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Product Selectivity Control in the Heteroannulation of *o*-(1-Alkynyl)benzamides

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Abstract: The selective synthesis of (*Z*)- or (*E*)-3-aryl/vinyl/alkylidene-isoindolones, and 2-benzopyran derivatives from *o*-(1-alkynyl)benzamides by means of a suitable choice of bases or silver catalysis is described.

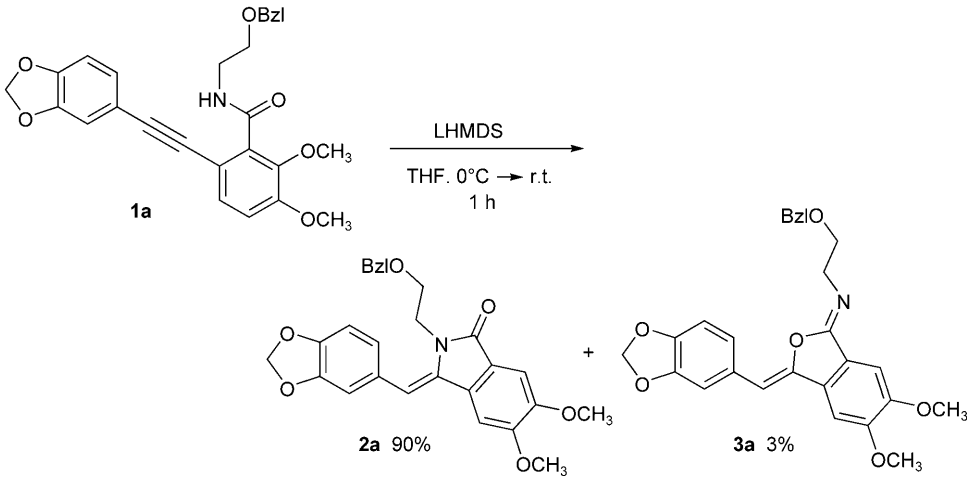
Keywords: *o*-(1-alkynyl)benzamides; chemoselectivity; cyclizations; regioselectivity; silver

Introduction

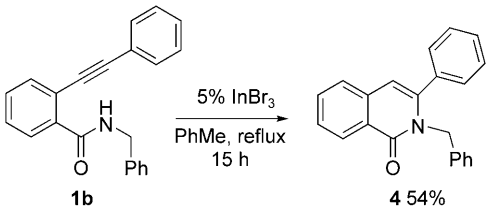
The selective synthesis of different products from the same starting materials by simple modification of the reaction conditions is an attractive challenge for chemists.[1] The amide functional group contains two nucleophilic positions: the oxygen and the nitrogen atoms. So, when a cyclization of products containing such functional group is performed different compounds may be obtained depending on which atom acts as nucleophile. *o*-(1-Alkynyl)benzamides **1** were cyclised with NaOEt in EtOH to give as major products the corresponding (*Z*)-3-aryl(alkyl)idene-isoindolones **2** by a 5-*exo*-dig process.[2] Similarly, CuI/L-proline-catalyzed coupling of 2-bromobenzamides and terminal alkynes in *i*-PrOH (or DMF and DMSO) at 85–110 °C and subsequent additive cyclization produced regioselectively the derivatives **2** and it was found that in most cases only Z-isomers were determined.[3] Moreover, the intramolecular cyclization of *o*-(1-alkynyl)benzamide derivatives by Et_3N in the presence of Ag_2CO_3 was shown to afford a mixture of **2** and iminolactone **3** (1:1), but when conducted with LHDMS in THF, the (*Z*)-3-aryl(alkyl)idene-isoindolone was obtained predominantly. Indeed the intramolecular cyclization of alkynylamide **1a** under these latter conditions was reported as the key step for the synthesis of lennoxamine, a rare alkaloid containing an isoindolo[2,1-*b*][3]benzazepine ring system (Scheme 1). Then, a general method for the base-catalyzed intramolecular cyclization of β-alkynylpropanamides to (*Z*)-γ-alkylidene-γ-butyrolactones in the presence of a catalytic amount of LHDMS/AgOTf (=2:1) was established.[5]

The 6-*endo-dig* annulation reaction leading to the formation of the isoquinolone derivatives was only observed in a few cases as a minor pathway under basic conditions, but the cyclization of *N*-benzyl-2-phenylethynylbenzamide **1b** led solely to the formation of the corresponding 2-benzyl-3-phenyl-2*H*-isoquinolin-1-one[6] **4** in 54% yield *via* an indium-catalyzed *endo-dig* cyclization process (Scheme 2). The intramolecular cyclization of derivatives **1** with different electrophiles (ICl, I_2, NBS, PhSeCl and *p*-$O_2NC_6H_4SCl$) was also studied.[7] The effect of ICl and I_2 on the regiochemistry of the ring closure of several different amide moieties was examined. Although the results varied with the nature of the substituents on the nitrogen and of the alkyne, I_2 afforded the five-membered ring lactam as the major isomer, while ICl produced the six-membered ring lactam. A mixture of the five- and six-membered lactams was always observed.

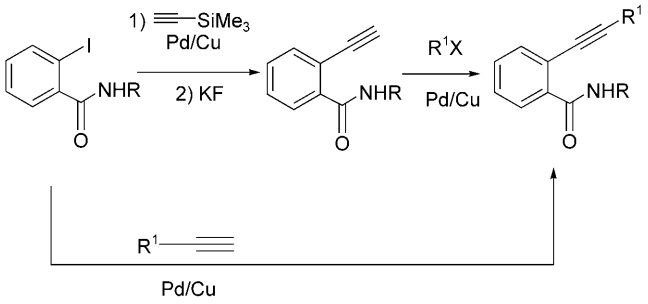
The strategy for intramolecular nitrogen heterocyclic ring formation has been also reported for synthesizing seven-membered ring analogues.[8] The synthe-



Scheme 1.



Scheme 2.



Scheme 3.

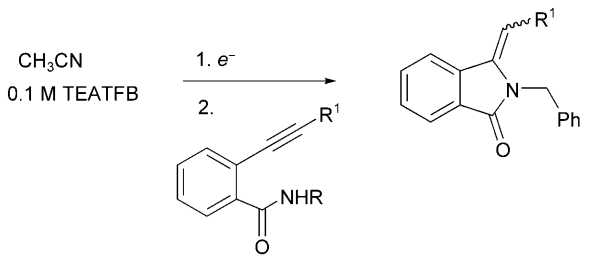
sis of 3-benzazepinones was reported to occur by the palladium-catalyzed intramolecular addition of amides to alkynes. The potential regioselectivity of such a transformation was examined. When the tethered group was an acetamide and an alkyl substituent was on the acetylene unit, a regioselective 3-benzazepinone synthesis has been achieved in good yields. On the other hand, heating phenylethynylbenzeneacetamide gave the *6-exo* cyclization product, the 3-isoquinolinone derivative. The formation of the *6-exo* cyclization product supports the assumption that the cyclization is oriented by the acetylene substrate. Very recently, an efficient cyclization of *o*-(1-alkynyl)benzamides **1** to give (1*H*)-isochromen-1-imines **5** through a silver(I)-promoted regiocontrolled intramolecular addition of the carbonyl group of the amide moiety on the carbon-carbon triple bond has been developed.[9]

As a continuation of our interest in the exploration of novel synthetic strategies for the construction of heterocycles from alkynes containing proximate nucleophiles,[10] we wish to report in this paper the results of our investigation directed to product selectivity control in the heteroannulation of derivatives **1**.

Results and Discussion

The *o*-(1-alkynyl)benzamides **1** required are readily synthesized by standard procedures (Scheme 3).[7,11] Initially, we tested the cyclization pattern of *o*-(1-alkynyl)benzamides **1** induced by electrogenerated bases (EGBs) (procedure A).[12] In particular, the electrochemically generated cyanomethyl anion ($^{-}CH_2CN$) has proved to be a effective base in a large number of organic reactions.[13] Electrochemical technology[14] represents a valuable alternative to the classical methodologies usually employed in the synthesis of fine chemicals.[15] We thought that cyclization of **1** induced by the electrogenerated cyanomethyl anion under milder reactions conditions than those previously described[2,3] should represent an improvement in terms of the product selectivity control.

The cyclization reaction of **1** was carried out using CH_3CN/0.1 M tetraethylammonium tetrafluoroborate (TEATFB) solutions as the solvent-supporting electrolyte system in a divided electrochemical cell equipped with platinum electrodes, under galvanostatic control ($J = 25.0\ mA \cdot cm^{-2}$) at 0 °C. The *o*-(1-alkynyl)benzamide derivative **1** was added just at the end of the electrolysis (Scheme 4).



Scheme 4.

In this way, molecules with potentially reducible functional groups can be used without problems. In order to obtain the best results an amount of current of $Q = 2.0$ F·mol^{-1} (referred to **1**) was used. A variety of derivatives **1** readily underwent chemo- and stereoselective 5-*exo-dig* cyclization. The results obtained are reported in Table 1. The methodology is quite general and can accommodate a considerable range of functionality. We examined the effect of substituents on the alkyne moiety. Aryl-substituted *o*-(1-alkynyl)benzamides bearing both electron-donating and electron-withdrawing groups on the aromatic ring afford similar results. Interestingly, by contrast with the results observed in the iodocyclization of vinyl-substituted *o*-(1-alkynyl)benzamides leading to the six-membered ring isoquinolone derivative as the major product,[7] the cyclization of derivatives **1g–h** (Table 1, entries 13 and 14) took place in a 5-*exo* manner exclusively. For the stereochemistry of the present transformation, it was found that only (*Z*)-isomers were determined by starting from aryl/vinyl-substituted *o*-(1-alkynyl)benzamides. The geometry was established *via* NOE difference experiment studies and by comparison of the analytical data with known compounds. (*E*)-Isomer **2i′** was isolated as a major product in the cyclization induced by cyanomethyl anion of the aliphatic derivative **1i** (Table 1, entry 15). It is worthy of note that only the formation of the (*Z*)-isomer has been observed in the CuI-mediated additive cyclization of the amide moiety to the triple bond of *o*-(1-alkynyl)benzamides.[3] Moreover a mixture of the (*Z*)-3-alkylidene-isoindol-1-one and the corresponding isoquinolone derivative has been isolated by treatment of *o*-(1-alkylethynyl)benzamides with NaOEt.[2] Since the mechanistic proposal supports the concept of an *anti* hydroamination over the triple bond to produce (*Z*)-derivatives **2** the question arises as to how (*E*) isomer **2i′** is produced. Control experiments argue in favour of the view that the (*E*) isomer **2i′** is generated through a thermal isomerization of the product arising from the *anti* addiction formed initially under the reaction conditions. Indeed, the formation of only the (*Z*)-**2i** was observed on carrying out the cyclization induced by the electrogenerated base at −20 °C for 0.1 h. In addition, a 60:40 (*E*)/(*Z*) ratio was observed on prolonging the reaction time to 2 h at 0 °C and monitoring the reaction at intervals. Only the presence of (*E*)-**2i′** was detected after 1 h a 20 °C (reactions were monitored by GC/MS). These data clearly point out the ease with which the addition product **2i** undergoes a *Z*/*E* isomerization under the cyclization of *o*-(1-alkynyl)benzamide **1i** induced by electrogenerated base and suggests that the observed stereochemistry is dependent on the relative thermodynamic stabilities of the *Z* and *E* derivatives. The scope of the cyclization of **1** induced by electrogenerated bases was further extended by replacing the *N*-alkyl substituent with an *N*-aryl group (Table, entry 20). For comparative reasons we also explored the cyclization reaction of derivatives **1** promoted by *t*-BuONa in DMF (procedure B). The cyclization with *t*-BuONa applied to substrates **1** revealed a dramatic substituent effect on the regioselective outcome of the reaction. Compounds **1c** and **1d** underwent a 5-*exo-dig* cyclization to give the corresponding (*E*)-3-alkylidene-isoindol-1-ones **2c′** and **2d′** as the only reaction products (Table 1, entries 4 and 7), whereas **1e** and **1k** led to the (*Z*)-3-alkylidene-isoindol-1-one derivatives **2e** and **2k** (Table 1, entries 10 and 21). Moreover, on the basis of the previously reported observations on the role of acids or bases[16] and silver or gold catalysts[17] in promoting the regiocontrolled intramolecular cyclizations of carboxylic acids to carbon-carbon triple bonds, we focused our attention on the role of AgOTf as catalyst in promoting a different cyclization mode of **1** in the absence of any added base (procedure C). Under these latter conditions the formation of the 2-benzopyran derivatives **5b–f** and **5k** occurred in 1,2-dichloroethane at room temperature in the presence of 5 mol% of the catalyst[18] in all the cases examined except with the trimethylsilyl derivative **1j** which afforded the same derivative **2j** under the conditions of both the procedures B and C. Very likely, under the conditions of procedure C, a silver(I)-catalyzed protiodesilylation[19] of 1-(trimethylsilyl)-1-alkynes **1j** is faster than the silver (I)-catalyzed cyclization. The derivatives **5** are prone to undergo hydrolysis to give the corresponding lactones **6**. The 3-(4-chlorophenyl)-2-benzopyran-1-one **6e** has been isolated directly in a one-pot reaction in 84% yield by prolonging the reaction time (Table 1, entry 11). The hydrolysis of **5i** to **6i** occurred during the work-up of the final reaction mixture (determined by GC/MS analysis) (Table 1, entry 17).

A plausible rationale for the product selectivity control in the cyclization of *o*-(1-alkynyl)benzamides **1** can be suggested. When the hydroamidation of the C-C triple bond is achieved by using strong bases which would directly deprotonate the amide, according to previous theoretical work,[16] the electronic bias on both carbons of the triple bonds favours *5-exo* cyc-

Table 1. Cyclization reactions of *o*-(1-alkynyl)benzamides **1**.

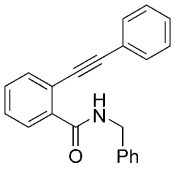
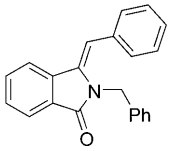
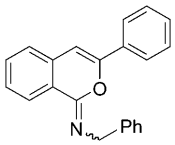
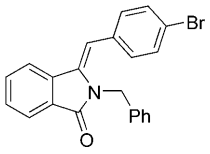
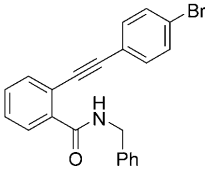
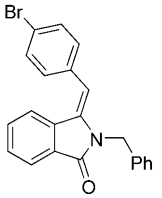
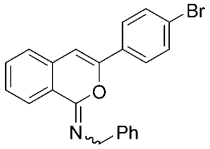
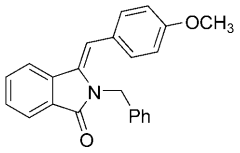
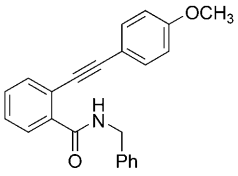
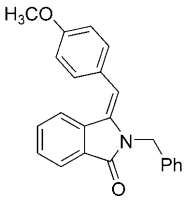
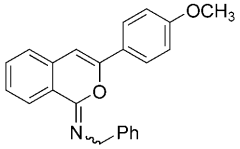
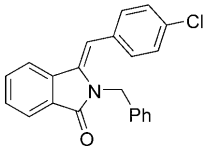
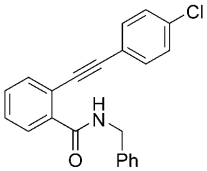
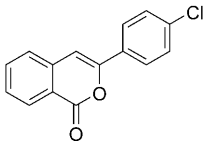
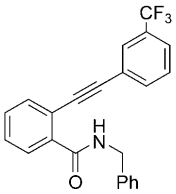
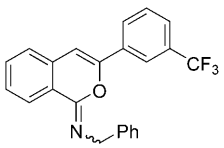
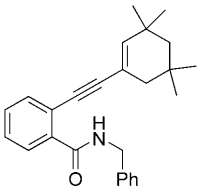
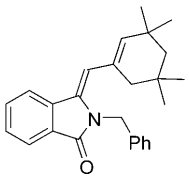
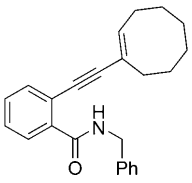
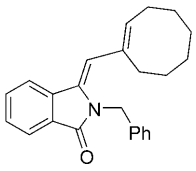
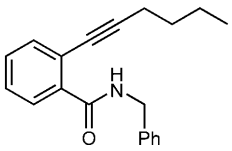
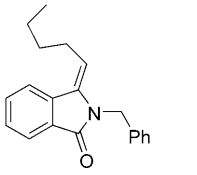
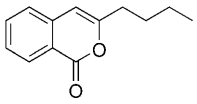
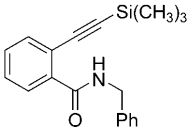
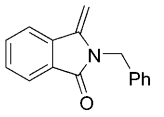
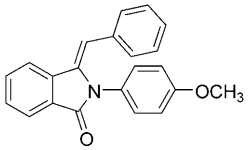
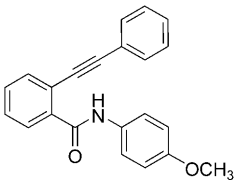
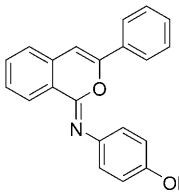
Entry	*o*-(1-Alkynyl)benzamide **1**	Conditions[a]	Time [h]	Product	Yield [%][b]
1	**1b** 	A	0.1	**2b** 	89
2	**1b**	C	1	**5b** 	84
3	**1c**	A	0.1	**2c** 	84
4	**1c** 	B	1	**2c'** 	82
5	**1c**	C	1.5	**5c** 	81
6	**1d**	A	0.1	**2d** 	78
7	**1d** 	B	0.5	**2d'** 	89
8	**1d**	C	24	**5d** 	74
9	**1e**	A	0.1	**2e**	92
10	**1e**	B	0.5	**2e** 	73
11	**1e** 	C	48	**6e** 	84

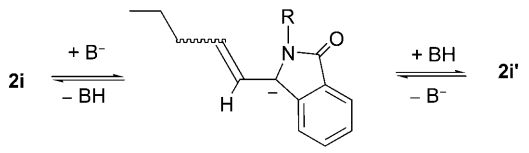
Table 1. (Continued)

Entry	*o*-(1-Alkynyl)benzamide **1**	Conditions[a]	Time [h]	Product	Yield [%][b]
12	**1f** 	C	4	**5f** 	83
13	**1g** 	A	0.1	**2g** 	94
14	**1h** 	A	0.1	**2h** 	92
15	**1i**	A	0.1	**2i′**	78
16	**1i** 	B	2	**2i'** 	76
17	**1i**	C	9	**6i** 	94
18	**1j**	B	0.5	**2j**	67
19	**1j** 	C	48	**2j** 	64
20	**1k**	A	0.1	**2k**	75
21	**1k**	B	0.5	**2k** 	83
22	**1k** 	C	1	**5k** 	92

[a] *Conditions A*: *o*-(1-alkynyl)benzamides **1** (0.025–0.5 mmol) were added at the end of the electrolysis. The electrolyses were carried out in CH_3CN 0.1 M TEATFB solutions (5.0 mL) at 0 °C in a divided cell equipped with platinum electrodes. An amount of current of 2.0 F·mol^{-1} [referred to the *o*-(1-alkynyl)benzamides **1**] was used ($J = 30$ mA cm^{-2}); reaction temperature: 20 °C; reaction time 0.1 h. *Conditions B*: The reaction was carried out in DMF at room temperature under the presence of *t*-BuONa; **1**:*t*-BuONa = 1:1. *Conditions C*: The reaction was carried out in 1,2-dichloethane at room temperature in the presence of AgOTf; **1**:AgOTf = 1:0.05.

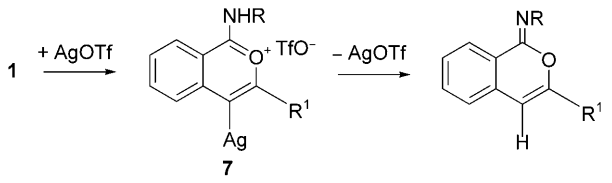
[b] Yields refer to single non-optimized runs, and are given for pure isolated products.

lization to give (*Z*)-3-aryl(alkyl)idene-isoindolone **2**. Moreover, the isomerization of the (*Z*)-3-alkylidene-isoindolone **2i** to the (*E*)-3-alkylidene-isoindolone **2i′** can be claimed under the strong basic conditions of both procedures A and B (Scheme 5). Under the conditions of procedure B the substrate dependence of the deprotonation step might determine the stereoselective outcome of the cyclization process.



Scheme 5.

On the other hand, silver(I) catalysis has been extensively studied on the cyclization reaction of a broad range of *ortho*-substituted ethynylbenzene derivatives.[20] An efficient Ag(I)-catalyzed regioselective cyclization reaction of *ortho*-alkynylaryl aldehyde oxime derivatives leading to isoquinolines or isoquinolin-1(2*H*)-ones as a consequence of subtle structure modification of the starting substrate has been investigated.[20b] Diversity in silver catalysis has been reported for the tandem process of acetalization and cycloisomerization reactions of 1-alkynyl-2-carbonylquinoline substrates. AgOTf allowed an efficient transformation to the *6-endo-dig* products. With Ag_2CO_3, the selectivity was reversed since the only compound detected was the *5-exo-dig* derivative.[20h] Diversity in gold- and silver-catalyzed cycloisomerization of epoxide-alkyne functionalties has been also studied.[20c] From the results shown in Table 1, the Ag-catalyzed cyclization of **1** showed very high regio- and chemoselectivity. Only the six-membered-ring 2-benzopyran derivative derived from *6-endo-dig* annulation was obtained and no six-membered 2*H*-isoquinolin-1-ones nor five-membered exocyclic products were detected. On the base of the above results, we propose the following mechanism for the silver-catalyzed process (Scheme 6): the oxygen atom undergoes regioselective



Scheme 6.

attack at the silver-coordinated triple bond *via 6-endo-dig* cyclization to the intermediate **7**; the organosilver intermediate regenerates the catalyst, which enters the next cycle and affords the 2-benzopyran derivative after rearrangement and proton shuttle *via* TfOH. It is worth noting the peculiar properties of silver compared to those of indium[6] which led to 2*H*-isoquinolin-1-ones **4** through a chemo-divergent *endo-dig* cyclization.

Conclusions

In summary, we have described the selective synthesis of different heterocycles from the same starting materials *o*-(1-alkynyl)benzamides by simple modification of the reaction conditions. The electrochemically generated cyanomethyl anion has proved to be effective to promote their chemo- and stereo-*5-exo-dig* cyclization to (*Z*)-3-aryl-/vinylidene-isoindolones. The *5-exo-dig* cyclization promoted by *t*-BuONa of the same starting materials to give the (*E*)-3-arylideneisoindolone derivative resulted from adramatic influence by the substrate features. The isomerization of the (*Z*)-3-alkylideneisoindolone to the corresponding (*E*)-isomer can occur both under electrochemical and strong basic conditions. Silver catalysis directs the cyclization in a regiodivergent *6-endo-dig* annulation to give six-membered ring 2-benzopyran derivatives. The tolerance of AgOTf (5 mol%) in 1,2-dichloroethane at room temperature is remarkable, and substrates with *N*-alkyl or *N*-aryl substituents gave high yields.

Experimental Section

Typical Procedure for the Cyclization of *o*-(1-Alkynyl)benzamides 1

Synthesis of **2c** *under conditions A:* A solution (5.0 mL) of CH_3CN/0.1 M TEATFB was electrolyzed under galvanostatic control (Pt cathode, 1.5 cm^2, $J = 25.0\ mA \cdot cm^{-2}$, $Q = 2.0\ F \cdot mol^{-1}$ referred to the amide) at 0 °C under an argon atmosphere [electrolyses were carried out in a divided glass cell separated through a G3-glass diaphragm fitted with an agar gel (methyl cellulose 0.5% vol dissolved in 1 M TEATFB/DMF solution) equipped with platinum electrodes]. At the end of the electrolysis, the cathodic solution was transferred into a previously flame-dried flask equipped with a cooling system, containing the *o*-(1-alkynyl)benzamide **1c** (0.1 g, 0.25 mmol). The reaction mixture was stirred at 20 °C for 0.1 h, then the solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography on silica gel (hexane:EtOAc = 90: 10) to afford **2c**; yield: 84.0 mg (84%).

Synthesis of **2c′** *under conditions B*: To a solution of **1c** (0.1 g, 0.25 mmol) in 2 mL DMF was added *t*-BuONa (25,0 mg, 0.25 mmol) under a nitrogen protection, the mixture was stirred at room temperature and the reaction was complete after 1 h as was determined by TLC and GC/MS analysis. 15 mL of water were added and the mixture was extracted by Et_2O three times. The combined organic layers were washed with saturated brine solution and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 90: 10) to afford **2c′**; yield: 82.0 mg (82%).

Synthesis of **5c** *under conditions C*: To a solution of **1c** (0.1 g, 0.25 mmol) in 2 mL 1,2-dichloroethane was added AgOTf (3.3 mg, 0. 013 mmol). The mixture was stirred at room temperature and the reaction was complete after 1.5 h as was determined by TLC and GC/MS analysis. The solvent

was evaporated under reduced pressure and the crude mixture was filtered through a silica gel pad. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 90: 10) to afford **5c**; yield: 81.0 mg (81%).

Supporting Information

Experimental details and copies of $^{1}H/^{13}C$ NMR spectra of all new compounds are available as supporting information.

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