Gold(I)-Catalyzed Intermolecular Cycloaddition of Allenamides with \(\alpha,\beta\)-Unsaturated Hydrazones: Efficient Access to Highly Substituted Cyclobutanes

Paloma Bernal-Albert,† Hélio Faustino,† Ana Gimeno,§ Gregorio Asensio,§ José L. Mascareñas,*,† and Fernando López*,†,‡

†Centro Singular de Investigación en Química Biológica e Materiales Moleculares (CIQUIS) and Departamento de Química Orgánica, Universidad de Santiago de Compostela, 15782, Santiago de Compostela, Spain
‡Instituto de Química Orgánica General CSIC, Juan de la Cierva 3, 28006, Madrid, Spain
§Departamento de Química Orgánica, Universidad de Valencia, Avda. Vicent Andrés Estellés s/n, 46100-Burjassot, Valencia, Spain

Supporting Information

ABSTRACT: \(\alpha,\beta\)-Unsaturated \(N,N\)-dialkyl hydrazones undergo a mild [2 + 2] cycloaddition to allenamides when treated with a suitable gold catalyst. The method, which represents the first application of \(N,N\)-dialkyl hydrazones in gold catalysis, is compatible with a wide variety of substituents at the alkenyl moiety of the hydrazone component, proceeds with excellent levels of regio- and diastereoselectivity, and provides densely substituted cyclobutanes with good to excellent yields.

Cyclobutanes not only constitute the basic structural motif of a wide range of biologically active products but, owing to their inherent strain energy, are also highly valuable synthetic building blocks. The most common strategies to assemble cyclobutanes are based on [2 + 2] cycloadditions of unsaturated precursors, reactions which are typically carried out under photochemical conditions, although in some cases they can also be promoted by Lewis acids. Alternatively, transition metal catalysis has recently emerged as a powerful tool for uncovering new types of [2 + 2] annulations. In this context, the groups of Chen, González, and ours have independently reported an efficient assembly of cyclobutanes based on the Au(I)-catalyzed intermolecular [2 + 2] cycloadditions between allenamides and electron-rich alkenes (Scheme 1, eq 1). Despite the relevance of these methods, their success is associated with the use of styrenes, enol ethers, or enamides as reaction partners, which restricts the type of substituents (R¹/R²) that can be incorporated in the resulting cyclobutanes, as well as access to cyclobutanes with quaternary stereocenters.

Considering the mechanism proposed for these cycloadditions, which involves the formation of intermediates I and II, we were curious to analyze the behavior of other types of electron-rich alkenes that could afford alternative, diversely substituted cyclobutanes. In particular, we focused our attention on \(\alpha,\beta\)-unsaturated \(N,N\)-dialkyl hydrazones, a relatively unexplored class of substrates that are easily prepared from \(N,N\)-dialkylhydrazines and enamides. Although these species have been typically used as azadienes in hetero-Diels–Alder cycloadditions, the electron-donor characteristics of the \(N,N\)-dialkylamino group convert them into umpoled enals (vinyllogous aza-enamines, Scheme 1, eq 2). Curiously, this umpoling reactivity has been scarcely exploited and, to the best of our knowledge, remains essentially unexplored in transition metal catalyzed processes. Herein, we report that \(\alpha,\beta\)-unsaturated \(N,N\)-dialkyl hydrazones are excellent two-carbon partners in gold-catalyzed cycloadditions with allenamides, providing for the efficient assembly of highly substituted cyclobutanes with excellent regio- and diastereoselectivities.

We started our research by analyzing the reactivity of allenamide 1a with the \(N,N\)-disopropylhydrazine 2a in the presence of several Au or Pt catalysts. As can be seen in Table 1, Pt(II) complexes, such as PtCl₂, PtBr₂, or [PtCl₂(C₂H₄)]₂/P(o-
Tol)3, promote intermolecular annulations between the conjugated hydrazone and the allenamide to yield, after a few hours at 85 °C, the [2 + 2] cycloadduct E-3aa, together with minor amounts of the [3 + 2] and [4 + 2] adducts 4aa and 5aa, respectively (Table 1, entries 1–3). On the other hand, the use of AuCl or the gold(III) complex PicAuCl2 led exclusively to the [2 + 2] cycloadducts 3aa, as 5:1 and 9:1 mixtures of E/Z isomers (entries 4 and 5). Gratifyingly, cationic Au(I) complexes were also active catalysts for the cycloaddition. Thus, while Ph3PAuNTf2 provided the [2 + 2] adduct Z-3aa, together with the acyclic product 6aa (7:3 ratio, entry 6), the Johnphos-based gold(I) complex Au1 exclusively provided Z-3aa, which was isolated after 10 min at rt, in 99% yield using just 5% of the catalyst (entry 7). The structure and stereochemical identity of this adduct could be further corroborated by X-ray analysis, which confirmed the cis disposition of the Ph and Me groups and the Z configuration of the enamide (Figure S2, Supporting Information).

Noteworthy, the cyclobutanes 3aa incorporate the phenyl substituent at the β-position of the exo-enamide and, therefore, can be considered as regioisomers of those obtained in the previous annulations of allenamides and styrenes.6

We next analyzed the scope of the process. The N,N-diisopropyl hydrazone derived from cinnamaldehyde (2b) did also participate in the cycloaddition, although full conversions required heating at 55 °C and longer reaction times (Table 2, entry 2). In any case, the corresponding cyclobutane, Z-3ab, was isolated in good yield and with complete stereoselectivity. The reaction tolerated electron-rich (e.g., p-OMe) or electron-poor (e.g., p-F) substituents at the hydrazone-phenyl moiety (entries 3 and 4). On the other hand, the introduction of a phenyl group at the α-position of the conjugate hydrazone (2e) allows the reaction to be completed at rt in <1 h; the [2 + 2] adduct 3ae was obtained in 95% yield (Z/E ratio = 6:4, entry 5).

The reaction is also efficient with α,β-unsaturated hydrazones bearing alkyl substituents at the β-position. Thus, hydrazones 2f and 2g, with a methyl substituent, provided the corresponding [2 + 2] adducts, 3af and 3ag, in excellent yields, as 8:2 and 6:4 mixtures of Z and E isomers, respectively (entries 6 and 7). In consonance with the lower reactivity of the α-unsubstituted hydrazone 2b with respect to its α-methylated analog 2a, inducing the reaction of hydrazone 2h, derived from crotonaldehyde, also required more drastic conditions (16 h at 85 °C and 10% of the catalyst). Using these conditions, the expected product was obtained in 95% yield and with complete Z selectivity (entry 8). Gratifyingly, hydrazone 2i, derived from cyclohexene-1-carbaldehyde, also participated in the [2 + 2]

| entry | hydrzone (2) | t (°C) | t (h) | cycloadduct (3) | Z/E | yield |
|-------|-------------|--------|------|----------------|-----|-------|
| 1     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 2     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 3     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 4     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 5     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 6     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 7     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 8     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 9     | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 10    | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |
| 11    | Ph3PAuNTf2  | 85     | 16   | 3ae            | Z   | 95%   |

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Table 1. Preliminary Screening with Pt and Au Catalystsa, b, d

| entry | [M] (10%) | time | Z-3aa | E-3aa | 4aa | 5aa | 6aa |
|-------|-----------|------|-------|-------|------|------|------|
| 1     | PtCl2     | 5 h  | 0     | 7     | 3    | 1    | 0    |
| 2     | PtBr6     | 3 h  | 0     | 12    | 3    | 1    | 0    |
| 3     | [PtCl2(C6H4)2]2/P(o-Tol)3 | 5 h | 0 | 13 | 1 | 1 | 0 |
| 4     | AuCl      | 6 h  | 1     | 5     | 0    | 0    | 0    |
| 5     | AuCl      | 16 h | 1     | 9     | 0    | 0    | 0    |
| 6     | Ph3PAuNTf2 | 20 h | 7    | 0     | 0    | 0    | 3    |

“1a (1 equiv), 2a (2 equiv) and [M] (10%) were heated at 85 °C (0.25 M in DCE), unless otherwise noted. The table indicates the proportion of products as deduced from 1H NMR of the crude mixtures. aConversions >99% after the indicated time. bCarried out at rt. cCarried out with 5% catalyst. dZ-3aa isolated in 99% yield.
cycloaddition providing, in excellent yield and complete syn selectivity at the ring fusion, the bicyclo[4.2.0]octane product 3ai, an attractive bicyclic scaffold quite common in many natural products (entry 9).14 The analog hydrazone 2j, derived from cyclopentene-carbaldehyde, did not afford the bicyclo[3.2.0]-heptane adduct (3aj), presumably because of the higher strain associated with the formation of this bicyclic system. Instead, the acyclic product 6aj was isolated in 65% yield (entry 10). Electron-withdrawing groups at the β-position of the hydrazone are tolerated. Indeed, 2k, featuring an ethyl carbamate at this position, provided the [2 + 2] adduct 3ak in 83% yield (entry 11).

The annulation reaction is not restricted to N,N-diisopropyl hydrazones. As can be seen in Table 3, N,N-dimethyl hydrazones with aryl or alkyl substituents at the alkene (2′a−c′,f′,k′) provided the [2 + 2] cycloadducts, although the reactions required slightly higher reaction times and temperatures (Table 3, entries 1−5). For example, while the cycloaddition of the diisopropyl hydrazone 2a occurred at rt in 5 min (99% yield, Table 2, entry 1), that of its N,N-dimethyl analog 2a′, which gives 3a′a, required 3.5 h at 55 °C (76% yield, Table 3, entry 1). Small amounts of the acyclic products of type 6 were also isolated in some cases (entries 1 and 4).15 The SAMP-derived chiral hydrazone 2a″ also participated in the process providing the corresponding [2 + 2] cycloadduct in 85% yield and moderate diastereoselectivity (dr = 7:3, entry 6). Similarly, the SAMP-hydrazone 2f″ provided the expected adduct as a 6:4 mixture of diastereomers. Thus, these preliminary results suggest that further modifications in the chiral hydrazone moiety might allow the development of asymmetric versions of the reaction.

The current methodology is not restricted to oxazolidinone-derived allenamides such as 1a. As can be seen in entries 8 and 9, the N-tosyl phenyl allenamide 1b also participated in the cycloaddition, providing the expected cycloadducts with complete selectivity and excellent yields (95−97% yield).

The cyclobutane adducts obtained in the above cycloadditions offer interesting potential for further manipulations (Scheme 2). Thus, the hydrazone moiety of 3aa can be converted into a nitrile by treatment with magnesium monoperoxiphthalate (MMPP). Alternatively, hydrolysis and subsequent reduction allow the hydrazone to be readily converted into the alcohol 8a in a good overall yield. Interestingly, a catalytic dihydroxylation of the oxo-enamide of 8a afforded, with total diastereoselection, the cyclobutane-fused γ-lactol 9a, a type of scaffold that recalls the core of biologically relevant products.16

**Table 3. Scope of the Hydrazone and Allenamide**

| entry | R1, R2 | NR2 | t (°C) | t (h) | yield (dr)% |
|-------|--------|-----|--------|-------|-------------|
| 1     | Ph, Me | 2a′ | 55     | 3.5   | 3aa′ 76%    |
| 2     | Ph, H  | 2b′ | 65     | 7     | 3ab′ 53%   |
| 3     | pOMePh, H | 2c′ | 65     | 4     | 3ac′ 41%   |
| 4     | Me, Me | 2f′ | 55     | 1     | 3af′ 47%/6 |
| 5     | EtOAc, Me | 2k′ | 65     | 0.5   | 3ak′ 63%   |
| 6     | Ph, Me | 2a″ | 55     | 1     | 3aa″ 85%(7:3) |
| 7     | Me, Me | 2f″ | 55     | 1     | 3af″ 63%/6(4:6) |
| 8     | Ph, Me | 2a  | N(Pr)2 | 185  | 0.2   | 3ba 95% |
| 9     | Ph, H  | 2b  | N(Pr)2 | 185  | 16    | 3bb 97% |

"1 (1 equiv) was added to a mixture of 2 (2 equiv) and Au1 (5%) in DCE (0.25 M), unless otherwise noted. "2Z/E ratios (determined by 1H NMR spectroscopy of the crude mixtures) are 1:0 unless otherwise noted. "6aa′ (6%) was also isolated. "6af′ (21%) was also isolated. "Z/E ratio = 9:3:0.7. "6af′ (9%) was also isolated.

A plausible mechanism for the cycloaddition reaction is proposed in Scheme 3. An initial activation of the allenamide by the carbophilic catalyst would provide the zwitterionic intermediate I, species that has been theoretically located in the context of intermolecular [4 + 2] Au-catalyzed cycloadditions between dienes and allenamides.17 Regioselective interception of I by the nucleophilic β-carbon of the alkynylhydrazone affords the acyclic intermediate II, which might evolve to the final cycloadduct 3 by direct cyclization with concomitant elimination of the catalyst.7 Alternatively, the cyclization might proceed through the alkyl gold intermediate III, which would explain the formation of Z/E mixtures of 3.17 The diastereoselectivity of the reaction, to give cyclobutanes in which R1 and R2 are in a cis disposition, is consistent with an approach of the vinyl gold moiety of II from the opposite face to that of the R2 group. A cyclization via rotamer II′, leading to a hypothetical trans isomer, should be less favorable due to steric reasons. Finally, the

**Scheme 2. Preliminary Manipulation of the Cycloadducts**

**Scheme 3. Mechanistic Proposal**
formation of acrylic side products of type 6 can be explained by assuming a hydrogen abstraction in intermediate II (i.e., R1 = CH3) followed by protodeauration of the resulting acyclic species IV.\(^\text{19}\) In consonance with this mechanistic proposal and the involvement of species of type II, we have found that the cycloaddition of Z-2b provides the same cycloadduct (Z-3ab) that is obtained from E-2b.\(^\text{18}\)

In summary, we have developed a new gold-catalyzed cycloaddition which involves allenamides and conjugate N,N-dialkyl hydrazones. The reaction provides densely substituted cyclobutanes in good yields with excellent levels of regio- and diastereoselectivity. To the best of our knowledge, this method constitutes the first transition-metal-catalyzed process in which this type of α,β-unsaturated hydrazones exhibits azaenamine vinylogous reactivity. Consequently, in just three simple steps, it is now possible to transform an enal into a highly substituted cyclobutane that incorporates a quaternary stereocenter.

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