A New Methodology for Preparing Benzylated Aminopyridines Yields Unprecedented Site-Selective Organocatalysts

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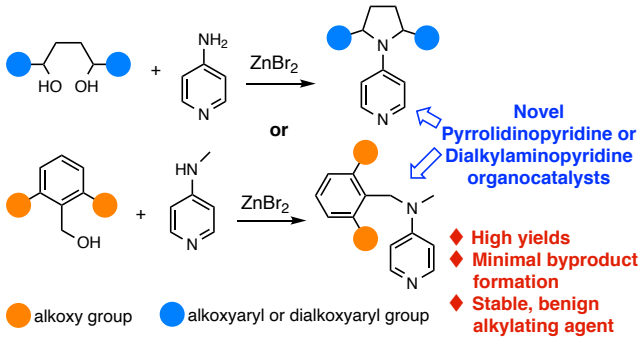
GRAPHICAL ABSTRACT:

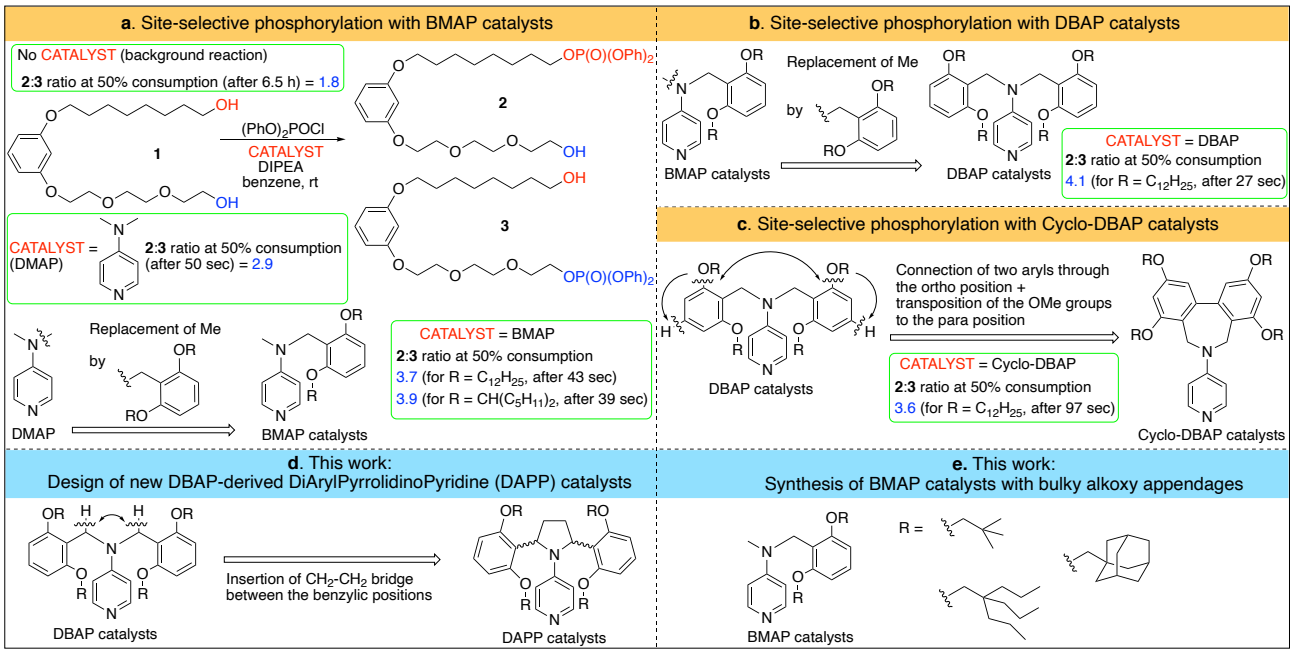


ABSTRACT: While developing site-selective alcohol-modifying catalysts, we found that Lewis acid-promoted benzylation or cyclative dibenzylation of aminopyridines with alcohols effectively overcomes the synthetic challenges typically thwarting access to new aminopyridines, a key family of nucleophilic organocatalysts. Using this innovative approach, we successfully prepared unprecedented (2,5-diarylpyrrolidino)pyridines and new (*N*-benzyl-*N*-methylamino)pyridines with expanded *ortho*-alkoxy tails on the aryls. The new catalysts, with their bulky outer sphere, exhibit remarkable activity and site-selectivity in the phosphorylation of a model diol amphiphile.

Site-selective organic transformations are paramount in contemporary organic synthesis, particularly for targeting functional groups prevalent in natural products.[1] Among these, selective modifications of polyol compounds, such as mono- and oligosaccharides, glycopeptides, and glycoconjugates of macrocycles, have been successfully developed by several research teams.[2] In recent years, our group has explored ways to selectively functionalize alcohols in amphiphilic compounds, targeting both polar and apolar domains.

In this context, we developed a range of catalysts nominally derived from DMAP and aimed at site-selective modifications of amphiphilic diols.[3] Notably, replacing one of the amine-substituting methyls in DMAP with a benzyl moiety bearing extensive alkoxy groups in the ortho positions (thereby forming the 4-(*N*-benzyl,*N*-methylamino)pyridine family of catalysts, henceforth BMAPs) led to catalytic compounds that substantially reinforced the innate preference of model amphiphilic diols to undergo phosphorylation at the apolar alcohol site (Scheme 1a).[3b,c] Moreover, catalysts incorporating branched alkoxy groups slightly outperformed those with linear appendages in both activity and selectivity,[3c,4] likely due to the increased steric bulk of the outer-sphere envelope.

Scheme 1. Previous site selectivity studies with 4-aminopyridine-based catalysts (a-c),[16] the proposed 4-pyrrolidinopyridine-based catalysts (d), and the proposed BMAP catalysts with bulky alkoxy appendages (e).



Additionally, replacing the remaining methyl in BMAPs with a matching benzyl substituent (thus establishing the 4-(*N*,*N*-dibenzylamino)pyridine family of catalysts, henceforth DBAPs) produced catalysts exhibiting even higher site selectivity in the model phosphorylation reaction (Scheme 1b).[3d] Remarkably, DBAP catalysts were also more active than their BMAP analogues, despite the increased steric demands of the substituents. This

suggests that the electronic influence of the electron-rich dialkoxybenzyl substituent outweighs the steric effects in determining catalyst activity. Concurrently, the improved site selectivity, favoring the apolar domain, likely arises from the expanded lipophilic outer sphere of the DBAP catalysts (compared to BMAPs).

While synthesizing additional DBAP catalysts with an expanded outer sphere (e.g., branched lipophilic alkoxy groups) appeared promising for further enhancing the apolar-site favoring selectivity, the approach was severely hampered by the lengthy synthetic sequence. Particularly challenging and yield-reducing was the last step: coupling the relevant dibenzylamine with the pyridine-based electrophile. Both a direct S_NAr thermal reaction and a Buchwald-Hartwig Pd-catalyzed method using 4-halopyridines (previously used approaches[3a,c]) failed to form the desired catalysts, which were prepared in low yields only via a more cumbersome reaction involving the acrylamide-chloropyridine adduct.[3d,5]

Following unsuccessful attempts to facilitate the synthetic sequence and improve the outcome of the final step, we saw two alternative strategies to build on the insights gained from the above-described studies while further enhancing the site selectivity of the catalytic phosphorylation of the model diol. One tactic involved reverting to BMAP catalysts and increasing the steric bulk of the alkoxy appendages on their single benzyl substituent (Scheme 1e). As we will detail subsequently, this approach was initially also seriously thwarted by disappointing yields of the C-N coupling step, which decreased sharply as the steric bulk of the alkoxy groups increased.

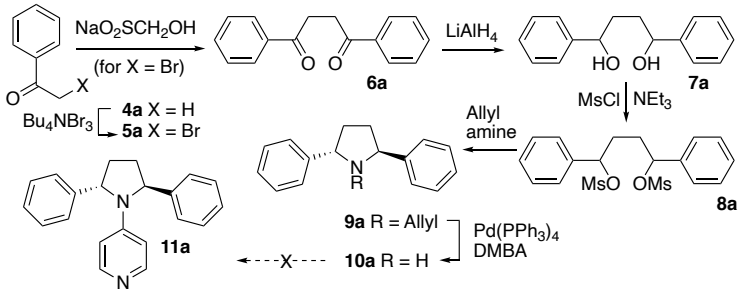
Another strategy we explored involved interconnecting the two benzyl substituents of DBAP, to reduce the bite angle of the dibenzylamine nucleophile and ease the C-N coupling step of the synthesis. Modifying the DBAP core structure by linking the two phenyls of the benzyl substituents at the ortho positions (thus forming a tricyclic pyridine-carrying scaffold with a biphenyl structural unit fused to a dihydroazepine ring) and transposing one alkoxy tail on each ring, yielded cyclo-DBAP catalyst series (Scheme 1c). However, these catalysts were less active and selective in the model phosphorylation reaction than their DBAP counterparts.[6] We suspected that the transposition of two alkoxy groups, which increased their distance from the reaction site and thinned the catalyst's outer sphere, was to be blamed for this inferior performance.

Another way to interconnect the benzyl substituents of the DBAP scaffold, but without requiring the transposition of the alkoxy substituent, involves linking the benzylic carbons, e.g., via a C_2 bridge (Scheme 1d). This design offers two additional benefits. First, the proposed catalysts can be viewed as formally derived from 4-pyrrolidinopyridine (PPY), a nucleophilic catalyst usually superior to DMAP in terms of activity.[7] Second, due to its chiral nature, the trans isomer of the proposed pyrrolidinopyridines may enable new opportunities for stereoselective catalysis in the future.

While attempting to prepare such diarylpyrrolidinopyridine (henceforth DAPP) prototype catalysts, we encountered several obstacles. Although trans-2,5-diphenylpyrrolidine (**10a**), a key intermediate en route to the DAPP catalyst without alkoxy appendages, could be prepared as described in the literature (Scheme 2),[8] its

coupling with 4-bromopyridine or related pyridine-including electrophiles consistently failed. This was surprising, as the Buchwald-Hartwig cross-coupling is typically highly efficient with cyclic secondary amines.[9] Moreover, we had previously performed this transformation with acyclic secondary amines, which are generally less suitable partners for this reaction.[3b,c] Furthermore, we could not prepare trans-2,5-diarylpyrrolidine featuring methoxy groups in the ortho positions of the aryl substituents, an analogue of key intermediate **10a**, by the route depicted in Scheme 2 or closely related variations. These attempts failed due to the low stability of the electrophilic intermediates.[10]

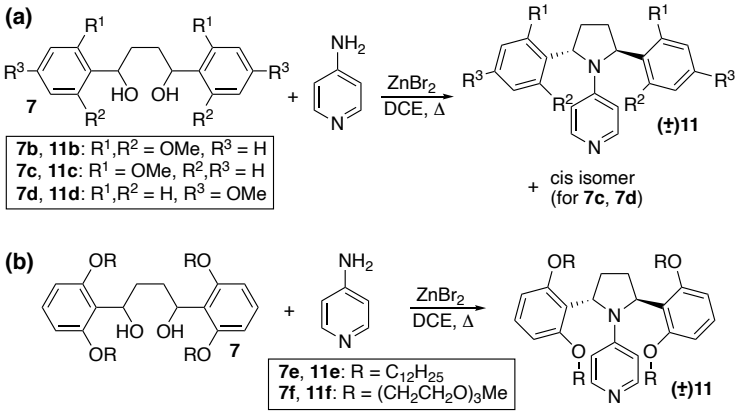
Scheme 2. Failed synthesis of DAPP.



Fortunately, a new methodology we describe here has recently enabled the preparation of both a series of unprecedented DAPP catalysts and BMAP catalysts with expanded, branched outer sphere appendages. To address difficulties in introducing the pyridine moiety into the final product, we switched from using an electrophilic pyridine-introducing reagent (e.g., 4-bromopyridine) to a nucleophilic one (e.g., 4-aminopyridine). While this approach can be implemented by deprotonating the aminopyridine derivative and reacting the formed anion with a typical electrophile (alkyl halide, mesylate, etc.),[11] this route requires strongly basic conditions and often suffers from poor yields, low electrophile stability (as previously noted for the analogue of **8a**), or byproduct formation.[12] Alcohols constitute alternative, more stable, and easier accessible electrophiles capable of alkylating aminopyridine under milder conditions.[13] In recent decades, amine alkylation by alcohols has typically relied on hydrogen-borrowing or hydrogen autotransfer mechanisms,[14,15] which have occasionally been used to synthesize pyrrolidines (or other saturated azaheterocycles) from diols and primary amines, most commonly when at least one of the alcohols in the diol is primary.[16-18] However, these methods have not yielded pyrrolidines with two aryl substituents at the 2 and 5 positions, nor have they been applied to electron-deficient heterocyclic arylamines.[19] We attempted to prepare DAPP catalysts from methoxy-bearing diols (**7b-7d**),[20] using some of these approaches,[15b,18a,c,19a] but unfortunately, these reactions were unsuccessful. In contrast, an alternative mechanism for amine alkylation by alcohols via a carbocationic pathway, as disclosed in a few recent reports,[21] appears better suited for forming 2,5-disubstituted pyrrolidine from 1,4-butanediol with electron-rich aryls at the 1- and 4-positions. Such cyclization could potentially lead to the desired catalytic structure, although cyclic amine formation from diols via this mechanism has not yet been reported.

Based on this reasoning, we applied a set of experimental conditions, similar to those in a report suggesting the carbocationic alkylation pathway,[21b] with appropriate modifications, to the reaction of diols **7b-7d** with 4-aminopyridine (Scheme 3a). Heating a solution of **7b** with a stoichiometric amount of $ZnBr_2$ in DCE under reflux yielded the racemic trans isomer of the catalyst prototype, **Cat(DAPP,C_1)** (**11b**), in ca. 60% isolated yield. The cis isomer was not observed, in contrast to the abovementioned reports of 2,5-disubstituted pyrrolidine formation via the hydrogen-borrowing mechanism, where the cis isomer predominated.[22] For diols **7c** and **7d** with a single OMe group in either the ortho or para position of each aryl moiety, full conversion required 24-hour reflux, compared to just one hour for **7b**. These reactions produced pyrrolidinopyridine products as mixtures of trans and cis isomers in a ca. 1.4:1 ratio, with 47 and 41% yields, respectively. From one of these mixtures, compound **Cat(DAPP,*o*-C_1)** (**11c**) was isolated.[23] When **7a**, the diol, bearing unsubstituted phenyl groups, was subjected to the same reaction conditions, no product was observed. The pronounced dependence of the amine di-alkylating cyclization on the electron-donating capacity of the aryl substituents in the diol convincingly supports the carbocationic mechanism of the transformation.

Scheme 3. DAPP formation by double alkylation of 4-aminopyridine with diols **7**.



Furthermore, monitoring the progress of the $ZnBr_2$-induced alkylative cyclization forming the catalysts with only one alkoxy moiety on each aryl revealed that, initially, a cyclic ether (THF) derivative is predominantly formed from the diol. Only after prolonged heating (ca. 24 h) do the pyrrolidinopyridines (trans and cis) become the major products, with the THF derivative disappearing from the reaction mixture. This observation aligns well with the carbocationic pathway mechanism, which involves an ether intermediate, proposed in the literature for the alkylation of arylamines by alcohols.[21a]

Building on our initial success, we prepared catalysts featuring extended alkoxy tails on the aryl substituents in place of the methoxy groups in the catalyst prototype, thereby obtaining **Cat(DAPP,C_{12})** (**11e**) and **Cat(DAPP,TEG)** (**11f**).[20] Notably, the cyclization step in these syntheses proceeded with yields of 44 and 46%, respectively (Scheme 3b).

Encouraged by these results, we sought to apply the new methodology to overcome difficulties in synthesizing BMAP catalysts with bulky secondary spheres. As mentioned above, increasing the steric bulk of the alkoxy groups on the benzyl substituent in BMAPs sharply reduced the yield of the finalizing Buchwald-Hartwig coupling step, from 70-80% for linear groups to a mere 4-20% for branched neopentyloxy and (2,2-dipropylpentyl)oxy tails (Scheme 4, path a). These low yields were further exacerbated by the formation of byproducts and difficult chromatographic purifications. Gratifyingly, alkylating 4-(N-methylamino)pyridine with appropriate benzylic alcohols produced the same BMAP catalysts with over 80% yield and excellent purity (Scheme 4, path b). Furthermore, for BMAPS with linear alkoxy tails, yields exceeded 90% in the final step of the new synthetic pathway. The high purity of the crude products facilitated straightforward purification. A comparison of the yields in the final steps of the BMAP synthesis sequences (Pd-catalyzed vs $ZnBr_2$-induced reactions, Table 1) highlights the advantages of the new methodology for preparing aminopyridines, particularly aminopyridine-based catalysts.

Scheme 4. The previously applied (path a) and the new (path b) pathways for preparing BMAPs.

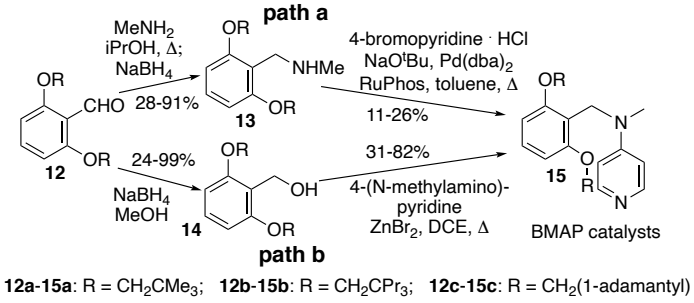


Table 1. The yields of the final step of BMAPs' synthesis via the previous and the new pathways.

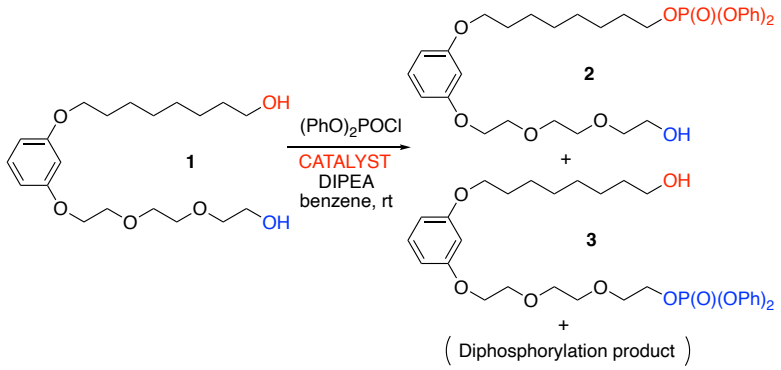
Entry	Catalyst	Yield of the Buchwald-Hartwig coupling (%)	Yield of the $ZnBr_2$-induced alkylation (%)[a]
1	**Cat(BMAP,C_1)**	74	92
2	**Cat(BMAP,C_{12})**	80	95
3	**Cat(BMAP,TEG)**	76	90
4	**Cat(BMAP,CH_2CMe_3)**	20	51(92)
5	**Cat(BMAP,CH_2CPr_3)**	4	82(88)
6	**Cat(BMAP,CH_2Ada)**	26	52

[a] Yield before chromatographic purification in parentheses.

Subsequent to their preparation, the new DAPP catalysts, **Cat(PPY,C_1)**, **Cat(PPY,C_{12})**, and **Cat(PPY,TEG)** (**11b**, **11e**, and **11f**), were examined in a site-selective phosphorylation model reaction (Scheme 5) and compared

to PPY. The new BMAP catalysts were similarly tested in the model reaction. The results, summarized in Table 2, reveal activity and selectivity trends consistent with those previously observed for the BMAP and DBAP families (for convenience, some prior results were included in the table).[3b-d] The addition of dimethoxyaryls to the PPY core yielded a more active and site-selective catalyst (entry 2 vs. 1), alike the influence of similar modifications on the DMAP structure that led to the BMAP and DBAP series (entries 6 and 12 vs. 5). This improvement is primarily attributed to the electronic influence of replacing alkyls with *o*,*o*-dialkoxybenzyls on the 4-dialkylaminopyridine frame. Expanding methoxy groups to longer dodecyloxy or triethyleneglycol-derived moieties in DAPP catalysts further enhanced the selectivity for the apolar site (entries 3 and 4 vs. 2, entries 7 and 8 vs. 6, and entry 13 vs. 12 for comparison). For BMAP catalysts, increased branching appears to offset the shortening of alkoxy tails compared to linear appendages (entries 10-11 vs. 7), though longer tails remain advantageous even within branched alkoxy groups (entry 10 vs. 9). The enhanced selectivity associated with the increased bulk of the catalyst's secondary sphere (composed of the alkoxy tails) highlights the strong influence of the latter on the reactive site of the catalyst and the incoming substrate. For DAPP catalysts, this long-range impact may induce other modes of selectivity in phosphorylation reactions. Moreover, the higher activity of the DAPP catalysts compared to their DBAP counterparts, combined with the greater increase in selectivity of DAPP catalysts vs. PPY compared to the selectivity improvement of BMAPs vs. DMAP, underscores the importance of core geometry in catalytic performance.

Scheme 5. The site-selective catalytic experiments with the model diol substrate and new catalysts.



Surprisingly, the TEG-based DAPP catalyst was less active than its analogues with methoxy and dodecyloxy appendages, contrary to the trend observed in the BMAP series (Table 2) and the family of imidazole-based catalysts.[24] This discrepancy was even more pronounced in the related acylation of the model diol amphiphile.[25] We infer that this anomaly in the DAPP series may be attributed to the overstabilization of the cationic catalytic intermediate caused by the four oligoether appendages of the **Cat(DAPP,TEG)** catalyst. While our studies demonstrated that *n*–cation interactions in intermediates with two oligoether tails, as seen in the BMAP series

and the imidazole-based catalysts, enhance catalytic activity, the cationic catalytic intermediate generated from **Cat(DAPP,TEG)** with four such tails may become so stable that the reaction rate is sharply reduced.[26]

Table 2. The results of the site selectivity studies with the new catalysts in comparison to previous results.[a]

Entry	Catalyst	Ratio of products 2:3[b,c]	Time (sec)[b]
1	PPY	2.4:1	28
2	**Cat(DAPP,C_1)**	3.4:1	16
3	**Cat(DAPP,C_{12})**	3.9:1	13
4	**Cat(DAPP,TEG)**	3.7:1	35
5[d]	DMAP	2.9:1	50
6[d]	**Cat(BMAP,C_1)**	3.1:1	42
7[d]	**Cat(BMAP,C_{12})**	3.7:1	43
8[d]	**Cat(BMAP,TEG)**	3.8:1	21
9	**Cat(BMAP,CH_2CMe_3)**	3.5:1	35
10	**Cat(BMAP,CH_2CPr_3)**	3.9:1	43
11	**Cat(BMAP,CH_2Ada)**	3.7:1	42
12[e]	**Cat(DBAP,C_1)**	3.3:1	19
13[e]	**Cat(DBAP,C_{12})**	4.1:1	27

[a] Reaction conditions: 0.1 mmol of substrate, 0.25 mmol of diphenylphosphoryl chloride, 0.25 mmol DIPEA and 0.005 mmol (5 mol %) of the catalyst in 1 mL benzene at room temperature. The reactions were followed by HPLC. [b] At 50% consumption. [c] At this consumption, 6% of the diphosphorylated product is typically formed. [d] From ref. 3b. [e] From ref. 3d.

In conclusion, the new synthetic methodology for preparing 4-aminopyridine-based structures efficiently yielded novel organocatalysts of the unprecedented diarylpyrrolidionopyridine type, as well as new benzylmethylaminopyridine catalysts, practically inaccessible by other routes. Both types of catalysts demonstrated highly promising phosphorylating site selectivity, with some DAPP catalysts exhibiting the highest activity among all nucleophilic organocatalysts we have explored in recent years for this transformation.

Acknowledgment

This research was supported by grant no. 2020345 from the United States – Israel Binational Science Foundation (BSF), Jerusalem, Israel.

Supporting Information

The Supporting Information is available free of charge and includes: general information, experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra, MS spectra (PDF).

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20. The route to these key diol intermediates generally followed the sequence in Scheme 2, beginning with the corresponding acetophenones, slightly changed from substrate to substrate and is detailed in the Supplementary Information.

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22. Ratios between ca. 1.4:1 to 3.8:1 in favor of the cis isomer were observed in those cases. See ref. 18.
23. **Cat(DAPP,*p*-C_1)** (**11d**) could not be purified from the contaminating cis isomer.
24. For the performance of imidazole-based catalysts in this reaction, see ref. 3c.
25. Ben Sason, S.; Kozlov, M.; Gorovoy A. In preparation.
26. This hypothesis will be examined in a separate publication, see ref. 25.