** obviously are the result of a 6-*endo*-dig cyclization, whereas the isoindoles **8** derive from the 5-*exo*-dig products **6**, which of course isomerize under aromatization under the acidic reaction conditions.

Alkynes **5** were applied as purified main diastereomers and gave **7a** and **7b** as single diastereomers according to TLC and NMR, thus indicating configurational stability under the acidic reaction conditions. In crystals of **7b** there are two independent molecules with identical configurations in the unit cell. Knowing the absolute configuration of the L-valine chiral centres to be *S* our X-ray structure analysis of **7b** (Fig. 1) then established that the other chiral centres have the *R*-configuration.[7]

To our knowledge **8a** and **8b** are the first examples of chiral isoindoles, prompting us to test the face selectivity of the Diels–Alder reaction of **8b** with acetylene dicarboxylic acid dimethyl ester

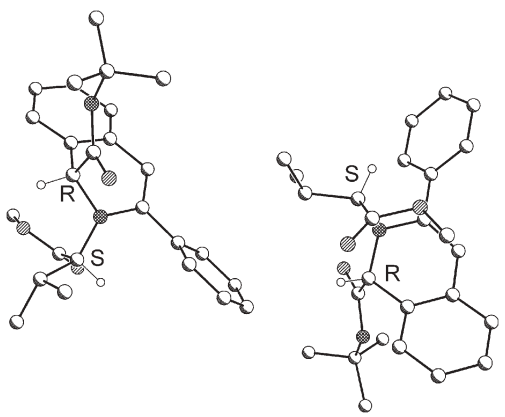


Fig. 1 Structure of the chiral isoquinoline **7b** in the crystal.

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9. As the result we obtained a 3 : 1 mixture of the diastereomers of **10b** as an oily product: further separation and purification failed because of partial decomposition during flash chromatography. In test tube experiments also the Diels–Alder reactions with *N*-methyl and *N*-4-tolyl maleimides were examined: the resulting cycloadducts were even more sensitive than **10b**, clearly undergoing retro-Diels–Alder reaction at room temperature on silica. The retro reaction obviously profits from the electronic stabilization of isoindoles **8** by the amide substituent, which is part of the conjugated donor–acceptor system with the isoindole nitrogen. Normally retro-Diels–Alder reactions of isoindole adducts take place at much more elevated temperatures.[8]

In summary, the combination of Ugi reaction and gold catalysis offers a valuable opportunity for building up chiral dihydroisoquinolines and isoindoles, which are highly functionalized and of interest for further stereoselective transformations.

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