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Lewis Acid-Catalyzed or Base-Promoted Regioselective Cycloisomerization of *N*-Imidoyl-*o*-alkynylanilines for Synthesis of *N*-Imidoyl-(1*H*)-indoles and 4-Alkylidene-3,4-dihydroquinazolines

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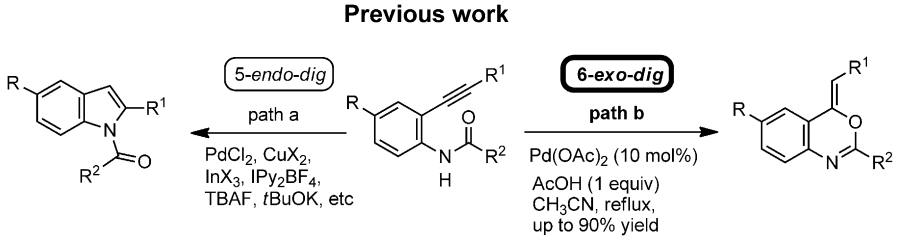
Abstract: Product selectivity control for the synthesis of imidoylindoles and 4-alkylidenedihydroquinazolines from *N*-imidoyl-*o*-alkynylanilines via silver triflate-catalyzed cycloisomerization or tetrabutylammonium fluoride-promoted cyclization is described. The product selectivity depends mainly on the catalyst/promoter used, and on the substituents on the alkyne and amidine functions of the substrates.

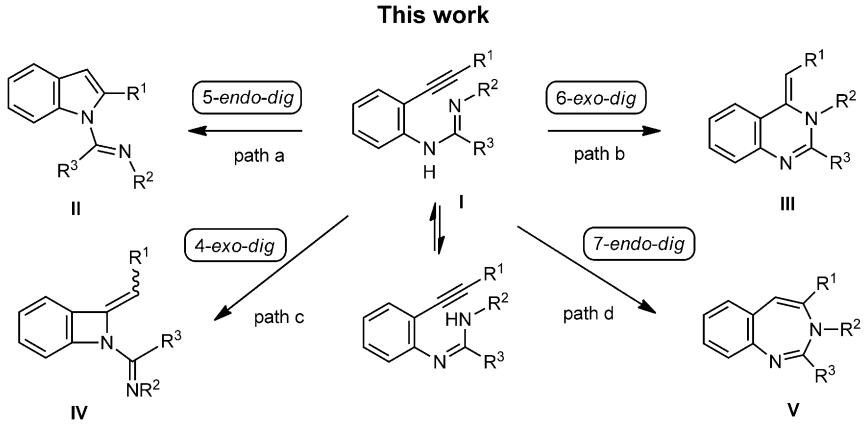
Keywords: cyclization; heterocycles; indoles; quinazolines; selectivity

Introduction

The development of methodologies for highly selective synthesis of different products from the same compounds by simple modification of catalysts, promoters, additives, and/or reaction conditions is a highly attractive and challenging task.[1] Among recent atom-economical methods for the synthesis of carbo- and heterocycles, transition metal- or Lewis acid- or base-mediated transformations of unsaturated species such as alkynes and alkenes reacting with an available nucleophilic function are powerful and attractive tools.[2] In these cases, substrates often bear both multiple bond-forming reaction sites and ambident nucleophilic centers in the same molecule, and hence control of regioselectivity and stereoselectivity if present in the processes is very important for the effective synthesis of desired products. In this context, we recently reported palladium-catalyzed highly regio- and stereoselective synthesis of (*Z*)-4-alkylidene-4*H*-3,1-benzoxazines from *N*-acyl-2-alkynylanilines (Scheme 1, path b).[3] This benzoxazine formation via the 6-*exo-dig* mode of cyclization by O-attack is still very rare and scarcely known,[4,5] but this cyclization bias was effectively controlled by use of $Pd(OAc)_2$ catalyst[3,6] together with acetic acid in pref-



Scheme 1. Catalyst-dependent, highly regio- and stereoselective cyclization modes.



Scheme 2. Four possible cycloisomerization modes of *N*-imidoyl-2-alkynylanilines **I**.

erence to the 5-*endo-dig* mode of cyclization by N-attack leading to the usual formation of indoles (Scheme 1, path a), for which a vast number of examples using a variety of catalysts has been reported.[6–8]

In continuation of our interest in exploring product selectivity associated with such cyclization modes, we aimed to examine experimentally Lewis acid- or base-promoted cycloisomerization of *N*-imidoyl-2-alkynylanilines (**I**) bearing various common substituents, such as alkyl and aryl groups at R^1, R^2, and R^3.[9] Scheme 2 illustrates four possible cyclization modes of **I** leading to indoles (**II**) via the 5-*endo-dig* mode (path a), 3,4-dihydroquinazolines (**III**) via the 6-*exo-dig* mode (path b), benzazetidines (**IV**) via the 4-*exo-dig* mode[10] (path c), and 3*H*-benzo[*d*][1,3]diazepines (**V**) via the 7-*endo-dig* mode (path d). What controls these cycloisomerization modes? In this paper we report our results on the product selectivity for cycloisomerizations of the simple substrate system **I**.

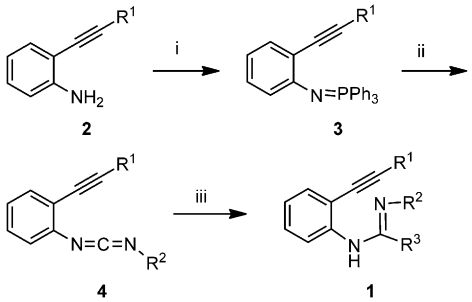
Results and Discussion

Preparation of *N*-imidoyl-2-alkynylanilines 1

N-imidoyl-2-alkynylanilines **1** were prepared according to the reactions from 2-alkynylanilines **2** as illustrated in Scheme 3 (see Supporting Information).

Lewis acid-catalyzed cyclization of *N*-imidoyl-2-alkynylanilines (1)

First, screening of Lewis acids was performed using substrates **1a** (R^1 = 4-Tol, R^2 = R^3 = Ph), **1b** (R^1 = 4-Tol, R^2 = *n*Pr, R^3 = Ph), and **1j** (R^1 = *t*Bu, R^2 = *n*Pr, R^3 = Ph) as model compounds. The reactions were carried out in the presence of various 10 mol% catalysts under the reaction conditions (solvent, temperature, and reaction time) listed. Representative results

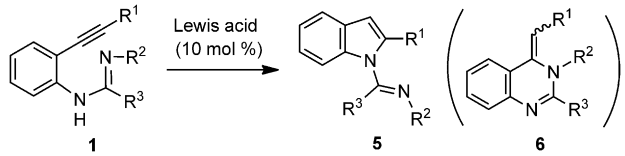


Scheme 3. (i) Ph_3P/C_2Cl_6, CH_2Cl_2, r.t.; (ii) R^2-NCO, CH_2Cl_2, r.t.; (iii) R^3-MgBr, THF, 0 °C → r.t.

are shown in Table 1. From the data, the following can be deduced in general: (1) In all of the cases, cycloisomerization products were the indole derivatives (**5a**, **5b**, and **5j**) without any other cyclized product(s), such as quinazolines **6**; (2) The relative reactivity of **1** for the reaction in the presence of the same Lewis acid depended mainly on the properties and positions of the substituents (R^1, R^2, and R^3); (3) silver triflate (AgOTf) was among the most effective catalysts for the cycloisomerization leading to *N*-imidoylindoles **5** (entries 6, 13, and 19).

With the best Lewis acid, AgOTf, in hand for the representative model substrates (**1a**, **1b**, and **1j**), we performed the reaction in the presence of 10 mol% AgOTf using substrates **1** with a variety of substituents in combinations of aryl and alkyl groups at R^1, R^2, and R^3. The results are shown in Table 2. The data suggest the following: (1) on the whole, indoles **5** were produced highly regioselectively, and only in the cases of **1c**, **1e** and **1h** were minor cyclization products **6c**, **6e** and **6h** observed (**6c**: 19%, **6e**: 44% and **6h**: 46% yield) (entries 3, 5 and 8). Comparison of entries **6–8** suggests that electronic effects of the substituent on R^1 also affect the selectivity for the cyclization; (2) the indoles **5** would be formed via the conceivable Ag–alkyne complex species (Figure 1, **A** and

Table 1. Screening of Lewis acids for cycloisomerization.



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Entry	Lewis acid	Solvent	Temp./time [h]	Yield
For **1a**: R^1=4-Tol, R^2=R^3=Ph				
1	$ZnCl_2$	toluene	r.t./90	87
2	$In(OTf)_3$	$(CH_2Cl)_2$	reflux/19	57[a]
3	$Cu(OTf)_2$	CH_2Cl_2	r.t./27	27[a]
4	$[Rh(cod)Cl]_2$	CH_2Cl_2	reflux/2	64
5	$Pd(OAc)_2$	CH_2Cl_2	r.t./7	87
6	AgOTf	CH_2Cl_2	r.t./0.7	99
For **1b**: R^1=4-Tol, R^2=*n*Pr, R^3=Ph				
7	Me_3SiOTf	CH_2Cl_2	r.t./72	57
8	$In(OTf)_3$	CH_2Cl_2	r.t./26	44
9	$Yb(OTf)_3$	CH_2Cl_2	r.t./70	14[a]
10	$Cu(OTf)_2$	CH_2Cl_2	r.t./96	43
11	$[Rh(cod)Cl]_2$	CH_2Cl_2	r.t./0.5	82
12	$Pd(OAc)_2$	CH_2Cl_2	r.t./1	53
13	AgOTf	CH_2Cl_2	r.t./0.5	93
For **1j**: R^1=*t*Bu, R^2=*n*Pr, R^3=Ph				
14	$ZnCl_2$	CH_2Cl_2	r.t./72	NR[b]
15	$In(OTf)_3$	toluene	r.t./24	NR[b]
16	$Cu(OTf)_2$	CH_2Cl_2	r.t./32	NR[b]
17	$[Rh(cod)Cl]_2$	CH_2Cl_2	reflux/12	NR[b]
18	AgOTf	CH_2Cl_2	r.t./24	65
19	AgOTf	$(CH_2Cl)_2$	reflux/3	94

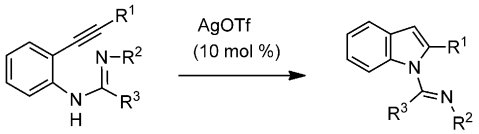
[a] Considerable amounts of **1** were recovered.
[b] Almost no reaction.

B; LUMO-umpolung[11]) in the stereoelectronically favorable 5-*endo-dig* cyclization mode (path a). The bent structure of the complex B would be advantageous for the 5-*endo* mode of cyclization with proximity for the N^1-nucleophilic attack (path a).

Interestingly, the 6-*exo-dig* mode of cyclization was observed in the AgOTf-catalyzed reaction when substrates **1y–β** (R^1=H) were employed (Table 3). Actually, 4-methylenequinazolines **6y–β** were exclusively formed. This observation is consistent with the view that substrate **1** with R^1=H prefers the 6-*exo-dig* mode of cyclization via π-complex **A** and σ-complex **C** with an *exo*-oriented form easily leading to **6** (path b), because of the less steric hindrance with H and the greater stabilization energy gain resulting from the benzylic carbocation present in the structure **C**[12] rather than the other terminal less stabilized carbocation with R^1=H.

It is worth comparing our results with those of other related work.[9] Medio-Simón et al.[9a] reported a mechanistic study on the cyclization that cationic $[IPrAu]SbF_6$ catalyst promoted 6-*exo-dig* mode cyclization to form quinazolin-2-one, whereas $[tBu_3PAu]SbF_6$ catalyst favored indole formation. Unfortunately, the results arose from the reaction of only one terminal alkyne substrate (R^1=H) bearing a urea nucleophile without any variation of substituents (Scheme 4, eq. (1)).[9a] In contrast, gold(AuCl)-catalyzed reactions of pyrazinone-bearing substrates afforded indoles, whereas the silver(AgOTf)-catalyzed reaction preferentially produced quinazoline derivatives (eq. (2)).[9b] Similar to the above AuCl-catalyzed reaction in eq. (2), the gold($NaAuCl_4$)-catalyzed reac-

Table 2. Silver triflate-catalyzed cycloisomerization of **1** to give *N*-imidoylindoles **5**.



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Entry	**1**, **5**	R^1	R^2	R^3	Solvent	Temp./Time [h]	Yield [%]
1	**a**	4-Tol	Ph	Ph	CH_2Cl_2	r.t./0.7	99
2	**b**	4-Tol	*n*Pr	Ph	CH_2Cl_2	r.t./0.5	93
3	**c**	4-Tol	Ph	Et	CH_2Cl_2	r.t./2	68[a]
4	**d**	4-Tol	*n*Pr	Et	CH_2Cl_2	r.t./0.5	86
5	**e**	Ph	Ph	Et	CH_2Cl_2	r.t./3	49[a]
6	**f**	Ph	Ph	Ph	CH_2Cl_2	r.t./1	98
7	**g**	4-$MeOC_6H_4$	Ph	Ph	CH_2Cl_2	r.t./0.5	83
8	**h**	4-$CF_3C_6H_4$	Ph	Ph	CH_2Cl_2	r.t./2	53[a]
9	**i**	*t*Bu	Ph	Ph	$(CH_2Cl)_2$	reflux/2	78
10	**j**	*t*Bu	*n*Pr	Ph	$(CH_2Cl)_2$	reflux/3	94
11	**k**	*t*Bu	Ph	Et	$(CH_2Cl)_2$	reflux/7.5	67
12	**l**	*t*Bu	*n*Pr	Et	$(CH_2Cl)_2$	reflux/9	65
13	**m**	*n*Pr	Ph	Ph	CH_2Cl_2	r.t./0.5	76
14	**n**	iPr	Ph	Ph	CH_2Cl_2	r.t./2	97

[a] Quinazolines **6c** (*E*), **6e** (*E*) and **6h** (*E*) were formed in 19%, 44% and 46% yields, respectively.

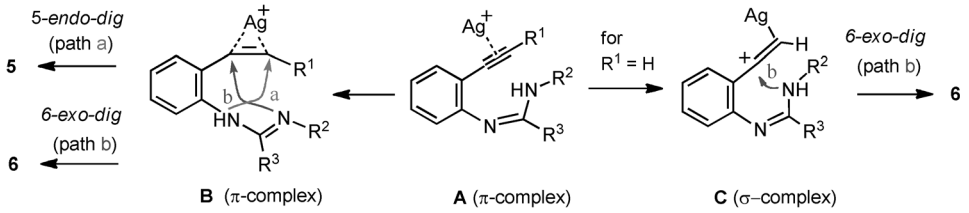
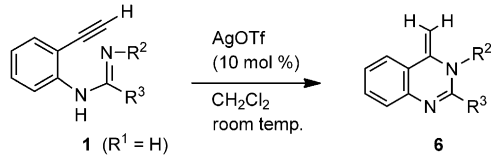


Figure 1. A possible mechanistic pathway leading to indoles **5** and quinazolines **6**.

Table 3. Silver triflate-catalyzed cycloisomerization of **1** to give 4-methylenequinazolines **6**.



Entry	**1**, **6**	R^2	R^3	Time [h]	Yield [%][a]
1	**y**	Ph	Ph	1	75
2	**z**	*n*Pr	Ph	15	71
3	α	Ph	Et	1	92
4	β	*n*Pr	Et	0.5	61

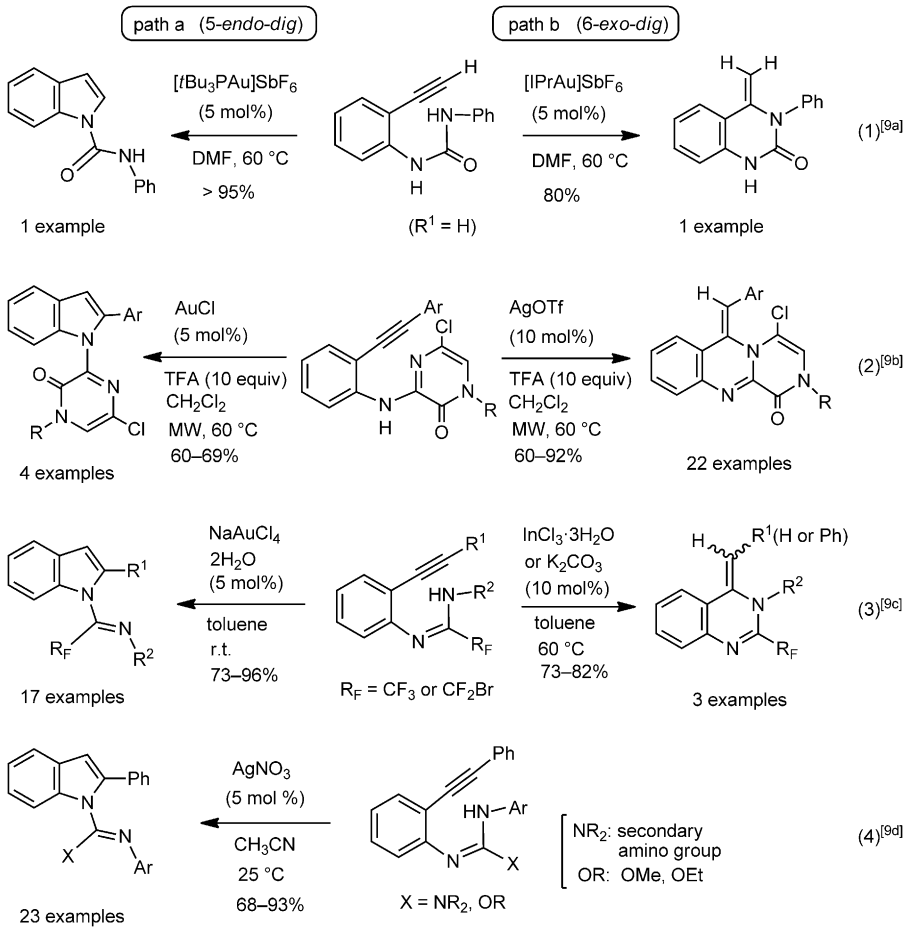
[a] Not detected for **5**.

tion of the electron-withdrawing substituent R_F-bearing substrates preferred the formation of indoles (17 examples), while $InCl_3$ ($CuSO_4$, etc.) or K_2CO_3 catalysts preferentially produced quinazolines (three examples; R^1 = H or Ph) (eq. (3)).[9c] The $AgNO_3$-catalyzed reaction of the guanidine- or isourea-bearing substrates (X = NR_2 or OR; R^1 = Ph, R^2 = aryl group only) exclusively afforded indoles (23 examples), no formation of quinazolines being described (eq. (4)).[9d,13] The reaction is highly regioselective, but unfortunately the scope of the substituents seemed to be rather limited (R^1 = Ph; R^2 = aryl group only).

Base-promoted cyclization of *N*-imidoyl-2-alkynylanilines (1)

Next, we examined the base-promoted cycloisomerization of **1** to examine the efficiency and selectivity of the reaction (Table 4). Preliminary experiments for the reaction showed that the reaction rates (effectiveness, namely yield) and regioselectivity were significantly dependent upon the substituents (R^1, R^2, and R^3) of **1**, bases, and the amounts used. First, we selected bases K_2CO_3, Et_3N, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), *t*BuONa, NaH, and TBAF (tetrabutylammonium fluoride) (3 equiv, 10 mol%) in a refluxing solvent such as acetonitrile, DMF, THF, toluene, $(CH_2Cl)_2$, and CH_2Cl_2 in the reactions of model substrates **1g**, **1i**, and **1m**. Several representative results are shown in Table 4. The bases *t*BuONa, NaH, and TBAF promoted the reaction; however, bases K_2CO_3, Et_3N, and DBU did not. The reactions of substrate **1g** in the presence of *t*BuONa, NaH, or TBAF gave quinazolines **6g** with good regioselectivity (entries 1–4), whereas indoles **5i** and **5m** were exclusively formed for the reactions of **1i** and **1m** in the presence of the same bases (entries 5–8 and 9–12). Among the bases used, TBAF was the best choice and acetonitrile was the best solvent (entries 12–17). Next, our efforts turned to reducing the amount of base, TBAF, under suitable reaction conditions for each substrate. The data (entries 3 vs. 4, 7 vs. 8, and 11 vs. 12) suggest that appropriate amounts of base (TBAF) are necessary for each substrate **1** to maintain a high yield and selectivity of the products.

On the basis of the results from the preliminary experiments (Table 4), we performed the TBAF-promoted reaction in acetonitrile using substrates **1** with a variety of substituents in combinations of aryl and alkyl groups at R^1, R^2, and R^3. The best and representative results for all of the various substrates **1** are shown in Table 5. The data suggest the following. (1) In cases where substrate **1** bears an alkyl group at substituent R^1 and an aryl (Ph) group at R^3 (entries 1–7), the reaction produced indoles **5** exclusively in high yield even when R^2 is either an aryl group (entries 1–3) or an alkyl group (entries 4–7). (2) Even when R^1 is an aryl group (entries 8–11), the reaction of **1** (R^3 = Ph) also produced indoles **5** regioselectively. In these cases, a bulky (alkyl) group at R^2 (*t*Bu, iPr) is necessary regioselectively to give indoles **5** (compare with the cases of less bulky R^2 = *n*Pr, vide infra: entries 19–22). (3) In cases of substrates **1k** and **1l** when R^1 (*t*Bu) and R^3 (Et) are both alkyl groups (entries 12 and 13), the TBAF-promoted reaction did not proceed at all even on prolonged heating. This was compensated by the fact that AgOTf-catalyzed reaction of the corresponding **1k**, **l** indeed occurred to give indoles **5k**, **l** in 67 and 65% yields, respectively (*vide supra*: Table 2, entries 11 and 12). (4) In contrast to the above results, substrates **1** bearing at least two aryl groups at R^1 and R^2, or R^1 and R^3 preferentially produced quinazolines **6** in high yields (entries 14–22), but for the latter cases (R^1 and R^3 = aryl group, entries 19–22), R^2 should be a less bulky (alkyl) group (*n*Pr) (cf. entries 8–11). (5) When both

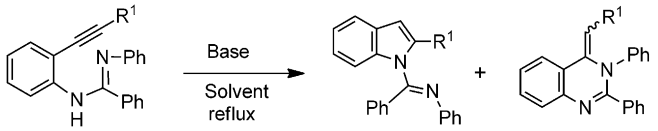


Scheme 4. Reported examples of alternative cyclization modes in the catalyzed cycloisomerization of various *o*-alkynylaniline derivatives.

R^2 and R^3 are alkyl groups (*n*Pr and Et) such as **1d** (entry 23), the reaction also afforded quinazoline **6d**, albeit in 37% yield. (6) In accordance with the silver triflate-catalyzed reaction, substrate **1y** readily underwent 6-*exo-dig* cyclization in the presence of 10 mol% of TBAF in refluxing acetonitrile for 10 min to give product **6y** exclusively (entry 24).

The thus formed 4-(R^1-methylene)quinazolines **6** were obtained as a mixture of *E*- and *Z*-isomers, where the *Z*-isomers were in the majority. However, the ratios seemed to be dependent mainly on the substituents R^1 and R^2 and circumstances. Interestingly, the ratio gradually changed in solution. For example, the isolated quinazoline **6a** (entry 14) in a ratio of *Z*/*E* = 92:8 before silica gel chromatography treatment[14] was dissolved in $CDCl_3$ and allowed to stand at room temperature for 50 h. During that time the ratios were traced by measuring integration of the olefinic protons for both isomers by ^{1}H NMR spectroscopy. The results are shown in Figure 2(a). The amount of the major *Z*-isomer (*Z*/*E* = 92:8) in the beginning slowly decreased with isomerization to the *E*-isomer, which increased with time, and after 50 h the ratio changed to *Z*/*E* = 8:92. This observation suggests that the *Z*-isomer is a kinetic product and the *E*-isomer is a thermodynamic product. Furthermore, it is noteworthy that these *Z*-isomers were actually rather stable without isomerization *in the presence of TBAF*. In fact, this observation was proved by tracing the ratio of *E*- and *Z*-isomers of **6a** by ^{1}H NMR spectroscopy. The ratio of *Z*- and *E*-isomers (*Z*/*E* = 87:13) of **6a** dissolved in $CDCl_3$ *in the presence of TBAF* (20 mol%) did not changed at all after 20 h (Figure 2(b)). Furthermore, when **1a** was treated *in the presence of TBAF* (5 mol%) in CD_3CN on heating at 80 °C in an NMR tube, ^{1}H NMR measurements after cooling showed that **1a** was consumed and the formed *Z*- and *E*-isomers of **6a** were in a ratio of 93:7 after 20 min, and in the same ratio even after 50 min and 6 h at 80 °C, and after an additional 16 h at room temperature (Figure 2(c)). As shown in Figure 3, because of the steric repulsion between the aryl groups of R^1 (4-Tol, Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$) and R^2 (Ph) present in the *Z*-isomer (*Z*-**6a**), the *Z*-isomer is less stable than the *E*-isomer with relatively less steric repulsion

Table 4. Screening of bases and solvents in base-promoted cycloisomerization using model substrates **1g**, **1i**, and **1m**.



1 **5** **6**

Entry	R^1	Base[a] (3 equiv–10 mol%)	Solvent	Time [h]	Yield [%] **5**	**6**
1	4-$MeOC_6H_4$ (**1g**)	*t*BuONa (3 equiv)	MeCN	33	12	72
2		NaH (3 equiv)	MeCN	28	6	60
3		TBAF (3 equiv)	MeCN	1	9	89
4		TBAF (1.5 equiv)	MeCN	1	8	87
5	*t*Bu (**1i**)	*t*BuONa (3 equiv)	MeCN	33	93	0
6		NaH (3 equiv)	MeCN	30	97	0
7		TBAF (3 equiv)	MeCN	11	99	0
8		TBAF (10 mol%)	MeCN	22	9	ND[b,c]
9	*n*Pr (**1m**)	*t*BuONa (3 equiv)	MeCN	29	11	ND[b,c]
10		NaH (3 equiv)	MeCN	15	50	ND[b,c]
11		TBAF (3 equiv)	MeCN	0.4	99	0
12		TBAF (10 mol%)	MeCN	0.5	99	0
13		TBAF (10 mol%)	DMF	26	82	ND[b,c]
14		TBAF (10 mol%)	THF	13	4	ND[b,c]
15		TBAF (10 mol%)	toluene	21	28	ND[b,c]
16		TBAF (10 mol%)	$(CH_2Cl)_2$	23	ND[b]	ND[b,c]
17		TBAF (10 mol%)	CH_2Cl_2	36	4	ND[b,c]

[a] TBAF (1 mol/L THF solution).
[b] Not detected.
[c] Considerable amounts of starting material **1** remained.

between the R^1 (4-Tol, Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$) group and the peri-H^5 of the benzo group.

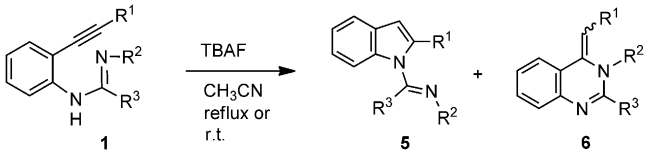
The olefinic protons present in the deshielded zone of the *Z*-isomers appeared at δ 6.20–6.63 as a singlet and those of the *E*-isomers at δ 5.00–5.26 as a singlet (for **6a**, **c**, **f–h**, entries 14–18), which also supports the stereochemical assignments of the *Z*- and *E*-isomers (see Supporting Information). In contrast to the above observations, for instance, both the *Z*- and *E*-isomers of **6b** (R^1=4-Tol, R^2=*n*Pr, R^3=Ph) were stable in $CDCl_3$ solution at room temperature for a long time without any isomerization, as shown in Figure 2(d). This is probably due to the much lower steric hindrance between the R^1 (4-Tol) and R^2 (*n*Pr) groups in the *Z*-isomer (for **6b**, **d**, **w, x**, entries 19–23) relative to the high barrier of the isomeric rotation (Figure 3).

Based on the above observations in the TBAF-promoted cyclization, we propose a plausible mechanistic pathway (Scheme 5). Initially, the fluoride anion deprotonates the amidine-NH to form the intermediate anion **A**, which possesses an ambident nucleophilic N-center. The adjacent nitrogen nucleophile attacks the proximal inner alkyne carbon to form the cyclized carbanion **B**, in which the *Z*-form is favored due to a stabilization by hyperconjugative $n_C\text{-} \rightarrow \sigma^*_{C-N}$ interaction of anionic carbon orbital and antiperiplanar C–N acceptor,[15] thereby *Z*-**6** preferably formed by the protonation. Thus, in such basic conditions the kinetically controlled, predominant formation of the *Z*-isomer was observed. In fact, the *Z*-isomers of **6**, having an enamine structure, were stable under the basic conditions described above. When the substituents R^1 and R^2 are both aryl groups, the *Z*-isomers of **6** *in a solution* ($CDCl_3$) or by silica gel (chromatography)[14] slowly isomerized to the corresponding thermodynamically stable *E*-isomers.

Conclusions

In conclusion, we have developed a AgOTf-catalyzed and TBAF-mediated cycloisomerization reaction of simple *N*-imidoyl-2-alkynylanilines bearing various common substituents, and evaluated experimentally the reactivity and product selectivity associated with the Baldwin cyclization modes. By these methods, indoles and 4-methylenequinazolines were synthesized in high yields with high regio- and stereoselectivities, and with remarkable tolerance to various substituents by a combination of substrate and catalyst control. Although at the present stage we could not have sufficient theoretical evidence nor any experimental evidence of potential key intermediates to account for

Table 5. TBAF-catalyzed cycloisomerization of **1** to give indoles **5** and/or quinazolines **6**.



Entry	1	R^1	R^2	R^3	TBAF amounts	Temp/Time [h]	Yield [%] **5**	**6**
1	**1i**	*t*Bu	Ph	Ph	1.5 equiv	reflux/5	97	0
2	**1m**	*n*Pr	Ph	Ph	10 mol%	reflux/0.5	99	0
3	**1o**	cHex	Ph	Ph	0.5 equiv	reflux/3	97	0
4	**1j**	*t*Bu	*n*Pr	Ph	3.0 equiv	reflux/20	86	0
5	**1p**	*t*Bu	iPr	Ph	3.0 equiv	reflux/44	87	0
6	**1q**	cHex	iPr	Ph	3.0 equiv	reflux/18	87	0
7	**1r**	*n*Pr	iPr	Ph	3.0 equiv	reflux/27	97	0
8	**1s**	4-Tol	iPr	Ph	3.0 equiv	reflux/26	76	12
9	**1t**	4-Tol	*t*Bu	Ph	3.0 equiv	reflux/26	80	14
10	**1u**	Ph	iPr	Ph	3.0 equiv	reflux/8	75	16
11	**1v**	4-$MeOC_6H_4$	iPr	Ph	3.0 equiv	reflux/33	86	9
12	**1k**	*t*Bu	Ph	Et	3.0 equiv	reflux/55	ND[a,b]	ND[a,b]
13	**1l**	*t*Bu	*n*Pr	Et	3.0 equiv	reflux/55	ND[a,b]	ND[a,b]
14	**1a**	4-Tol	Ph	Ph	5 mol%	reflux/0.3	3	96
15	**1f**	Ph	Ph	Ph	5 mol%	reflux/0.2	2	96
16	**1g**	4-$MeOC_6H_4$	Ph	Ph	10 mol%	reflux/0.3	3	95
17	**1h**	4-$CF_3C_6H_4$	Ph	Ph	1.0 mol%	reflux/0.2	0	96
18	**1c**	4-Tol	Ph	Et	10 mol%	reflux/0.4	trace	95
19	**1b**	4-Tol	*n*Pr	Ph	0.5 equiv	reflux/2	8	89
20	**1b**	4-Tol	*n*Pr	Ph	1.5 equiv	r.t./48	3	96
21	**1w**	Ph	*n*Pr	Ph	1.0 equiv	reflux/2	4	89
22	**1x**	4-$MeOC_6H_4$	*n*Pr	Ph	0.5 equiv	reflux/0.5	8	91
23	**1d**	4-Tol	*n*Pr	Et	1.5 equiv	reflux/10	trace	37[c]
24	**1y**	H	Ph	Ph	10 mol%	reflux/0.2	0	91

[a] Not detected for **5**/**6**.
[b] Considerable amounts of starting material **1** remained.
[c] Intractable complex mixture remained.

the regioselectivity of the reaction, we could predict some preferential regioselectivity and *E*/*Z*-stereoselectivity, viz. formation of indoles vs. quinazolines, when our simple substrates were used. With our results and the precedent results in mind, we conclude that a more detailed study will be necessary for more general and detailed explanation of the reaction.

Experimental Section

Silver triflate-catalyzed cyclization of *N*-imidoyl-2-alkynylanilines 1. A typical procedure (Table 2, entry 1):

To a solution of (*E*)-*N*′-phenyl-*N*-[2-(*p*-tolylethynyl)phenyl]-benzimidamide **1a** (30.0 mg, 0.078 mmol) in dry dichloromethane (1 mL), AgOTf (2.0 mg, 0.0078 mmol, 10 mol%) was added, and the reaction mixture was stirred at room temperature for 40 min under an argon atmosphere. The reaction mixture was quenched by addition of saturated aqueous sodium carbonate (5 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). Combined organic layers were washed with saturated aqueous sodium chloride (5 mL) and water (5 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo and column chromatography of the residue on silica gel (ethyl acetate/hexane = 1:16) gave **5a** (29.7 mg, 99%).

Tetrabutylammonium fluoride-promoted cyclization of *N*-imidoyl-2-alkynylanilines 1. A typical procedure (Table 5, entry 14):

To a solution of benzimidamide **1a** (45.0 mg, 0.116 mmol) in acetonitrile (1.2 mL), a THF solution (1.0 M, 5.8 μL) of TBAF (0.0058 mmol, 5 mol%) was added at 0 °C with stirring under an argon atmosphere. The reaction mixture was heated under reflux (80 °C) with stirring for 20 min, and after cooling to 0 °C, quenched by addition of saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride (10 mL) and water (5 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo and column chromatography of the residue on silica gel (ethyl acetate/hexane =

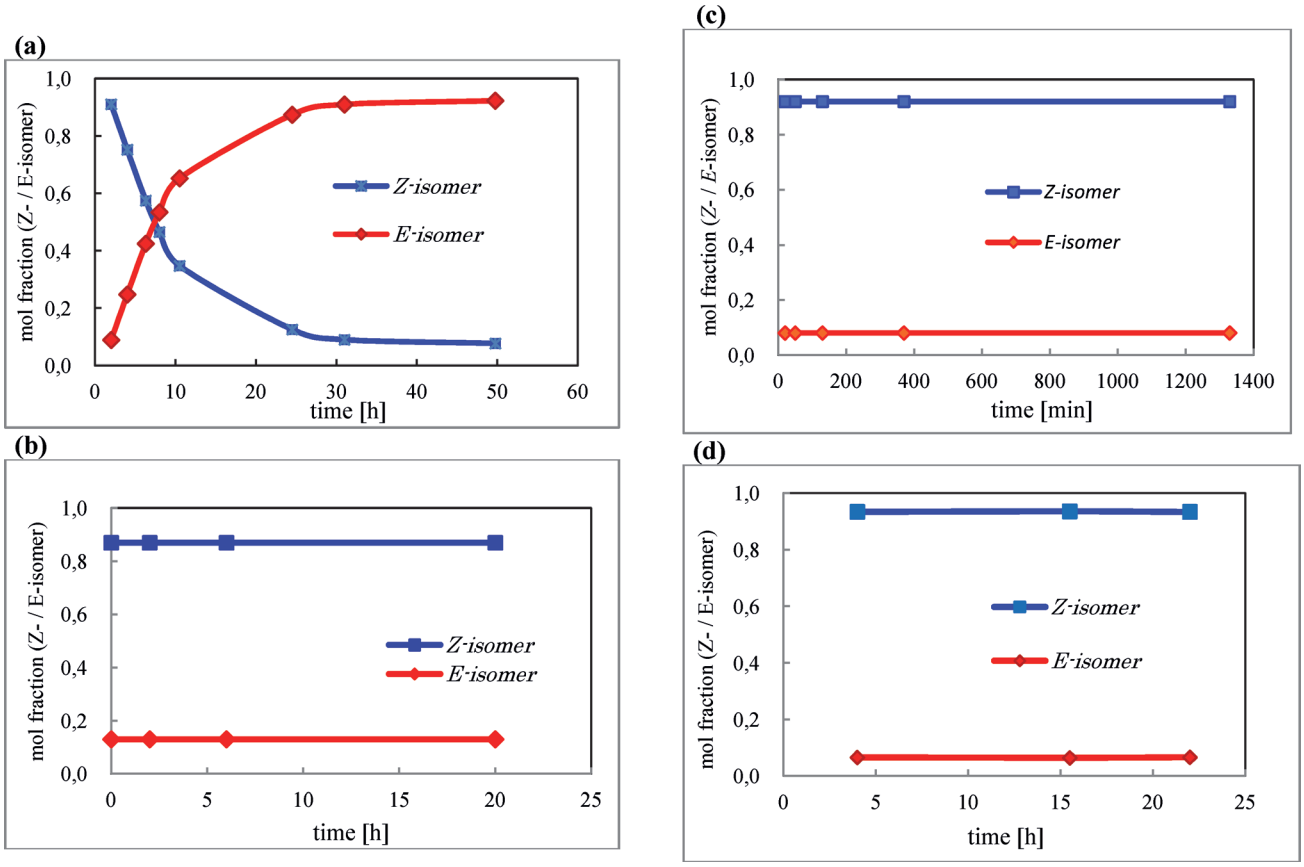


Figure 2. (**a**) Variation of mole fractions of *E*- and *Z*-isomers (**6a**) with time (h) in $CDCl_3$ at room temperature. (**b**) Variation of mole fractions of *E*- and *Z*-isomers (**6a**) with time (h) in the presence of TBAF in $CDCl_3$ at room temperature. (**c**) Formation of **6a** from **1a** in the presence of TBAF (10 mol%) in CD_3CN on heating at 80 °C, and the subsequent mole fractions of *E*- and *Z*-isomers with time (min). (**d**) Variation of mole fractions of *E*- and *Z*-isomers (**6b**) with time (h) in $CDCl_3$ at room temperature.

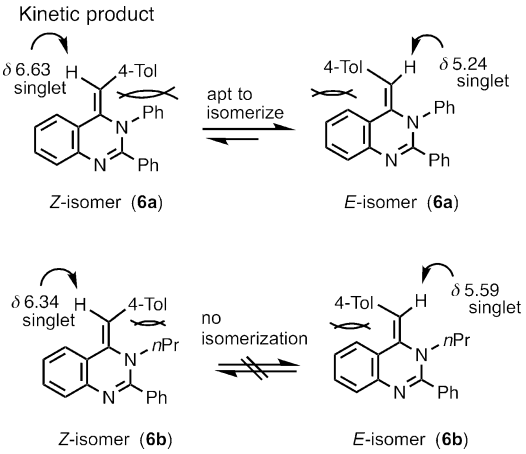
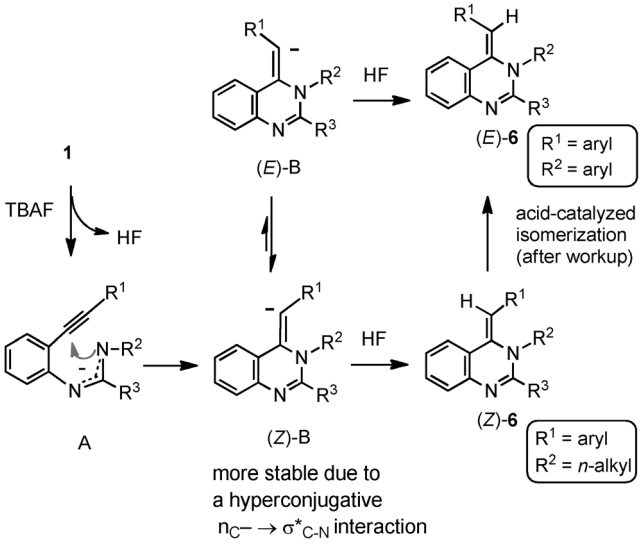


Figure 3. Chemical shifts of the olefinic protons in the *E*- and *Z*-isomers.

1:8) gave indole **5a** (1.35 mg, 0.00349 mmol, 3%) as colorless crystals and quinazoline **6a** (43.2 mg, 0.111 mmol, 96%) as yellow crystals (recrystallized from ethyl acetate/hexane, or 1,2-dichloroethane/hexane for X-ray crystallography of **6g**).



Scheme 5. A plausible mechanistic pathway leading to *Z*- and *E*-isomers (**6**) for the TBAF-promoted cyclization.

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

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[13] Previously, we reported the formation of 4-alkyldihydroquinazolines via *6-exo-trig* mode cyclization, namely via intramolecular aza-conjugate addition of *o*-amidinocinnamates ($X=NR_2$ or OR) starting from the corresponding carbodiimides as a tandem intermolecular N- or O-nucleophile addition/intramolecular aza-Michael addition in one pot: T. Saito, K. Tsuda, Y. Saito, *Tetrahedron Lett.* **1996**, *37*, 209.

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[15] For the discussion of stereoelectronic features in *exo-dig* cyclizations of anionic N-centered nucleophiles, see: S. F. Vasilevsky, T. F. Mikhailovskaya, V. I. Mamatyuk, G. E. Salnikov, G. A. Bogdanchikov, M. Manoharan, I. V. Alabugin, *J. Org. Chem.* **2009**, *74*, 8106.

