Novel Extensions of the *tert*-Amino Effect: Formation of Phenanthridines and Diarene-Fused Azocines from *ortho*-*ortho′*-Functionalized Biaryls

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This work is kindly dedicated to Prof. László Tőke on the occasion of his 75th birthday.

Abstract: Phenanthridines and azocines fused to two benzene rings or one benzene and one pyridazinone ring, which are otherwise difficult to access, were prepared via two new extensions of the *tert*-amino effect. The synthetic pathway includes three steps: i) Suzuki reaction of an *ortho*-functionalized phenylboronic acid with *ortho*-disubstituted benzenes or pyridazinones; ii) the Knoevenagel condensation reaction of the biaryl aldehydes formed with active methylene compounds to obtain vinyl derivatives or, through their cyclization, phenanthridines via a *tert*-amino effect; and iii) thermal isomerization of vinyl or phenanthridinium compounds to fused azocines via another type of *tert*-amino effect.

Key words: *tert*-amino effect, dibenzazocines, pyridazinobenzazocines, nonbonding interactions, Suzuki reaction

The term '*tert*-amino effect' was originally coined by Meth-Cohn and Suschitzky to describe the thermal ring-closure reactions of tertiary anilines containing an unsaturated *ortho* substituent with at least one heteroatom to afford fused aza-ring systems incorporating a *tert*-amino nitrogen.[1] Subsequently, six types of *t*-amino effect (or synonymously *tert*-amino effect) have been distinguished, based on the ring size and the mode of its formation.[2]

During the 1980s, the Reinhoudt group studied the thermal isomerization of *tert*-anilines with an *o*-dicyanovinyl substituent, which furnished dicyanotetrahydroquinolines via a type 2 *tert*-amino effect. This type of transformation has received considerable attention, in consequence of the predictable stereo- and regiochemical features of the isomerization.[3] In our ongoing studies, started in the early 1990s, we have extended such isomerizations to pyridazine analogues of *tert*-anilines, and we were able to recognize some interesting structure–reactivity relationships[4] and overcome the limitations of the solvent-phased reactions through applications of microwave and/or solvent-free conditions.[4e,f]

Surprisingly, possible extensions of the *tert*-amino effect to suitably tailored polyaryl systems in order to obtain medium-sized or large rings have hardly been explored. One unexpected finding was made by Meth-Cohn, when the attempted formylation of *para*-substituted *tert*-anilines with *N*-methylformanilide led to the formation of diazocines via hydrogen migration, followed by C–C bond formation between α-carbon of the *tert*-amino group and the phenyl ring of the formanilide moiety.[5]

As a continuation of our studies, we set out to extend the scope of the *tert*-amino effect to biaryl, triaryl, and fused systems containing the *tert*-amino and vinyl groups in the *ortho* positions of aryl rings connected, directly or attached to another aryl ring or in *peri* positions of a fused ring system, respectively. The isomerization of such compounds might provide facile routes to fused medium and macrocyclic ring systems that are otherwise difficult to access. This paper reports on our attempts to synthesize 2-(2-vinylphenyl)-*tert*-anilines and their pyridazinone analogues and to isomerize them to biologically interesting fused azocines with some structural resemblance to the naturally occurring anticancer allocolchicine (**1**) and allocolchicinoid derivatives **2**–**4** (Figure 1).[6]

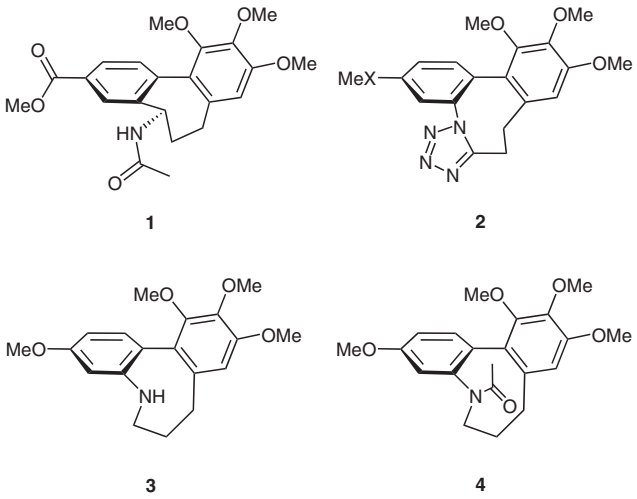

Figure 1 Allocolchicine (**1**) and its derivatives **2**–**4** (X = O or S)

It was considered that appropriately *ortho*,*ortho′*-functionalized biphenyl or phenylpyridazine derivatives could be synthesized in the most straightforward way via the Knoevenagel condensation of biaryl carbaldehydes **7a**–**c** and **12a**–**c**. For the preparation of the required aldehydes, aryl–aryl bond formation between two *ortho*-substituted

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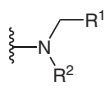
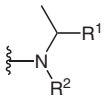
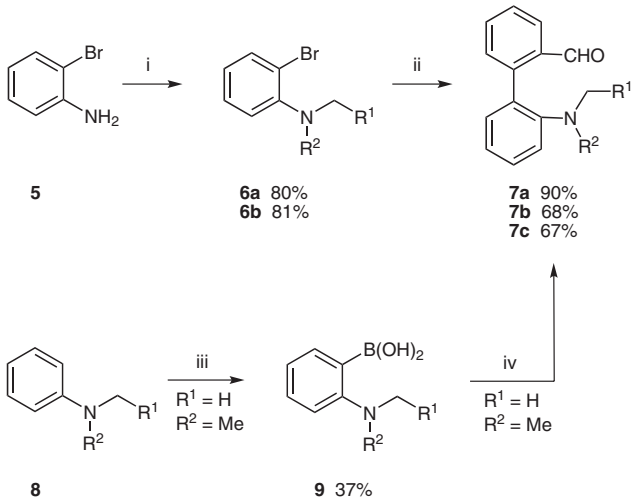
Table 1 Notation of Basic Functional Groups R for All Schemes

		or	
a	$R^1,R^2 = (CH_2)_3$		
b	$R^1,R^2 = (CH_2)_4$		
c	$R^1 = H$, $R^2 = Me$		

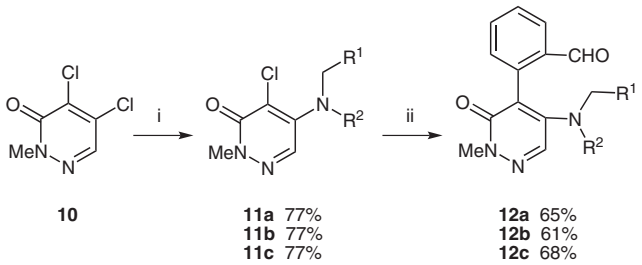
arenes, one of which possessing a formyl and the other a dialkylamino group, was foreseen. Accordingly, we took two different types of Suzuki reactions into account for this step, using either *o*-formylboronic acid or *o*-(dialkylamino)boronic acid.[7] The choice of the required reagents was based on their availability and reactivity. Aldehydes **7a**,**b** and **12a**–**c** were prepared from commercially available *o*-formylphenylboronic acid with easily obtainable *o*-haloarylamines **6a**,**b**[8] and **11a**–**c**[9] (Tables 1 and 2), respectively, whereas aldehyde **7c** was synthesized through the known reaction of *o*-(dimethylamino)phenylboronic acid with *o*-bromobenzaldehyde.[10] Each Suzuki reaction could be carried out smoothly in the presence of tetrakis(triphenylphosphine)palladium as catalyst (Schemes 1 and 2). In the pyridazinone series, chloropyridazinones were conveniently used instead of the less readily available and more expensive bromo derivatives, since the chloro atom has been found to be sufficiently reactive for Suzuki coupling of pyridazinones, due to the electron-withdrawing properties of the pyridazinone ring.[11]

It is noteworthy that single-crystal X-ray diffraction of aldehyde **7b** confirmed a short distance (2.835 Å)[12] between the nitrogen and carbonyl carbon, similarly as found for aldehyde **7c** (2.989 Å).[10]

We designed three series of vinyl derivatives, one series with acyclic and two with cyclic vinyl substituents. First, dicyanomethylene compounds were targeted as 'gold standard'.

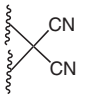
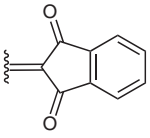
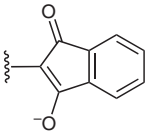
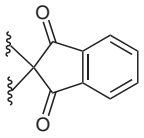
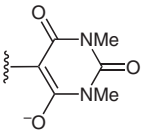
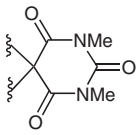


Scheme 1 *Reagents and conditions*: i) $Br(CH_2)_nBr$ (n = 4 for **7a**, n = 5 for **7b**), *i*-Pr_2EtN, toluene, 110 °C, 15 h; ii) *o*-formylphenylboronic acid, $Pd(PPh_3)_4$, aq 2 N Na_2CO_3, DME, 110 °C, argon, 29 h; iii) a) TMEDA, Et_2O; b) *n*-BuLi, 8 h; c) $B(OMe)_3$, –70 °C, argon, 24 h; d) H_2O, 1 h; iv) *o*-bromobenzaldehyde, $Pd(PPh_3)_4$, aq 2 N Na_2CO_3, DME, 110 °C, argon, 48 h.

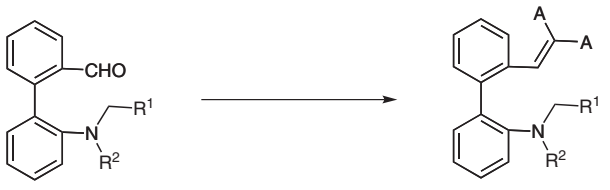


Scheme 2 *Reagents and conditions*: i) base [pyrrolidine (for **11a**), piperidine (for **11b**), *N*,*N*-dimethylamine–EtOH (for **11c**)], EtOH–H_2O, 100 °C, 2 h; ii) *o*-formylphenylboronic acid, $Pd(PPh_3)_4$, aq 2 N Na_2CO_3, DME, 110 °C, argon, 15 h.

Table 2 Notation of Basic Functional Groups A for All Schemes

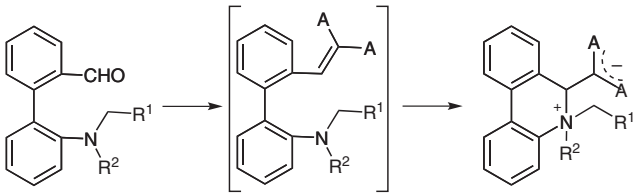
					
13a–c **17a–c**				**19a**,**c** **23a**	
14b **18a–c**		**15a**,**c**		**20a** **24a**	
		16a–c		**21a**	

The Knoevenagel condensations of aldehydes **7a–c** and **12a–c** (Schemes 3– 5) with malononitrile took place smoothly under mild conditions to afford the expected vinyl compounds **13a–c** and **17a–c** in good yields (Schemes 3 and 5).



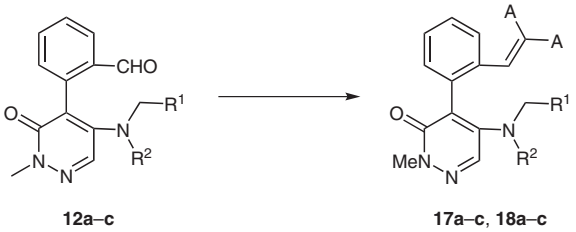
7a → **13a** 95%
7b → **13b** 68%
7b → **14b** 36%
7c → **13c** 84%

Scheme 3 *Reagents and conditions*: malononitrile (**13a–c**) or 1*H*-indene-1,3(2*H*)-dione (**14b**), EtOH, r.t., 24 h.



7a → **15a** 30%
7a → **16a** 83%
7b → **16b** 36%
7c → **15c** 18%
7c → **16c** 75%

Scheme 4 *Reagents and conditions*: 1*H*-indene-1,3(2*H*)-dione (**15a**,**c**) or *N*,*N*-dimethylbarbituric acid (**16a–c**), EtOH, r.t., 24 h.



12a → **17a** 87%
12a → **18a** 63%
12b → **17b** 84%
12b → **18b** 65%
12c → **17c** 96%
12c → **18c** 63%

Scheme 5 *Reagents and conditions*: for **17**: malononitrile, piperidine, EtOH, r.t., 24 h; for **18**: 1*H*-indene-1,3(2*H*)-dione–dioxane, piperidine, EtOH, r.t., 48 h.

With a view to acquiring information on the geometric arrangement of the functionalities located in the *ortho*,*ortho*′positions, X-ray analysis was also carried out. Suitable crystals for single-crystal X-ray diffraction were obtained from **13a**,[12] and it was found that the pyrrolidino and vinyl groups were located on the same side of the biaryl system; moreover, the nitrogen was located at a relatively short distance from the α-vinylic carbon (2.878 Å for N1–C18; for the numbering of each compound, see Supporting Information), indicating a nonbonding interaction between the tertiary nitrogen and the α-vinylic carbon.

Next, two cyclic active methylene compounds, indane-1,3-dione (ID) and *N*,*N*-dimethylbarbituric acid (DMB), were reacted with biphenyl carbaldehydes to obtain vinyl groups, in which the β-carbon was incorporated into a ring. Such a structural motif was expected to lead to significant acceleration of the isomerization reactions via a type 2 *tert*-amino effect.[4b–g] The reactions of biphenyl carbaldehydes **7a–c** with ID and DMB in ethanol at room temperature furnished the expected vinyl compound in only one case: the reaction of piperidino derivative **7b** with ID gave **14b** as an isolable product (Scheme 3); in all the other cases, surprisingly, phenanthridinium compounds **15a**,**c** and **16a–c** were isolated (Scheme 4).

The structures of **15** and **16** could be easily distinguished from those of the vinyl compounds by NMR spectroscopy; in particular, the up-field shifts of the α-hydrogen and α-carbon signals proved to be of diagnostic value (see Supporting Information). The structure of **16c** was confirmed by X-ray diffraction.[12] The formation of this novel type of compound can be explained by ring closure between the positively polarized carbon of the vinyl group formed in the condensation reaction and the *tert*-amino nitrogen via a new type of *tert*-amino effect.

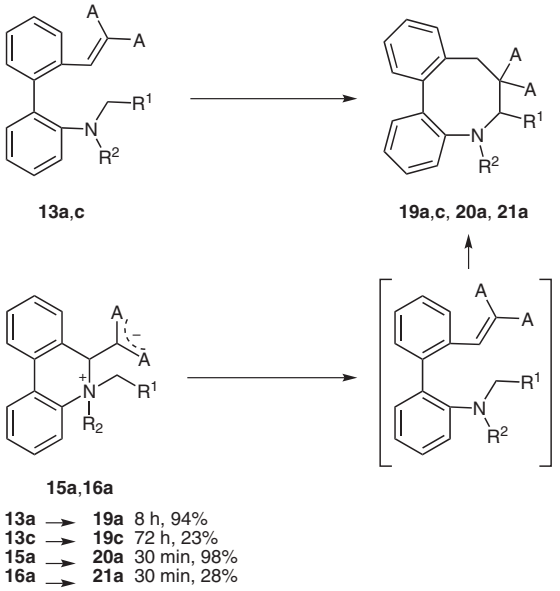
The enhanced isomerization ability of indanedione and barbituric acid derivatives versus malononitriles might be related to stereoelectronic factors: the transition states of **15a**,**c** and **16a–c** are more favorable geometrically and also because of the more efficient delocalization of the negative charge developing at the vinyl carbon bearing the two electron-withdrawing groups.

In contrast with these findings, the reactions of pyridazinylphenyl aldehydes **12a–c** with ID at room temperature in ethanol and in the presence of piperidine as catalyst, gave vinyl compounds **18a–c** (Scheme 5). This difference in behavior could be well explained by the electron-withdrawing property of the pyridazinone ring, which decreases the nucleophilicity of the *tert*-amino nitrogen.

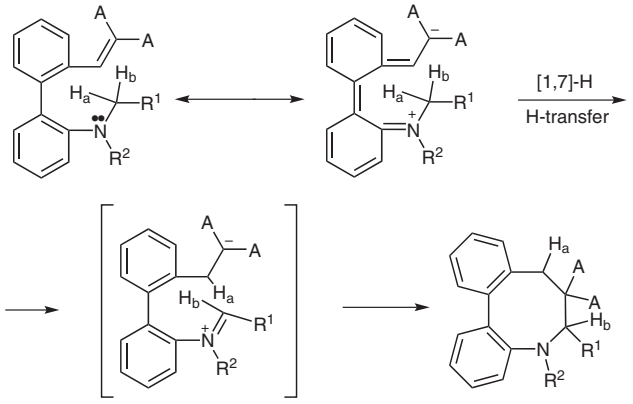
A search of the literature for similar phenomena revealed that an attractive interaction and even bond formation between a dimethylamino group and an acceptor substituent located in *peri* positions of disubstituted naphthalenes had been identified in excellent studies by the Wallis group, but no relationship to the *tert*-amino effect was indicated.[13] With regard to these results together with the findings of our own studies on series of naphthalenes and triaryl systems,[14] we now propose that the isomerizations leading to phenanthridinium compounds **15a**,**c** and **16a–c** and those of the *peri*-fused naphthalenes reported by the Wallis group proceed via a novel *tert*-amino effect.

In the following series of experiments, biphenylvinyl and phenanthridinium derivatives could be isomerized to dibenzazocines via another novel type of *tert*-amino effect. When **13a**,**c**, **15a** and **16a** were heated in dimethyl sulfoxide solutions, **19a**,**c**, **20a**, and **21a**, respectively,

were obtained (Scheme 6). These compounds could readily be distinguished from the starting materials via the NMR data (see Supporting Information). The structure of **19a** was also analyzed by X-ray diffraction.[12] The phenanthridinium derivatives are presumably first transformed to the vinyl compounds, which isomerize to the dibenzo-fused system in two steps. In the rate-limiting first step, a dipolar intermediate is formed via either antarafacial [1,7]-hydrogen migration or, more probably, hydride anion transfer, and in the next step the intermediate cyclizes to the fused ring system (Scheme 7).

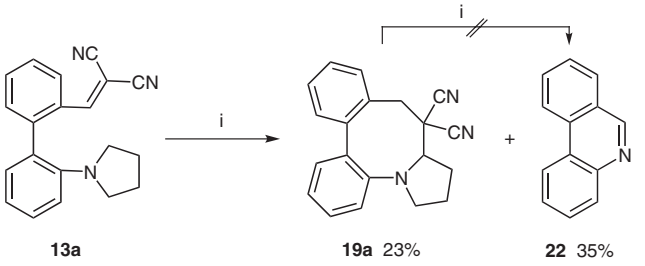


Scheme 6 *Reagents and conditions*: for **19a**, **20a**, **21a**: DMSO, 110 °C, argon; for **19c**: DMSO, 160 °C, argon.



Scheme 7

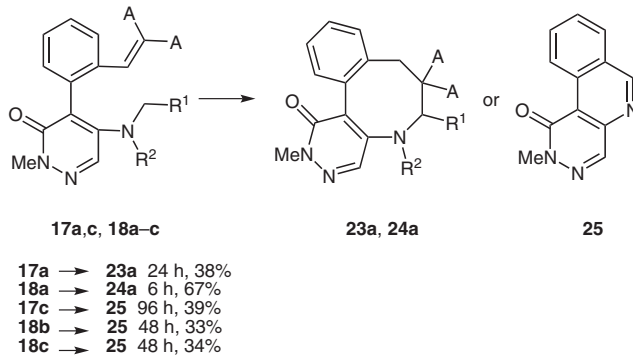
In an attempt to accelerate the reaction, microwave heating was applied. Surprisingly, irradiation of neat **13a** permitted the isolation of two different fused ring systems: dibenzazocine **19a**, which is the main product under traditional heating, and phenanthridine (**22**) in 23% and 35% yields, respectively (Scheme 8).



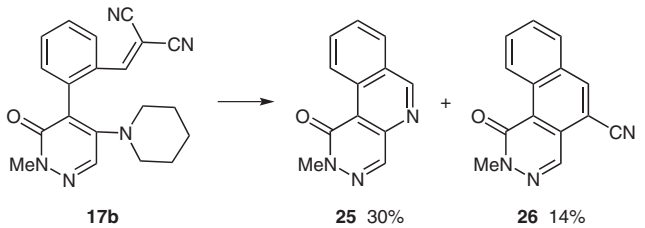
Scheme 8 *Reagents and conditions*: i) MW, neat, 300 μW, 100 °C, argon, 30 min.

Importantly, **19a** proved to be stable under the conditions applied in the microwave reactor, suggesting that it is not an intermediate in the transformation of **13a** to **22**.

Pyridazine analogues even behaved differently in their reactions in DMSO at 160 °C, the product type depending on the substituents on the starting vinyl derivative. Compounds **17a** and **18a**, containing a pyrrolidino group, gave pyridazinazocines **23a** (the structure of which was confirmed by X-ray diffraction)[12] and **24a**, whereas **17c** and **18b**,**c** containing a piperidino or dimethylamino substituent, afforded pyridazinoisoquinoline **25** (Scheme 9). Interestingly, in the reaction of **17b**, besides pyridazinoisoquinoline **25**, benzophthalazinone **26** could be isolated (Scheme 10).[15]



Scheme 9 *Reagents and conditions*: DMSO, 160 °C, argon.



Scheme 10 *Reagents and conditions*: DMSO, 160 °C, argon, 48 h.

In conclusion, this paper has described two new extensions of the *tert*-amino effect. Isomerization of *o*-(*o*-vinylaryl)aryl-*tert*-amines may lead through nitrogen–carbon or carbon–carbon bond formation to novel types of phenanthridines or diarene-fused azocines, respectively. The latter transformation may proceed through [1,7]-hy-

drogen migration or hydride transfer. The X-ray analysis demonstrated that the *tert*-amino and vinyl groups of *o*-(*o*-vinylaryl)aryl-*tert*-amines are located on the same face of the biaryl system, and their distances from each other indicate a weak interaction between them via a *tert*-amino effect.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(12) The X-ray data are available from the Cambridge Crystallographic Data Centre CCDC under the numbers 692718–692722 for **7b**, **13a**, **16c**, **19a**, and **23a**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit @ccdc.cam.ac.uk. The details of the X-ray structures will be published elsewhere.
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