Tetrahedron Letters 53 (2012) 1468–1471

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric induction in domino Heck-aza-Michael reactions

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ARTICLE INFO

Article history:
Received 12 July 2011
Revised 21 December 2011
Accepted 10 January 2012
Available online 18 January 2012

Keywords:
Stereoselective
Domino reaction
Palladium
N-heterocycles

ABSTRACT

Domino Heck-aza-Michael reactions are an efficient method for the rapid synthesis of functionalised N-heterocycles. An asymmetric version of this domino process has been developed to access chiral 1,3-disubstituted N-heterocycles from amino acid precursors in excellent yields (68–81%) with moderate to high diastereoselectivity (up to 92% de).

Chiral C1-substituted N-heterocyclic scaffolds are prevalent in many biologically important natural products and medicinal chemistry agents, including ajmalicine (**1**) and quinocarcinol (**2**) (Fig. 1).[1] As such, the synthetic methods employed for the preparation of ring systems of such N-heterocycles must allow for the introduction of the desired chiral centre at the C1-position.

Recent publications have described rapid and high yielding domino Heck-aza-Michael reactions for the synthesis of C1-substituted N-heterocycles (including tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines),[2] however a method that is efficient and highly stereoselective has not yet been reported. To this end, we herein describe the development of an asymmetric domino Heck-aza-Michael process for the synthesis of a range of

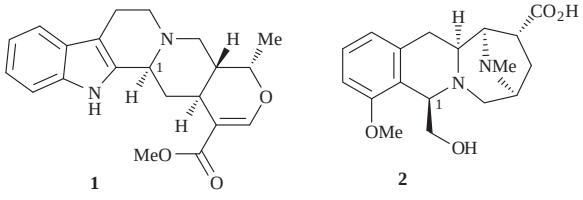
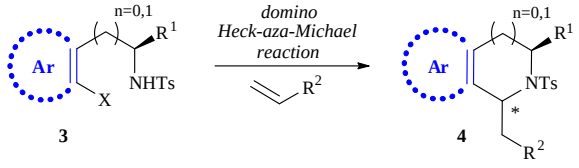
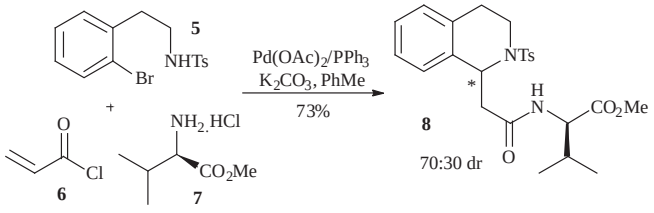


Figure 1. Natural products containing a chiral C1-substituent.



Scheme 1. The proposed stereoselective domino Heck-aza-Michael reaction employing chiral amine substrates.



Scheme 2. The asymmetric three-component domino Heck-aza-Michael reaction.

chiral 1,3-disubstituted N-heterocycles (general structure **4**) from amino acid derived precursors (**3**) in good yields with moderate to high diastereoselectivity (Scheme 1).

During previous investigations into a three-component domino Heck-aza-Michael protocol with 2-bromophenethylamine substrates,[2b] for example compound **5**, the use of L-valine methyl ester (**7**) afforded the tetrahydroisoquinoline amide **8** as a 3:7 mixture of diastereomers (Scheme 2). Unfortunately, further attempts to exploit this approach using other amino acids, (−)-pantolactone acrylate or (+)-menthol acrylate did not improve the diastereoselectivity.

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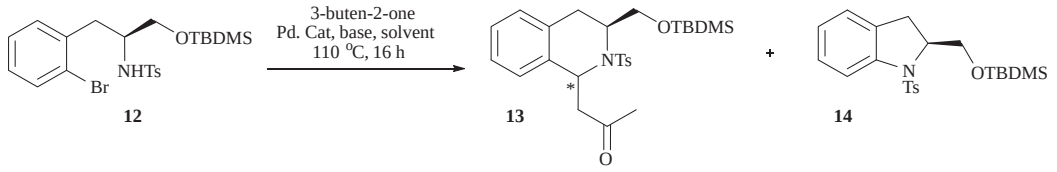
doi:10.1016/j.tetlet.2012.01.037

Table 1
Optimisation of the asymmetric domino process for tetrahydroisoquinoline synthesis



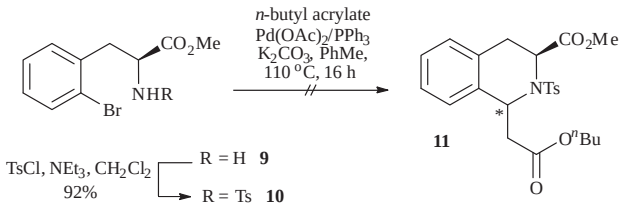
Entry	Pd catalyst [a]	Base	Major products (% conversion)
1	$Pd(OAc)_2/PPh_3$	K_2CO_3	THIQ **13** (30%)
2	$Pd_2(dba)_3$/DavePhos	K_2CO_3	THIQ **13** (50%), indoline **14** (50%)
3	$Pd_2(dba)_3/P(tBu)_3$	K_2CO_3	Indoline **14** (100%)
4	$Pd_2(dba)_3/PPh_3$	K_2CO_3	THIQ **13** (10%), indoline **14** (90%)
5	$Pd(OAc)_2/P(tBu)_3$	K_2CO_3	Indoline **14** (100%) [b]
6	$Pd(OAc)_2/PPh_3$	Cy_2NMe	No reaction
7	$Pd(OAc)_2/PPh_3$	Na_2CO_3	No reaction
8	$Pd(OAc)_2/PPh_3$	K_2CO_3 [c]	THIQ **13** (70%)[d], indoline **14** (30%)

Reaction conditions: Reaction was performed in a sealed tube containing the aryl halide (1.0 equiv), 3-buten-2-one (1.2 equiv), Pd catalyst (10 mol %), and base (3.0 equiv) in PhMe (4 mL). The reaction mixture was then heated to 120 °C for 16 h.
[a] Palladium catalyst loading: 10 mol %. Pd–ligand ratio was 1:1.
[b] The C–N cross coupling adduct was isolated in a yield of 97%.
[c] 5.0 equiv of K_2CO_3 and 2.0 equiv of 3-buten-2-one were used.
[d] The domino adduct was isolated in a yield of 68%.

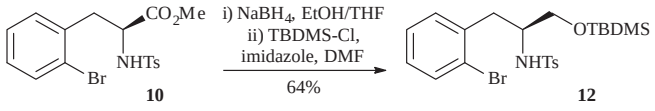
As such, attention turned to the use of chiral amine starting materials, which have been used to great effect in asymmetric synthesis, especially in the case of stereoselective aza-Michael addition.[2g,3] Initial investigations into the asymmetric domino Heck-aza-Michael reaction using chiral amines were performed with L-2-bromophenylalanine (**9**). Following protection of the amine with a tosyl group in a 92% yield (this was identified as the optimal protecting group in previous studies),[2a–c] the domino substrate **10** was subjected to the previously identified domino Heck-aza-Michael conditions for tetrahydroisoquinoline synthesis (Scheme 3).[2c]

Following a simple work-up, analysis of the crude product reaction mixture indicated that only a Heck reaction had occurred and no domino reaction product **11** was observed. It was reasoned that the methyl ester in close proximity to the sulfonamide was inductively drawing electron density away from the sulfonamide, making it much less nucleophilic than in the case of 2-bromophenethylamine **5** previously employed by our group.[2c]

In an effort to improve the nucleophilicity of the nitrogen of phenylalanine **10**, the ester was reduced to the corresponding alcohol using $NaBH_4$ and subsequently converted into the TBDMS ether



Scheme 3. Attempted stereoselective synthesis of 1,3-disubstituted tetrahydroisoquinolines.



Scheme 4. Modification of the domino precursor for the asymmetric synthesis of tetrahydroisoquinolines.

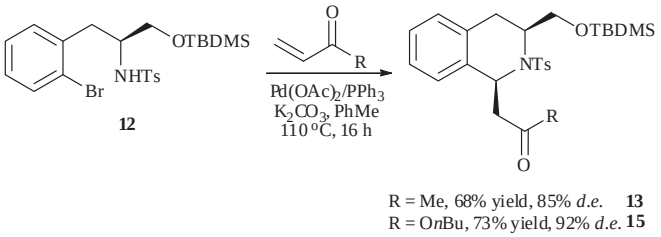
12 (Scheme 4). In this way, amine **12** should become more nucleophilic than its precursor **10**, whilst retaining the requisite stereogenic centre—in fact the additional steric bulk of the *tert*-butyldimethylsilyl ether should further improve the stereoselectivity of this domino process.

The stereoselective synthesis of tetrahydroisoquinolines (THIQs) with this new precursor was then investigated using a range of catalytic conditions and the major product in each attempt was initially assessed by ^1H NMR spectroscopy (Table 1). It was noteworthy that during these optimisation studies, the major by-product identified was due to the intramolecular C–N (or Buchwald–Hartwig) cross-coupling to form the five-membered indoline scaffold **14**, even when traditional catalysts for this type of reaction were not employed.[‡]

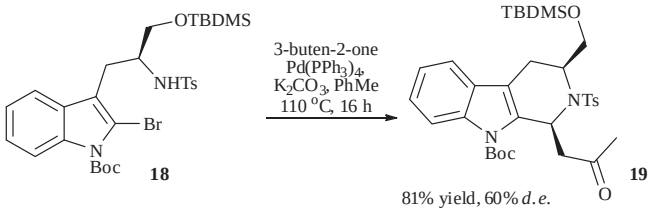
The first reaction was trialled using the conditions previously reported for the synthesis of tetrahydroisoquinolines (Table 1, entry 1).[2c] The major product identified from this reaction was the Heck-aza-Michael adduct **13**, however, the conversion was poor (<30%). To increase the rate of the intermolecular Heck reaction, other catalytic conditions employing electron-rich phosphines were trialled (Table 1, entries 2–5). In these reactions, conversion into the desired domino product was increased (up to 50%, entry 2), however, formation of the indoline **14** through an intramolecular C–N cross-coupling reaction (Buchwald–Hartwig reaction) was favoured under these more active catalytic conditions. In fact, complete conversion (97% isolated yield) to this indoline **14** was realised when the $P(tBu)_3{\cdot}HBF_4$ salt was employed as a ligand (Table 1, entries 3 and 5).[4] Further attempts using the $Pd(OAc)_2/PPh_3$ catalyst with two alternative bases failed to produce the domino adduct (Table 1, entries 6 and 7).

Eventually it was discovered that by increasing the equivalents of both the alkene (from 1.2 to 2.0), and base (from 3.0 to 5.0), the domino reaction produced tetrahydroisoquinoline **13** in 70% conversion (with 30% of the C–N adduct **14** also identified, Table 1, entry 8). Following column chromatography, the tetrahydroisoquinoline ketone **13** was isolated in a yield of 68%. The diastereomeric excess was determined by chiral HPLC, confirming the

[‡] Although always considered a possibility, the product formed due to C–N coupling had not been observed during previous investigations into the domino Heck-aza-Michael process.[2a–c]



Scheme 5. The asymmetric domino Heck-aza-Michael reaction for the synthesis of chiral 1,3-disubstituted tetrahydroisoquinolines.



Scheme 7. The asymmetric domino Heck-aza-Michael reaction for the synthesis of a C1-substituted tetrahydro-β-carboline.

asymmetric domino reaction had afforded the major diastereomer in 85% de. When *n*-butyl acrylate was employed as the alkene substrate in the asymmetric domino reaction, the butyl ester tetrahydroisoquinoline **15** was produced in a 73% yield with 92% de (Scheme 5).

The *cis*-diastereomer was determined to be the major isomer formed during this domino process, with both the C1 and C3 proton resonances exhibiting a through space NOE interaction with the aromatic protons of the tosyl protecting group, closest to the sulfonyl motif, an interaction that can only be achieved if both these protons are *syn* related (Fig. 2). The stereochemistry was imparted during aza-Michael addition, where following formation of the Heck adduct, the chiral amine was held in such a position that it could only attack the planar double bond from one side preferentially, resulting in the formation of *cis*-isomer as the major product. It was further proposed that the additional bulk of the silyl ether group, and the resultant unfavourable steric interaction with the proximal tosyl group, retained the position of the chiral amine intermediate during the domino reaction, even at high temperatures, enhancing the stereoselectivity of this process.

The asymmetric domino Heck-aza-Michael reaction was then investigated for the synthesis of chiral 1,3-disubstituted isoindolines. Reaction of the phenylglycine based domino substrate **16** with *n*-butyl acrylate (Scheme 6) was performed using the conditions previously identified for isoindoline formation.[2c]

The butyl ester isoindoline **17** was isolated in a 79% yield. The stereoselectivity of this domino process was confirmed by chiral HPLC (revealing an 87% de). In accordance with previous experiments, the major diastereomer from the reaction sequence to form

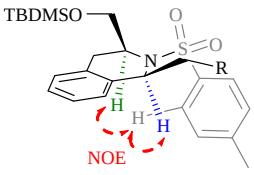
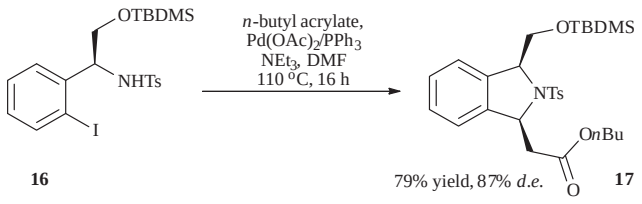


Figure 2. The *cis*-isomer was the major diastereomer formed during the asymmetric domino process.



Scheme 6. The asymmetric domino reaction for the synthesis of a 1,3-disubstituted isoindoline.

isoindoline **17** (Scheme 6) was again identified as the *cis*-isomer by means of NOE experiments.

The third N-heterocycle pursued using an asymmetric domino Heck-aza-Michael reaction was a tetrahydro-β-carboline. The introduction of a stereocentre at the C1-position of the tetrahydro-β-carboline (THβC), using tryptophan with a protected carboxylic acid moiety, has been employed using the Pictet–Spengler reaction.[5] Following a similar procedure to that employed for the THIQ and isoindoline precursors, the domino substrate **18** was prepared from L-tryptophan methyl ester (refer to Supplementary data). The asymmetric domino process was again attempted, this time using 3-buten-2-one (Scheme 7).[2a]

Following a simple work-up, the crude product was purified by column chromatography to afford the desired tetrahydro-β-carboline ketone **19** in an 81% yield as an inseparable mixture of diastereomers (Scheme 7). Following analysis by chiral HPLC, the diastereomeric ratio of the product was identified as 80:20 and the major product formed from this domino process was the *cis*-isomer (again determined using NOE experiments).

In summary, a general asymmetric domino Heck-aza-Michael process, using precursors derived from chiral amino acids, was successfully developed for the synthesis of 1,3-disubstituted tetrahydro-β-carbolines, tetrahydroisoquinolines and isoindolines in good yields (68–81%) and with moderate to excellent diastereoselectivity (60–92% de). Further extension of the substrate scope to include additional alkenes and the role of the silyl protecting group are currently under investigation.

Supplementary data

Supplementary data (experimental procedures and selected NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.037.

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