A three-component approach to isoquinoline derivatives by cycloaddition/Heck reaction sequence

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Abstract—Here, we report a three-component coupling reaction approach between an aldehyde, an allyloxyamine, and a maleimide toward isoquinoline derivatives. At first, an oxime O-allylic ether, prepared by dehydrative condensation of the aldehyde and the allyloxyamine, was reacted with the maleimide in the presence of a Pd 2+ species. The cycloadduct obtained was then subjected to the Heck cyclization employing a Pd 0 species to give thermodynamically stable diastereomer of isoquinoline derivatives selectively in 25–78% yields.

Not only frequently found in naturally occurring alkaloids, the di- and tetrahydroisoquinoline nuclei are but also an important pharmacophore. Typical examples include papaverine (smooth muscle relaxant),1 safranycin-B (antitumor agent),2 indenoisoquinoline (topoisomerase I inhibitor),3 and narciclasine (antitumor agent).4 Several methods have been reported to construct the isoquinoline framework, including the Bischler–Napieralski reaction approach on β-phenethylamine derivatives toward dihydroisoquinolines.5

We have been interested in the construction of the isoquinoline scaffold by multicomponent coupling reactions so that a library of diverse isoquinoline derivatives can be accessible by a split-pool synthesis on insoluble polymer beads. Our approach is shown in Scheme 1. The components employed in this study are iodobenzaldehydes 1, allyloxyamines 2, and maleimides 5. These components were coupled sequentially leading to di- or tetrahydroisoquinolines 8 as follows. First, aldehyde 1 and allyloxyamine 2 were dehydratively condensed to the chemically stable oxime O-allylic ether 3, which was then subjected to isomerization to nitrone 4 by the action of Pd 2+, followed by 1,3-dipolar cyclization with the dialpolarophile maleimides 5 to give iodoolefin 6. Upon exposure to Pd 0, 6 underwent intramolecular Heck cyclization to the isoquinoline derivative 8.

Two questions arose in this work: (1) does the isomerization toward nitrone (3 → 4) proceed intramolecularly? and (2) is the stereochemistry of the isoquinoline derivative 8 controlled throughout the synthesis? The first question is particularly important if the synthesis is attempted in a split-pool manner, and the second issue arose since stereocontrol of oxime formation and 1,3-dipolar cycloaddition is generally quite poor.

The 1,3-dipolar cycloaddition was performed by the procedure originally reported by Grigg et al.6 Since they have examined only the oxime O-allyl ether and O-crotyl ether, we at first synthesized benzoxime O-(α-methylallyl) ether (11)7 by a dehydrative condensation (Na2SO4, THF, 60 °C) of benzaldehyde (9) with (α-methyl)allylloxamine (10)8 in 93% isolated yield (trans/cis = 86:14) to invest the reaction course (Scheme 2). By exposure to 0.15 equiv of PdCl2(CH3CN)2, in the presence of N-methylmaleimide (12), nitroine formation from 11 followed by the cycloaddition took place smoothly to give cycloadduct 13 in 85% yield with no significant stereoselectivity (54:46).9 However, the α-methylallyl group in 11...
was completely transformed into the crotyl group in 13, indicating that the nitrone formation proceeds by a formal [2,3]-sigmatropic rearrangement process obviously through addition/elimination of the Pd$^{2+}$ species.

We then synthesized three oxime O-allylic ethers 14, 16$^6$ and 17 for crossover experiments to know if the nitrone formation has possibilities to allow scrambling of the partners (Scheme 3). At first, equimolar amounts of 11 and 14 were mixed and subjected to the cycloaddition with N-methylmaleimide. After 72 h, two products were chromatographically separated, and the less polar and the polar products were determined to be 13 ($96\%$, $\alpha$-H/$\beta$-H = 57:43) and 15 ($65\%$, $\alpha$-H/$\beta$-H = 57:43), respectively.$^{11}$ Another combination (16 and 17$^6$) was next subjected to the reaction, and two products 18 (polar, $58\%$, $\alpha$-H/$\beta$-H = 50:50)$^{11}$ and 19 (less polar, $99\%$, $\alpha$-H/$\beta$-H = 56:44)$^6$ were also isolated cleanly. Not even trace amounts of crossover products (18 and 19 in the former reaction, and 13 and 15 in the latter reaction) were detected, indicating that nitrone formation proceeds completely in an intramolecular fashion.

Efficient conditions for the Heck cyclization of iodoolefin 20$^5$ leading to the dihydroisoquinoline scaffold were next investigated. After several experiments with various catalysts, ligands, bases, additives, and solvents, the best result was found to be achieved by employing a simple combination of 0.15 equiv of Pd(PPh$_3$)$_4$ and 2.0 equiv $i$-Pr$_2$NEt in $N,N$-dimethylacetamide (DMA) at 100 °C for 4 h (Scheme 4). It should be especially noted that triphenylphosphine, frequently used as an additive, causes significant reductive decomposition presumably at the N–O bond to lower the yield to 49%. Another finding in this reaction is that the diastereomeric ratio of the cyclized product 21, $\alpha$-H/$\beta$-H = 80:20, is inconsistent with that of iodoolefin 20 ($\alpha$-H/$\beta$-H = 53:47) employed. Since thermodynamic equilibrium was suspected from the result, we carried out several experiments, and finally found that $\beta$-isomer 21$\beta$ completely isomerizes into $\alpha$-isomer 21$\alpha$ just upon heating to 100 °C for 5 h in DMA. A prolonged reaction (22 h) for the Heck reaction of 20 gave 21$\alpha$ with complete stereoselectivity but in lower yield (68%) because of the decomposition. The structure of product 21$\alpha$ was unambiguously determined by a single crystal X-ray diffraction analysis.$^{13,14}$ Although the mechanistic comprehension of this isomerization requires further study, this is reasonably accounted for by the energy difference (3.33 kcal/mol) between 21$\alpha$ and 21$\beta$ calculated at the MMFF94S force field (CON- 

Finally, iodoolefins with substituents on the allyl moiety were subjected to the Heck cyclization (Scheme 5). As compared to the unsubstituted substrate 20, these reac-

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**Scheme 1.**

**Scheme 2.** Reagents and conditions: (a) Na$_2$SO$_4$, THF, 60 °C, 24 h, 93%, (b) PdCl$_2$(CH$_3$CN)$_2$ (0.15 equiv), CHCl$_3$, 60 °C, 50 h, 85%.
tions on 24–26 were found to be sluggish, and the yields for 27–29 were apparently lower (33–63%). However, the point that should be much emphasized is that the stereoselectivity is completely controlled in these cases; (1) the stereochemistry of the carbon α to the N–O functionality is α-orientated as in the cases for 21α–23α,16,17 (2) the double bond takes trans configuration, and (3) another benzylic carbon nearby the allyl group is also controlled to be R*. These stereochemistries, determined from NMR analysis, are the thermodynamically most stable configurations from the molecular modeling at

Scheme 3. Reagents and conditions: (a) N-methylmaleimide (12), PdCl₂(CH₃CN)₂ (0.15 equiv), CHCl₃, 60 °C, 72 h.

Scheme 4. Reagents and conditions: (a) Pd(PPh₃)₄ (0.15 equiv), t-Pr₂NEt (2.0 equiv), N,N-dimethylacetamide, 100 °C, 4 h, 21α/21β = 78%:20%, (b) N,N-dimethylacetamide, 100 °C, 5 h, 92%.

Figure 1. Dihydroisoquinolines 22α and 23α synthesized by the cycloaddition/Heck reaction approach.
the MMFF94S force field (CONFLEX).\textsuperscript{14,15} In all cases, unreacted iodoolefins were recovered after the reaction.

In summary, we have developed a stereoselective three-component coupling approach to isoquinoline derivatives. Though the intermediary cycloadducts \textsuperscript{6} were obtained as a diastereomeric mixture, the finally synthesized isoquinolines \textsuperscript{8} were diastereomerically controlled to one isomer under thermodynamic conditions by an as yet unclear mechanism. In addition, we have given clear evidence for the intramolecular, formal [2,3]-sigmatropic rearrangement of the Pd\textsuperscript{2+}-catalyzed nitrone formation. Work is in progress toward realization of a di- and tetrahydroisoquinoline library, and application of the present methodology to biologically important natural products.

References and notes

9. The change of the diastereomeric ratio in this 1,3-dipolar cycloaddition would be attributed to the isomerization of the intermediary nitrone.\textsuperscript{6} The stereochemistries of these products (13\textsuperscript{a}, 13\textsuperscript{b}) were determined by \textsuperscript{1}H–\textsuperscript{1}H J-coupling constants and NOESY experiments, and finally confirmed by X-ray diffraction analysis of 21\textsuperscript{a}.
10. Oxime O-allylic ethers 14 and 16 were prepared from 2-bromo-3-hydroxy-4-methoxybenzaldehyde over 4 and 5 steps for 60\% and 46\% yields, respectively.
11. The stereochemistries of these products were determined by \textsuperscript{1}H–\textsuperscript{1}H J-coupling constants and NOESY experiments, and finally confirmed by analogy with the synthesis of 21\textsuperscript{a}.
12. Prepared from 2-iodobenzaldehyde as for 13 shown in Scheme 2 over 2 steps (66\% yield).
13. The crystallographic data for 21\textsuperscript{a} have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number, CCDC 620027. Dihydroisoquinoline 21\textsuperscript{a} has been also recently synthesized by an alternative four-component coupling approach, see: Don-das, H. A.; Fishwick, C. W. G.; Gai, X. J.; Grigg, R.; Kilner, C.; Dumrongchai, N.; Kongkathip, B.; Kongkathip, N.; Polysuk, C.; Sridharan, V. Angew. Chem., Int. Ed. 2005, 44, 7570–7574.
14. The details will be reported in the full account of this research.
15. Calculated on BARISTA software (BARISTA, version 1.2.2; CONFLEX Co., Yotsuya 4-30, Shinjuku-ku, Tokyo 160-0004, Japan).
16. A considerable amount (30\%) of the trisubstituted, olefin isomer of 27\textsuperscript{a} was also detected in the Heck cyclization of 24.
17. In the cases for the synthesis of 28\textsuperscript{a} and 29\textsuperscript{a}, unreacted \(\beta\)-isomer of 25 (33\%) and 26 (33\%) were recovered after the reaction, indicating these \(\beta\)-isons are less reactive than the \(\alpha\)-isomer. Because prolonged reaction was found to cause decomposition from the experiment of 20, we are currently optimizing the other reaction conditions for this transformation.