Cascade Reactions

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Catalytic Generation and Selective Heterocoupling of Two Electron-Rich Alkenes**

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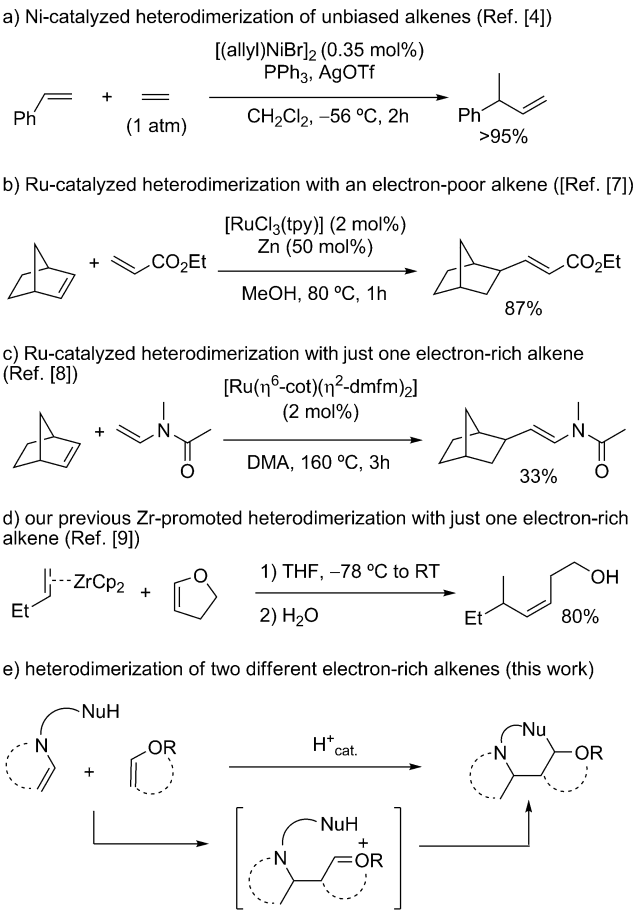
The heterocoupling of two different alkenes (heterodimerization) is a very attractive reaction to obtain elongated carbon chains from abundant and inexpensive starting materials through the formation of a new carbon–carbon bond.[1] In particular, the intramolecular version of this reaction, the cycloisomerization of dienes, has become a powerful method for the construction of carbo- and heterocyclic compounds.[2] A much more difficult process is the intermolecular carbon–carbon bond formation between two different olefinic molecules.[3] The limited success in this area is probably a result of the fact that homocoupling of each reaction partner and oligomerization reactions are much more favored than the desired heterodimerization. However, the Ni-catalyzed hydrovinylation of alkenes (i.e., the codimerization of alkenes with ethene), which has been known for a long time, is an example of this process (Scheme 1a).[4] This reaction has been widely studied and extended to its asymmetric version.[5] However, the main limitation of the process is related to its poor selectivity when alkenes different from ethene are codimerized with other alkenes.[6] Moreover, the heterocoupling of simple alkenes with electron-poor or electron-rich olefins is developed to a much lesser extent. Regarding the use of electron-poor alkenes, a ruthenium-catalyzed codimerization of 2-norbornenes with acrylic compounds has been reported (Scheme 1b).[7] Regarding the use of electron-rich olefins, a ruthenium-catalyzed codimerization of *N*-vinylamides and different alkenes has been described (Scheme 1c).[8] We have also contributed to this field by the development of a zirconium-promoted coupling of a simple alkene with an enol ether (Scheme 1d).[9] However, the heterocoupling of two different electron-rich alkenes is underdeveloped. Following our above-mentioned investigations in this area, we thus initiated a study on the heterodimerization of two electron-rich alkenes. Specifically, we became interested in the possibility of performing a cross-coupling reaction between *N*-alkenyl amine derivatives and enol ethers (Scheme 1e). Moreover, considering that these substrates are easily available through a cycloisomerization reaction of alkynamine and alkynol derivatives, our final objective was the transformation of these simple starting materials into structurally complex heterocyclic compounds through a double cycloisomerization/heterodimerization cascade reaction.



Scheme 1. Previously reported heterodimerizations and our approach. cot = 1,3,5-cyclooctatriene, Cp = cyclopentadienyl, dmfm = dimethyl fumarate, Tf = trifluoromethanesulfonyl, tpy = 2,2′:6′,2″-terpyridine.

We first focused on the heterocoupling reaction of enamine derivatives and enol ethers. We thought that the simplest way to catalytically activate these reagents was by a protic acid. This reaction should result in the formation of an iminium (or oxonium) intermediate, which would be attacked by the enol ether (or enamine), thus giving the corresponding cross-coupling product. However, this theoretically simple concept has several weaknesses and drawbacks, which probably prevented its earlier development. As both alkenes have a similar electronic nature, the acid may

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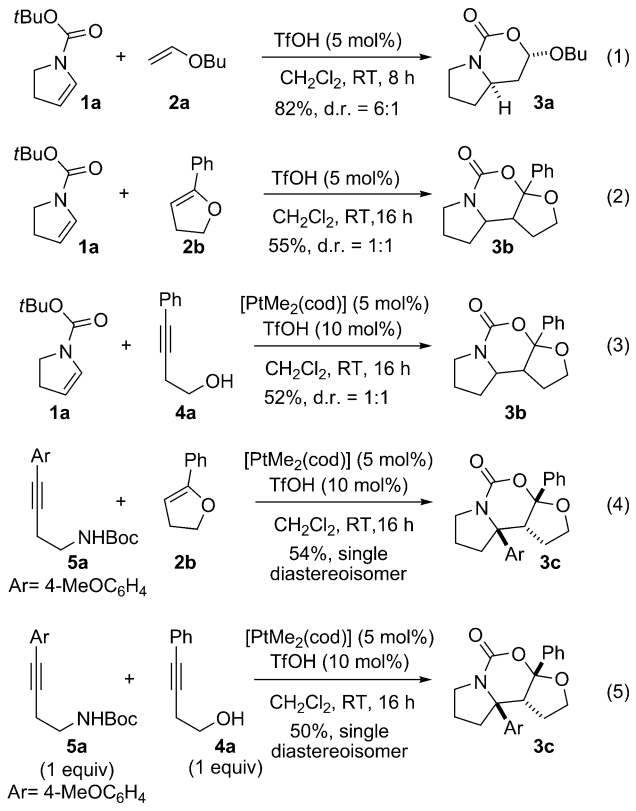
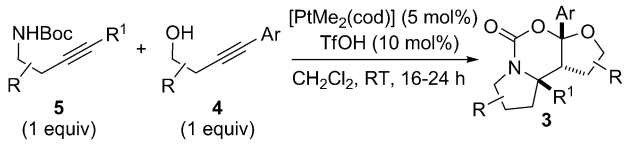
activate either one of them. Moreover, once the activation occurs, both substrates (enol ether and enamine) are nucleophiles and they could react with the activated intermediates (iminium or oxonium). All these obstacles could result in the formation of different products and also in undesired homocoupling processes. Considering that the initial activation by the acid is an equilibrium reaction, we believed that we might be able to control the process by installing another nucleophile in one of the reactants and thus, this nucleophile could trap some of the cationic intermediates that are formed (iminium or oxonium) through an irreversible process. In this context, the simplest way to install such nucleophilic group is through a nitrogen atom of the enamine. Moreover, the appropriate choice of this nucleophile would result in the recovery of a proton, thus rendering the process catalytic (Scheme 1e).

With all these considerations in mind, we initially proofed the concept by investigating the acid-catalyzed coupling of two commercially available starting materials, *tert*-butyl 2,3-dihydro-1*H*-pyrrole-1-carboxylate **1a** and butyl vinyl ether **2a** [Scheme 2, Eq. (1)]. Particularly, enamide **1a** was chosen because the *tert*-butyloxycarbonyl (Boc) group may act as a nucleophilic group through a process in which a molecule of isobutylene and a proton, which could initiate a new catalytic cycle, are released.[10] To our delight, when **1a** and **2a** were reacted in dichloromethane as solvent in the presence of triflic acid (TfOH, 5 mol%), we observed the clean transformation of the starting materials into the desired product **3a**, which was isolated in 82% yield (d.r. = 6:1). Under the same conditions, the reaction could also be performed with the cyclic enol ether **2b** [Scheme 2, Eq. (2)]. Although the yield of this reaction was not very high, the result was very encouraging for our purpose of performing the reaction as part of a cascade process that involves an initial cycloisomerization reaction of alkynamine and alkynol derivatives. To test the feasibility of this cascade reaction, we investigated the reaction of dihydropyrrole **1a** and alkynol **4a** [Scheme 2, Eq. (3)]. It should be noted that the cycloisomerization reaction of this alkynol **4a** should lead to the cyclic enol ether **2b**, and the cascade reaction should therefore give product **3b**. We thought that the combination of [$PtMe_2$(cod)] (cod = 1,5-cyclooctadiene) and TfOH would be ideal for our purpose. On the one hand, under protic conditions, the [$PtMe_2$(cod)] complex would be transformed into a highly reactive cationic platinum complex that is able to catalyze the transformation of **4a** to the cyclic enol ether **2b**. On the other hand, the remaining triflic acid would favor the heterodimerization reaction, as proved before [see Scheme 2, Eq. (2)]. As shown in the Equation (3) of Scheme 2, the reaction of **1a** with **4a** in the presence of [$PtMe_2$(cod)] (5 mol%) and TfOH (10 mol%) led to the formation of compound **3b** in a yield similar to that obtained with preformed cyclic enol ether **2b**. Next, we checked the possibility of generating in situ cyclic enamine derivatives similar to **1a** through a cycloisomerization reaction. For this purpose, we carried out the reaction of alkynamine derivative **5a** and preformed cyclic enol ether **2b** in the presence of [$PtMe_2$(cod)] and TfOH. This reaction led to the formation of compound **3c** in moderate yield (54%), but, interestingly, as a single diastereoisomer [Scheme 2, Eq. (4)]. Finally, we targeted the most challenging reaction, the double cycloisomerization/heterocyclization cascade process. Gratifyingly, when one equivalent of alkynamine derivative **5a** was reacted with one equivalent of alkynol **4a** in the presence of [$PtMe_2$(cod)] and TfOH, we were able to isolate the desired tricyclic product **3c** as a single diastereoisomer in 50% yield [Scheme 2, Eq. (5)]. This transformation is remarkable. In a single step and starting from two very simple acyclic compounds, a tricyclic product is formed in a process in which four new bonds and three stereocenters (two of them quaternary) are selectively created.

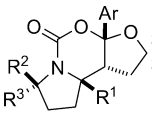


Scheme 2. Initial experiments.

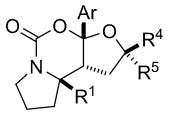
The scope of this new reaction was surveyed by probing changes to the alkynamine **5** and the alkynol **4**. A series of heterodimeric products **3** were synthesized, most of which were isolated in high yield and all as single diastereoisomers (Scheme 3). Notably, the reaction was performed with equimolar amounts of the reactants; the use of an excess of some of the reactants is not required. The flexibility of the method allows substituents at several positions of both the alkynamine derivative **5** and alkynol **4**. Regarding the alkynamine **5**, the reaction could be performed with aryl- (R^1 = aryl, **3a–w,z**) and alkyl-substituted alkynes (R^1 = methyl, **3x,y**). However, the reaction was not effective with terminal alkynes (R^1 = H). The best results were obtained with alkynol derivatives **4** that contain internal alkynes substituted with electron-rich aromatic rings. The yields were slightly lower (**3a**,**p**,**q**) with alkynol derivatives **4** that are substituted with a simple phenyl group, and we were not able to obtain the desired products with alkynol derivatives that were substi-



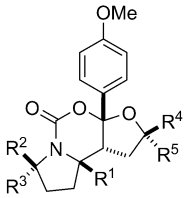
3d, R^1, Ar= 4-MeO-C_6H_4, 90%
3e, R^1= 4-Me-C_6H_4, Ar= 4-MeO-C_6H_4, 78%
3f, R^1= Ph, Ar= 4-MeO-C_6H_4, 80%
3g, R^1= 4-Cl-C_6H_4, Ar= 4-MeO-C_6H_4, 80%
3h, R^1= 4-Br-C_6H_4, Ar= 4-MeO-C_6H_4, 78%
3i, R^1= 4-MeO-C_6H_4, Ar= 4-Me-C_6H_4, 78% (1.7 g scale)
3j, R^1= Ph, Ar= 4-Me-C_6H_4, 70%
3k, R^1= 4-MeO-C_6H_4, Ar= 3-MeO-C_6H_4, 78%



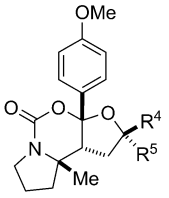
3l, R^1, Ar= 4-MeO-C_6H_4, R^2, R^3= -$(CH_2)_4$-, 68%
3m, R^1= 4-Me-C_6H_4, Ar= 4-MeO-C_6H_4, R^2, R^3= Me, 70%



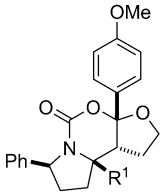
3n, R^1, Ar= 4-MeO-C_6H_4, R^4, R^5= -$(CH_2)_5$-, 68%
3o, R^1= 4-Me-C_6H_4, Ar= 4-MeO-C_6H_4, R^4, R^5= -$(CH_2)_5$-, 65%
3p, R^1= 4-MeO-C_6H_4, Ar= Ph, R^4, R^5= -$(CH_2)_5$-, 58%
3q, R^1= 4-Me-C_6H_4, Ar= Ph, R^4, R^5= -$(CH_2)_5$-, 55%
3r, R^1, Ar= 4-MeO-C_6H_4, R^4, R^5= -$(CH_2)_4$-, 72%
3s R^1= 4-Me-C_6H_4, Ar= 4-MeO-C_6H_4, R^4, R^5= -$(CH_2)_4$-, 70%
3t, R^1= 4-Ph-C_6H_4, Ar= 4-MeO-C_6H_4, R^4, R^5= -$(CH_2)_4$-, 66%



3u, R^1= 4-Me-C_6H_4, R^2, R^3= Me, R^4, R^5= -$(CH_2)_5$-, 68%
3v, R^1= 4-Me-C_6H_4, R^2, R^3= Me, R^4, R^5= -$(CH_2)_4$-, 69%
3w, R^1= 4-MeO-C_6H_4, R^2, R^3= -$(CH_2)_4$-, R^4, R^5= -$(CH_2)_5$-, 67%



3x, R^4, R^5= H, 92%
3y, R^4, R^5= -$(CH_2)_4$-, 90%

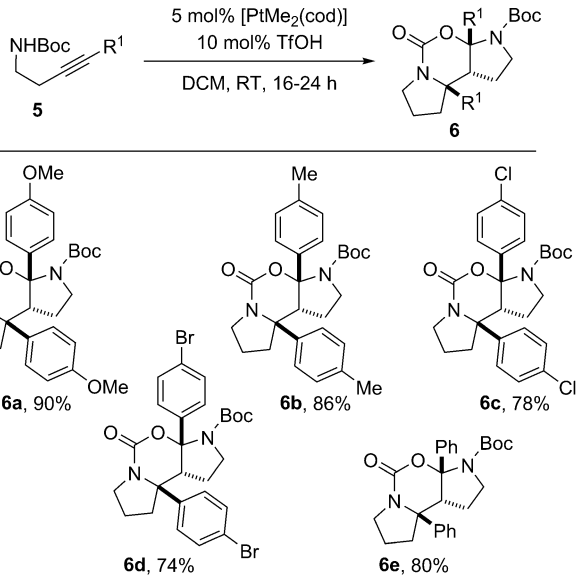


3z, R^1= 4-Me-C_6H_4, 88%

Scheme 3. Synthesis of heterocoupling products **3** from simple alkynamines **5** and alkynols **4**.

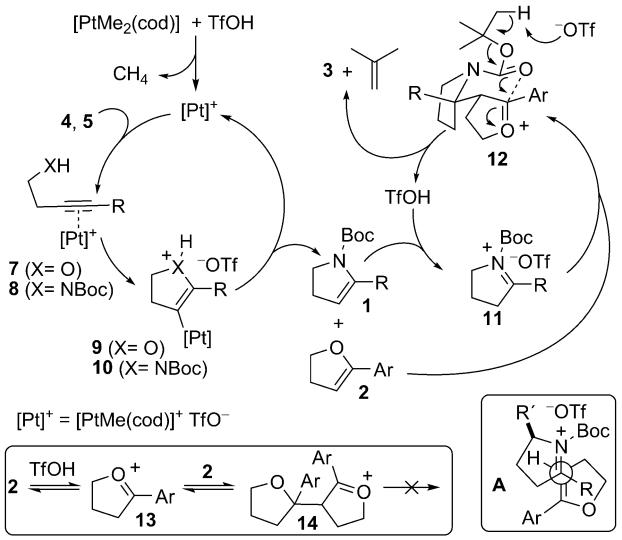
tuted with an alkyl group or with unsubstituted alkynols. The last example shown in Scheme 3 (compound **3z**) is particularly interesting. This product was obtained as a single diastereoisomer in very high yield using a chiral (racemic) starting material, the alkynamine derivative **5** that was substituted with a phenyl group at the carbon atom carrying the nitrogen atom. Thus, a product with four stereocenters was selectively obtained from a starting material with just one stereocenter. This result is significant because it indicates that it is possible to efficiently synthesize enantiomerically pure products **3** through a substrate-controlled process. Furthermore, we verified that the reaction can be performed on a gram scale by easily preparing 1.7 grams of **3i** in one batch without any problem. Structural assignments of all these new compounds were based on a series of NMR studies. Additionally, the structure of compound **3h** was confirmed by single-crystal X-ray diffraction analysis.[11]

It is important to remark that under the reaction conditions described above, we did not observe the formation of homocoupling products to an appreciable extent.[12] However, when the reaction was performed in the absence of an alkynol derivative **4**, homodimers **6**, which result from the reaction of two molecules of the corresponding alkynamine derivative **5**, were formed and isolated in high yield and as single diastereoisomers (Scheme 4). Again, structural assignments of these new homocoupling compounds were based on a series of NMR studies and confirmed by single-crystal X-ray diffraction analysis performed on compound **6b**.[11]



Scheme 4. Synthesis of homocoupling products **6** from simple alkynamines **5**.

A plausible mechanism for the formation of heterocoupling products **3** from alkynols **4** and alkynamines derivatives **5** is illustrated in Scheme 5. In first place, we suppose the formation of a reactive cationic platinum complex from [$PtMe_2$(cod)] by reaction with TfOH in a process in which a molecule of methane is released.[13] This cationic platinum complex promotes the cycloisomerization of both the enol ether **4** and alkynamine derivative **5**. These reactions are initiated by coordination of the metallic complex to the triple bond of **4** and **5** to form intermediates **7** and **8**, respectively. Intramolecular addition of the hydroxy group of **7** and the amino group of **8** to the distal carbon atom of the triple bond generates **9** and **10**, respectively. Further protodemetalation processes afford the enol ether **2** and enamine derivatives **1**, respectively, after the release of the catalytic species. Once enol ether **2** and enamine derivatives **1** are formed, they enter the second catalytic cycle. Thus, triflic acid promotes the



Scheme 5. Proposed mechanism for the formation of products **3** through a double cycloisomerization/heterodimerization cascade process.

formation of the iminium species **11**, which reacts with the preformed enol ether **2** to give the oxonium intermediate **12**. The observed stereochemical outcome of the reaction is consistent with model **A** (Scheme 5), in which the steric interactions are minimized. This model also justifies the substrate-directed formation of a single product, when a chiral starting alkynamine derivative **5** is used (product **3z**). Thus, in model **A**, the enol ether **2** approaches the corresponding iminium species **11** from the opposite face from where the R' substituent is placed. Once intermediate **12** is formed, we supposed a final cyclization step through a chair-like transition state that it is also consistent with the stereoselectivity observed in the final products **3**. In this model, the R and Ar groups are placed in a pseudoequatorial position. The situation of the oxygen atom of the oxonium ion in a pseudoaxial position may also be favored by an anomeric effect. This final cyclization would render the final products **3**, a molecule of isobutylene and a molecule of triflic acid, which initiates a new catalytic cycle.

As previously described, one of the most interesting features of the process described herein is the chemoselectivity (heterodimerization vs. homodimerization) that is observed when one equivalent of **5** and one equivalent of **4** are reacted with each other. Surprisingly, the exclusive formation of heterodimers **3** is observed. This result could be tentatively explained by the nucleophilicity of enamide and enol ether intermediates **1** and **2**, and also by considering that several equilibrium reactions could be involved when these two intermediates react in the presence of an acid. Although the nucleophilicity of **1** and **2** should not be so different,[14] we suppose that enol ether **2** is a better nucleophile.[15] Thus, in the presence of triflic acid, enol ether **2** should be in equilibrium with oxonium species **13**, which in the presence of another molecule of **2** (the best nucleophile in the reaction media) should be in equilibrium with dimer **14**. We believe that these species **14** do not evolve further because of the absence of any terminating group that is able to trap the formed oxonium species. Thus, these equilibrium reactions are a nonproductive process. Although probably less favorable, an alternative pathway implies the protonation of enamide derivatives **1** to give intermediate **12** in small equilibrium concentrations through iminium species **11**. The presence of the Boc group in intermediate **12** seems crucial, because it serves as a terminating group that traps oxonium species **12** through an irreversible step and makes the global reaction a productive process. The absence of homodimerization products when the reaction is performed in the presence of alkynol derivatives **4** (Scheme 3) seems to be due to the higher nucleophilicity of enol ether **2** compared with enamide derivative **1**. The experimental results corroborate that once iminium species **11** are formed, nucleophilic addition of enol ethers **2** is preferred over the alternative addition of enamide derivatives **1**.

In summary, we have developed a new catalytic cascade reaction for the synthesis of complex heterocyclic products from simple alkynamine and alkynol derivatives. This new double cycloisomerization/heterodimerization cascade reaction includes an unprecedented heterocoupling reaction of two different electron-rich alkenes. Notably, the global transformation includes the formation of a tricyclic product from two simple acyclic starting materials in a process in which four new bonds and three stereogenic centers (two of them quaternary) are created in a stereocontrolled fashion. We believe that the high complexity generated in this one-step reaction could be exploited in diversity-oriented syntheses. Further application of this reaction in natural product synthesis is also considered.

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