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# Palladium-catalyzed olefin migration and 7-*endo-trig* cyclization of dehydroalanines

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ABSTRACT

1,4- or 1,5-migration of a double bond of dehydroalanines under palladium catalysis is reported. The process occurred with several highly-substituted dehydroalanines under mild typical Heck reaction conditions. Although this was one of the first reports of a palladium-catalyzed 1,5-olefin migration, the outcome of the reaction was susceptible to the starting material. Mechanistically, the process involved a five- (1,4-migration) or six-membered ring (1,5-migration) organopalladium intermediate, which cleaved a C–N bond in an β-amino elimination process.



Undoubtedly, palladium-mediated carbon–carbon bond-forming reactions are essential tools in the armory of the synthetic organic chemist.[1] Indeed, complex transformations, which in the past were not accessible by traditional methodologies, are now possible with palladium chemistry.[2] Within this field, the Heck-Mizoroki cross-coupling reaction has been a great contribution to organic synthesis.[3] Several heterocyclic compounds of biological significance[4] or complex natural products[5] have been assembled using a Heck reaction.[6] Thus, because of its versatility, this methodology has also been applied in certain intramolecular reactions to construct carbocycles and heterocycles of various sizes.[7] Palladium catalysis has also been applied in particular types of rearrangement processes. For example, ring expansion of spirocyclopropanes,[8] synthesis of 4-arylnicotinates through a domino reaction,[9] and 1,4-hydrogen shift,[10] have been mediated by palladium catalysis. Interestingly, during the palladium catalyzed synthesis of 7-, 8-, and 9-membered rings under typical Heck conditions, Gibson detected the formation of the rearranged by-product **2**, derived from the *ortho* iodo precursor **1** (after 120 h!), but no further details of this observation were disclosed (Scheme 1).[11] More recently, Xu and co-workers observed the Pd $(OAc)_2$ catalyzed formation of the styrene derivatives **4** from enamine **3**. In this study, the 1,4-alkene migration was highly dependent both on the nature of the ligand and the base used in the reaction.[12]

In our ongoing efforts to develop useful synthetic protocols based on Pd-catalyzed domino processes applied to Ugi 4-CR-derived (four-component reaction) dehydroalanines, we recently observed that palladium-mediated 1,4- and 1,5-double bond migrations are possible in the this system. Given the paucity of information associated with this rearrangement, we decided to explore its scope, and the preliminary results are disclosed herein (Scheme 1).

Our endeavour commenced with the study of the dehydroalanine **5a** (Scheme 2) which was easily prepared from *o*-bromobenzyl amine, acetic acid, *tert*-butyl isocyanide and benzoyloxy acetaldehyde in two steps (Ugi 4-CR/elimination) in 65% yield under previously reported conditions.[13] Surprisingly, when **5a** was submitted to the action of $PdCl_2(PPh_3)_2$ (10 mol%) and 2 equivalents of AcONa in refluxing dimethylacetamide (DMA), a mixture of the pyrroloisoindolone **13a** and the corresponding rearranged acrylamide **6a** was achieved in good yield (61%) after 6 h (entry 1, Table 1). In principle, both products could have been produced through a Pd-catalyzed tandem process, consisting initially of a *5-exo* Heck-type cyclization to generate intermediate palladium species **12**, which may then react by two different processes. It may undergo the interesting formation of an sp3-sp3 bond generating a second 5-membered ring to afford **13a**, or undergo a β-amino elimination process by C–N bond fragmentation with concomitant double bond regeneration to produce the rearranged

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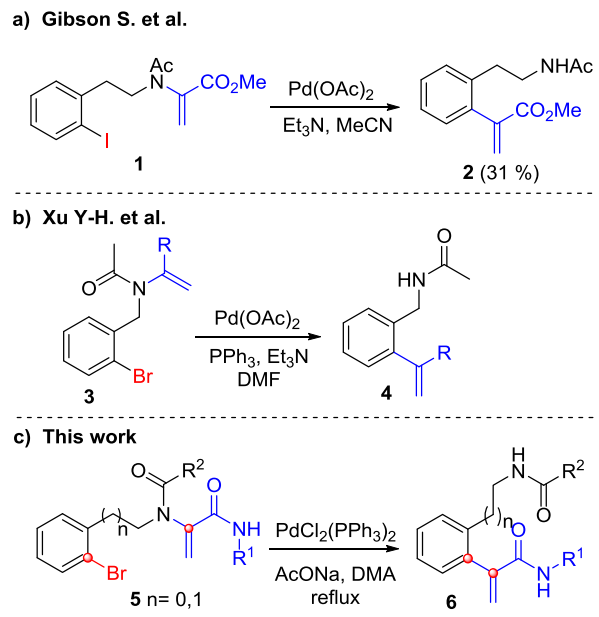
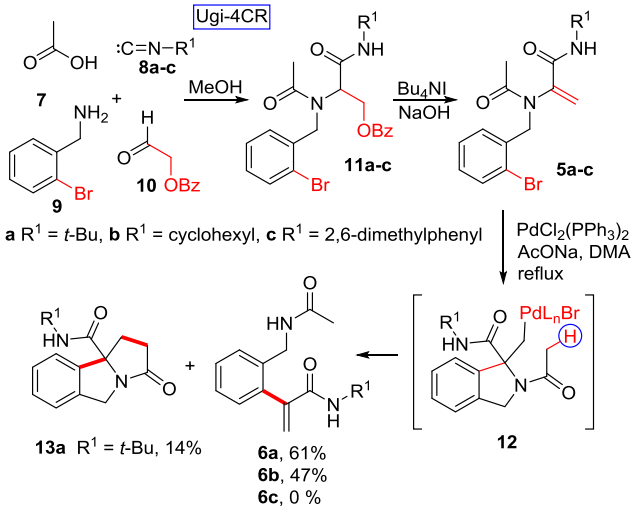



**Scheme 1.** Palladium-catalyzed rearrangements of alkenes.




**Scheme 2.** Pd-Catalyzed sp3-sp3 C–C bond formation and olefin 1,4-migration.

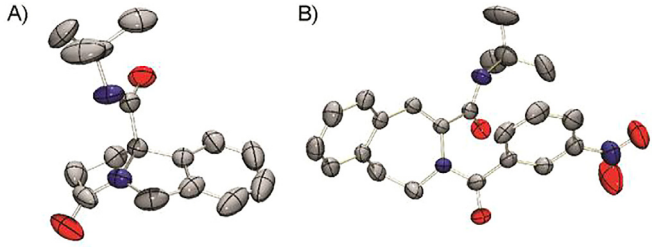



**Fig. 1.** X-ray structure of: (A) tricycle **13a** (CCDC number 1532303); (B) benzoazepine **14a** (CCDC 1532294). Hydrogen atoms were removed for clarity.

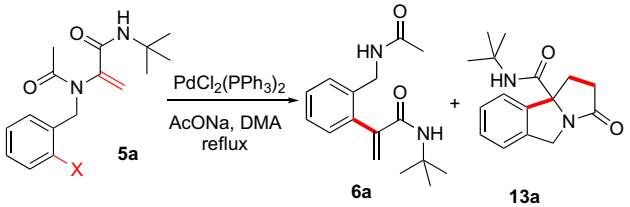
acrylamide **6a** (The lack of an alpha hydrogen in **12a** prevents the typical β-hydride elimination of a Heck process).[14]

The structure **13a** was unambiguously established by single crystal X-ray analysis (Fig. 1). It is worth noting that even though the yield of the tricycle **13a** was low (14%), the outcome is relevant because it represents a novel example of a Pd-catalyzed formation of an sp3-sp3 single bond, featuring a C–H functionalization. In an attempt to increase the yield of the tricyclic compound, the reaction temperature was maintained at reflux for three days, although no significant differences were detected (51% for **6a** and 10% for **13a**). On the assumption that the acrylamide **6a** might be an intermediate in the formation of the pyrroloisoindolone **13a**, it was subjected to the above conditions for 5 days. However, no transformation of **6a** into **13a** was detected, thus indicating that the generation of the two compounds follows independent pathways from intermediate **12**.

When equivalents of the base were reduced, the rearrangement product **6a** was isolated in lower yields and longer reaction times (entry 2–3, Table 1). Interestingly, the tricyclic derivative **13a** was not observed under these conditions. When the load of the palladium catalyst was reduced, **6a** was obtained in only 27% yield along with recovered starting material (25%, entry 4). Similar result was found when chloride derivative was submitted to the same conditions (entry 5); 25% yield of **6a** and 38% of the starting material was recovered after 48 h.

Surprisingly, when the *tert*-butyl group was replaced by cyclohexyl in the amide moiety of **5b**, the main product isolated was the corresponding rearranged acrylamide **6b** (47% yield), and the benzofused heterocycle **13b** was not detected (Scheme 2). Further modification of the substituent in the amide with a 2,6-dimethylphenyl group (**5c**) resulted in decomposition of the starting material and no major product was isolated. The limited information regarding such rearrangements led us to examine the scope of

**Table 1**
Influence of the equivalents of catalyst, base and halide used in the transformation.




| Entry | X | Time (h) | Catalyst | Base | **6a** (%) | **13a** (%) |
|---|---|---|---|---|---|---|
| 1 | Br | 6 | 10% | 2.0 eq | 61 | 14 |
| 2 | Br | 12 | 10% | 1.5 eq | 33 | – |
| 3 | Br | 12 | 10% | 1.0 eq | 30 | – |
| 4 | Br | 12 | 5% | 2.0 eq | 27[a] | – |
| 5 | Cl | 48 | 10% | 2.0 eq | 25[b] | – |

[a] 25% of starting material recovered.
[b] 38% of starting material recovered.

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the process with different dehydroalanines. Interestingly, these starting materials are likely to rapidly accessed through the same Ugi-4CR/elimination protocol used for the preparation of **5a–c** (Scheme 2).[13] At the outset, we envisioned that since the Ugi 4-CR couples four different substrates (an aldehyde, a carboxylic acid, an amine, and an isocyanide) in a single adduct, this approach would offer the opportunity to prepare diversely functionalized dehydroalanines. Thus, several of these molecules were synthesized in good yields using benzyl and phenethyl amines, and various carboxylic acids and isocyanides (Table 1). 2-benzoyloxy acetaldehyde was used in all experiments, since this component is the source of the double bond in the final product (See Table 1 in the Supplementary material structures and yields of the synthesis of dehydroalanines).

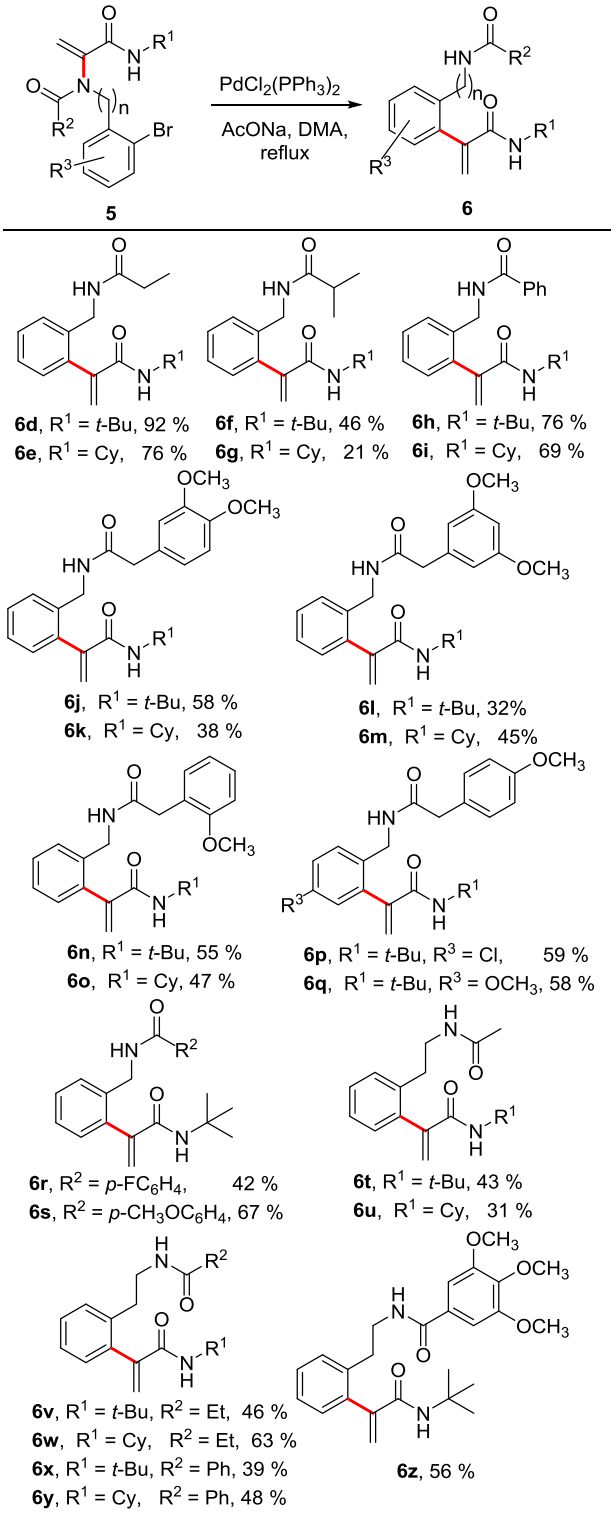
With the starting materials in hand, we turned our attention to the scope and limitations of the Pd-catalyzed olefin-rearrangement process. Straightforwardly, a wide range of dehydroalanines with different substitution patterns were used in this reaction, affording the corresponding 2-arylacrylamides in moderate to good yields (Table 2).

When **5d** (Table 2, $R^1$ = *tert*-butyl, $R^2$ = ethyl) was exposed to the palladium-mediated transformation used for **5a** [10 mol% of $PdCl_2(PPh_3)_2$ and 2 equivalents of AcONa in refluxing DMA], the 1,4-migration product **6d** was obtained exclusively in high yield (92%). This styrene derivative remained as the main product even when the experiment was conducted at reflux temperature for 96 h. Neither the 5-*exo* cyclization nor the pyrroloisoindolone products were detected. Firstly, we were interested in determining if the isocyanide used in the Ugi 4-CR had an effect on the course of the transformation. Gratifyingly, when the *tert*-butyl group was replaced by a cyclohexyl, we observed the formation of a structurally analogous rearrangement product (**6e**) in 76% yield, indicating that the nature of the isocyanide had only a minor effect on the 1,4-migration process.

We next modified the structure of the carboxylic acids utilized in the Ugi 4-CR set and subjected these compounds to the rearrangement conditions. Both the isobutyric and benzoic acid derived Ugi compounds afforded the expected styrene derivatives (**6f–g** and **6h–i**) respectively in yields of 21–76%. Furthermore, arenes substituted with different methoxy substitution patterns (**6j–q**) when submitted to the 1,4-migration conditions also gave the expected styrene derivatives. Notably, neither electron withdrawing nor electron donating substituents in the benzylamine ring (**6p** and **6q**, respectively) had a significant effect on the global yield. In a similar way, when the phenyl ring was decorated with an electron withdrawing (F, **6r**) or an electron donating group ($OCH_3$, **6s**), the reaction also proceeded.

At this point, the viability of the 1,4-migration was corroborated with the synthesis of several examples in modest to good yields. Nonetheless, in the search for expanding the molecular diversity in the chemical space and the scope of the methodology, we extended the reaction by using dehydroalanines derived from phenethylamine. We envisioned that this slight change in the structure of the starting materials would provide 1,5-migration products that have been scarcely reported in the literature. We treated the dehydroalanine obtained from phenethylamine, *tert*-butyl isocyanide, and acetic acid with the standard 1,4-migration conditions and, satisfactorily, the expected 1,5-migration product styrene **6t** was obtained in moderate yield. Guided by this result, several phenethyl-containing dehydroalanines were obtained and reacted under the same migration conditions. This transformation was effective with aliphatic chains in moderate yields (**6u–w**) and also with aromatic rings with or without electron donating groups (**6x–z**, Table 2). This outcome was significant since, to our knowledge, only one example concerning a related 1,5-double bond migration has been reported so far.[11]

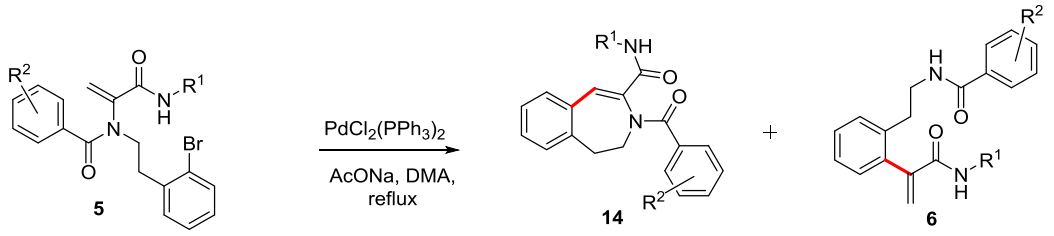
**Table 2**
Scope of the migration reaction *via* palladium catalysis.




Reaction conditions: $PdCl_2(PPh_3)_2$ (10 mol%), AcONa (20 mol%), DMA (0.06 M), reflux, 6–12 h.

Interestingly, when dehydroalanine contained a phenethyl moiety, bearing an electron withdrawing group (F, Cl, $NO_2$), the major isolated product corresponded to the benzoazepine **14a**, formed through an uncommon 7-*endo* cyclization (Entry 1–3, Table 3).[11] The structure of **14a** was confirmed by X-ray crystallography (CCDC number 1532294). Similarly, the 7-*endo* cyclization products were

**Table 3**
Synthesis of benzoazepines **14a–f** and 1,5-migration products.




| Entry | Substrate | $R^1$ | $R^2$ | **14** (%yield) | **6** (%yield) |
|---|---|---|---|---|---|
| 1 | **5aa** | *t*-Bu | *m*-$NO_2$ | 48 | – |
| 2 | **5ab** | *t*-Bu | *p*-Cl | 43 | – |
| 3 | **5ac** | *t*-Bu | *p*-F | 43 | – |
| 4 | **5ad** | Cy | *p*-Cl | – | 11 |
| 5 | **5ae** | Adamantyl | *p*-Cl | 17 | 20 |
| 6 | **5af** | Cy | *p*-F | 18 | Traces |

Reaction conditions: $PdCl_2(PPh_3)_2$ (10 mol%), AcONa (20 mol%), DMA (0.06 M), reflux, 6–12 h.

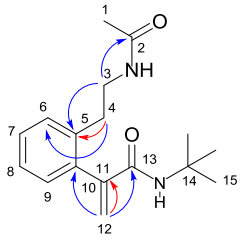
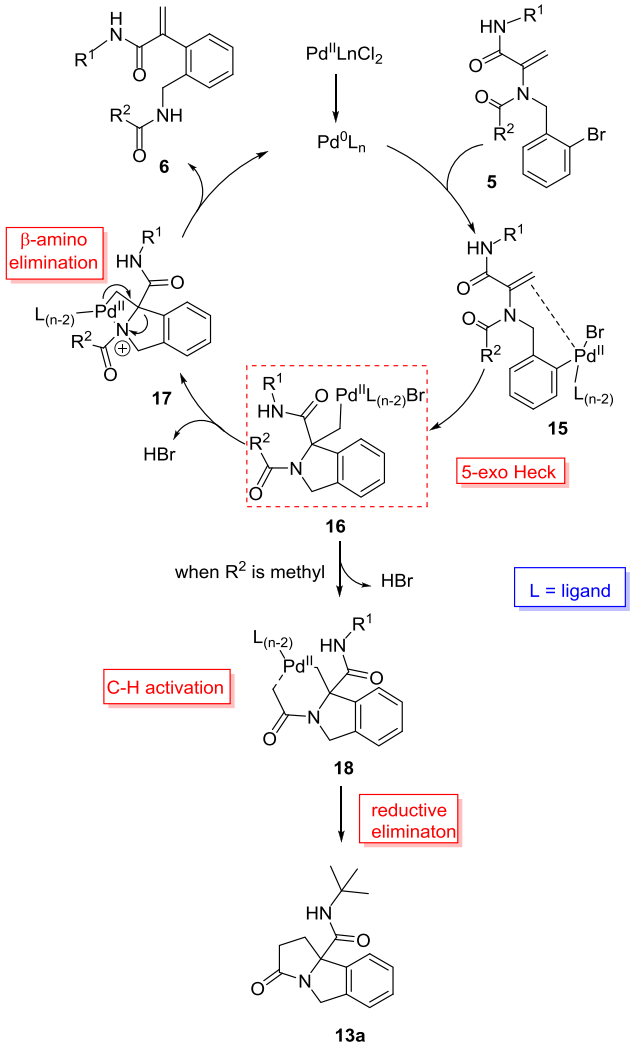



**Fig. 2.** Selected HMBC correlation of **6t**. Red and blue arrows show two and three bond correlations, respectively.

observed when dehydroalanines **5aa** and **5ab**, ($R^1$ = *tert*-butyl) were reacted under the same conditions. Nonetheless, when the *tert*-butyl group was replaced by cyclohexyl or adamantly groups (Entry 4–6, Table 3) both cyclization and rearrangement products were observed, although in low yields.

Even though the desired 1,5-double bond migration was not observed, the *7-endo* cyclization makes this result significant, since normally *6-exo* paths are expected to predominate over the *7-endo* counterparts.[11,15] Apparently, the electron-withdrawing groups strongly affect the electronic nature of the double bond and the molecular conformation of the dehydroalanine, in a way that the *7-endo* pathway efficiently competes with the *6-exo* cyclization. However, the actual reason for this preference remains unclear so far. Nevertheless, these experiments streamline and expand the scope of the *7-endo* Heck cyclization.[11] In this context, Overman and co-workers have described a related cyclization through typical Heck conditions during the synthesis of the terpene guanacastepene N,[16] while Gevorgyan reported a *7-endo* cyclization of phenolic ethylsilyl ethers to construct allyl silanes through a Pd-radical process.[17]

The characterization of all compounds was made through conventional spectroscopy and spectrometry. Additional bidimensional experiments (COSY, HSQC and HMBC) and DEPT-135 were necessary to confirm the structure of alkene-migration products (see Supplementary material). As an example, the NMR characterization of **6t** will be discussed. $^1$H NMR signals indicated the presence of a terminal alkene, thus no cyclization had occurred. Moreover, the existence of four hydrogens in the aromatic region confirmed that two positions of the aromatic ring were substituted. Furthermore, the methyl of the acetyl group also remained unchanged. On the other hand, DEPT-135 confirmed the presence of three methylenes, one being an alkene. A COSY experiment indicated that the methylene from the aliphatic region was coupled




**Scheme 3.** Proposed mechanism for 1,4- and 1,5-double bond rearrangement of dehydroalanines.

with the NH proton (broad signal). Finally, the expected correlations were observed in the bidimensional HMBC experiment (Fig. 2): correlations for H-12 (alkene) with C-13 ($\delta$ 166.6), C-10 ($\delta$ 137.5), C-11 ($\delta$ 145.3). Additionally, H-3 was correlated with

C-2 ($\delta$ 170.2) and C-5 ($\delta$ 137.2), and H-4 with C-5($\delta$ 137.2) and C-6 ($\delta$ 129.7).

A plausible mechanism for the 1,4- and 1,5-double bond migration reported in this work may involve the oxidative addition to form the intermediate **15** from dehydroalanine **5** (Scheme 3). Then, an intramolecular *5-exo* reaction takes place to form **16**,[18] and, as a key step, the N–C bond cleavage occurs through β-amino elimination of **17**. In the final stage, protonolysis provides **6** and Pd(0), completing the catalytic cycle. Indeed, this mechanistic proposal is supported by the isolation of compound **13a** via **18** (Scheme 3), which in principle results from a C–H insertion.[11] Thus, the transformation discussed in this work streamlines the Pd-catalyzed C–N bond cleavage observed previously in related substrates.[19]

In summary, we have developed a palladium catalyzed 1,4-alkene migration of dehydroalanine-type compounds catalyzed with palladium. It is interesting to note that this type of rearrangement has not been fully explored previously and we consider it to be an important contribution to modern palladium-based chemistry. Additionally, and more meaningfully, we expanded the protocol by obtaining 1,5-migration products of homologated starting materials, a rare transformation with only one example reported to date. The synthesis of benzoazepines through a *7-endo* Heck cyclization was also observed, starting from the same substrate. Further studies should be required to explore scope of the benzopyrrolizidine formation process outlined in Scheme 2.

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## A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.058.

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