C–H Functionalization Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202106716
German Edition: doi.org/10.1002/ange.202106716

Expedient Synthesis of Bridged Bicyclic Nitrogen Scaffolds via Orthogonal Tandem Catalysis

*Sovan Biswas[+], Ben F. Van Steijvoort[+], Marjo Waeterschoot, Narendraprasad Reddy Bheemireddy, Gwilherm Evano, and Bert U. W. Maes**

Abstract: *Bridged nitrogen bicyclic skeletons have been accessed via unprecedented site- and diastereoselective orthogonal tandem catalysis from readily accessible reactants in a step economic manner. Directed Pd-catalyzed γ-C(sp^3)-H olefination of aminocyclohexane with gem-dibromoalkenes, followed by a consecutive intramolecular Cu-catalyzed amidation of the 1-bromo-1-alkenylated product delivers the interesting normorphan skeleton. The tandem protocol can be applied on substituted aminocyclohexanes and aminoheterocycles, easily providing access to the corresponding substituted, aza- and oxa-analogues. The Cu catalyst of the Ullmann-Goldberg reaction additionally avoids off-cycle Pd catalyst scavenging by alkenylated reaction product. The picolinamide directing group stabilizes the enamine of the 7-alkylidenenormorphan, allowing further product post functionalizations. Without Cu catalyst, regio- and diastereoselective Pd-catalyzed γ-C(sp^3)-H olefination is achieved.*

Introduction

Conformational restriction by joining two rings is an effective tool to modify pharmacological characteristics of drug candidates and is a key, yet underrated, strategy in medicinal chemistry.[1] The fixation of functional groups in a biologically active conformation can provide more efficient and selective ligands for various targets, often also featuring improved ADME parameters (lipophilicity, solubility, metabolic stability) in comparison to the non-restricted scaffolds. Bridged bicyclic nitrogen scaffolds are conformationally restricted analogues of saturated aminocarbo- and aminoazacycles, ubiquitous structural motifs in natural products and active pharmaceutical ingredients (APIs).[2,3] Moreover complexity (as measured by fraction sp^3) and the presence of chiral centers correlates with success as compounds transition from discovery, through clinical testing, to drugs.[4] Considering these factors, bridged bicyclic nitrogen scaffolds have a huge potential in drug discovery, as exemplified with varenicline and tiotropium bromide commercial drugs featured in the top 200 pharmaceutical sales list of 2020.[5]

Among these bridged bicyclic nitrogen scaffolds, the normorphan (6-azabicyclo[3.2.1]octane) skeleton is especially attractive due to its rigidity, 3-dimensionality, high sp^3 carbon fraction (F sp^3),[4] and low molecular weight.[6] Moreover, it forms the backbone of several natural products (Figure 1)

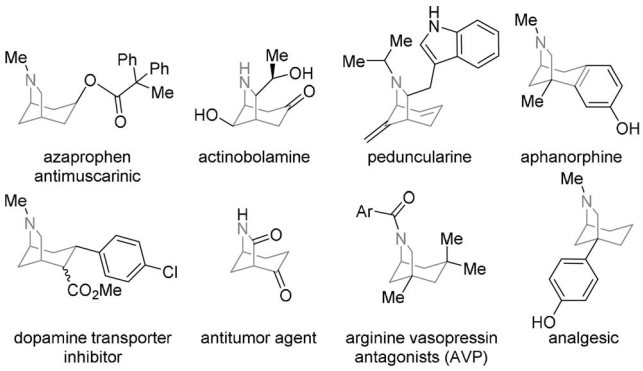

Figure 1. Selected natural products (first row) and synthetic bioactive molecules (second row) containing the normorphan nucleus.

and appears as a subunit in numerous alkaloids such as *D*-normorphinans, *C*-norbenzomorphans, sarain A, and hetisine.[7] They are interesting leads for drug development based on their biological activity.[6,8] While a number of synthetic strategies (Supporting Information, Figure S1) have been developed in the past decades to access the normorphan scaffold, the routes to 7-alkylidenenormorphans in which the exocyclic enamine provides ample possibilities for post functionalization is still limited. There are to date only three synthetic approaches disclosed to these structures (Figure 2 A).[7,9] While innovative in design, the routes still suffer from drawbacks including the number of steps and associated low overall yields, product selectivity issues, limited substrate scope and divergence, notably to access C-substituted derivatives and oxa- and aza-analogues from readily available substrates. Hence, practical syntheses (small number of steps from readily available precursors in high overall yield) of these bridged bicyclic nitrogen scaffolds is highly warranted to speed up the drug discovery process, still rate limited by organic synthesis.[10] Disconnections based on an uncommon

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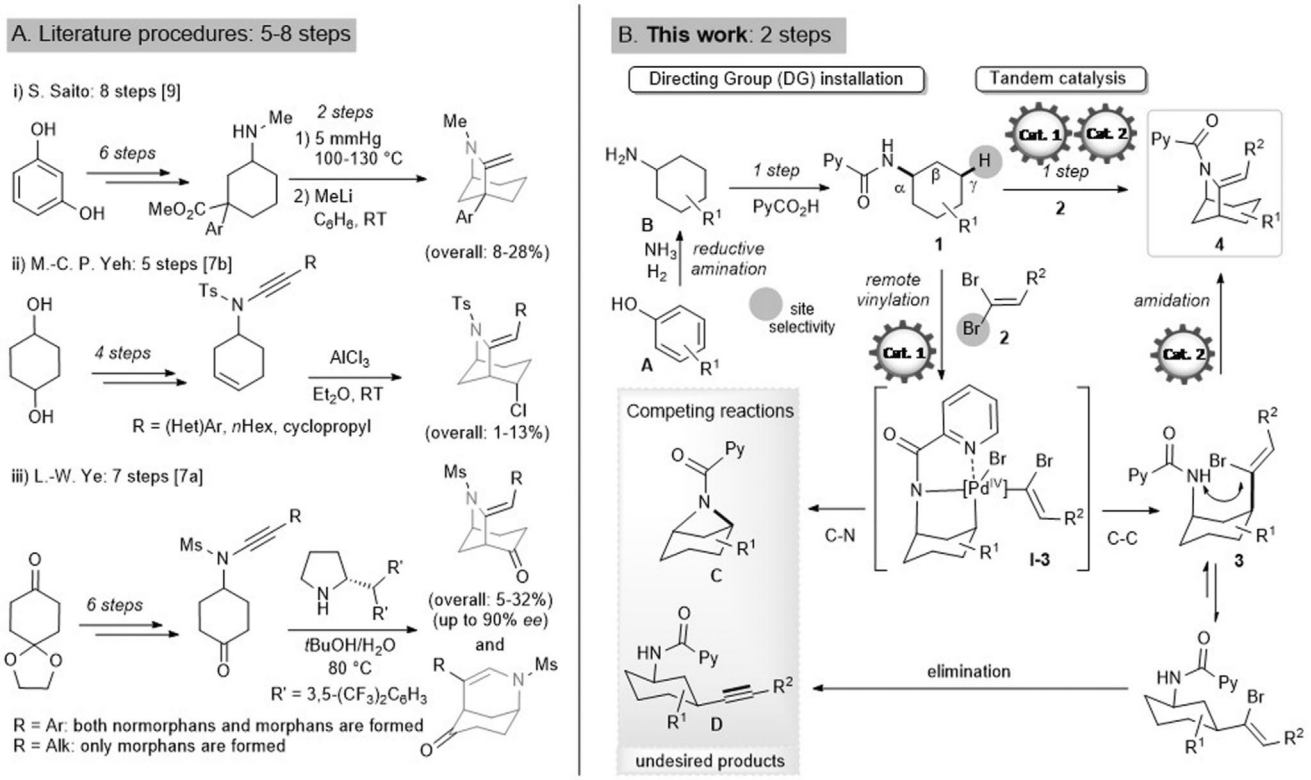


Figure 2. Synthesis of 7-alkylidenenormorphans. A) Literature approaches. B) New approach and challenges.

C–C bond formation via C(sp^3)-H functionalization and tandem catalysis are attractive to achieve this goal, though to date not yet explored.

Based on our interest in C(sp^3)-H functionalization reactions, a practical synthesis was envisioned by combining a directed C(sp^3)-H alkenylation with a consecutive amination from readily available aminocyclohexane derivatives **1** and 1,1-dibromo-1-alkenes **2** (Figure 2B).[11] The combination of C–C bond formation via unactivated C(sp^3)-H functionalization with other catalytic reactions in tandem catalysis has received little attention, despite its attractiveness.[12–14] Moreover, for the construction of challenging bridged bicycles it is not known. This enables an expedient synthesis of 7-alkylidenenormorphans provided that high levels of regio- and diastereoselectivities can be obtained. Our approach would actually involve the directed remote bromoalkenylation of **1** to **3** via transient palladium complex **I-3**, followed by a Pd- or Cu-catalyzed intramolecular amidation to the target normorphan **4** (Figure 2B). In our design, the amide DG has a dual role as it also stabilizes the enamine in the reaction product as its enamide, a valuable and versatile functional group in organic synthesis.[15] There are challenges associated to our strategy (Figure 2B). Based on reports on the use of directing groups,[16] the picolinamide is expected to provide γ-regioselectivity, though competing dehydrogenation cannot be excluded (not shown). Moreover, besides the desired product **3**, an alternative pathway from **I-3** could result in a ring closure to **C**. However, we assumed that this product selectivity could be controlled by both the difference in ring strain and by the nature of the halogen.[17] Finally, while 1,1-dihalo-1-alkenes are attractive and versatile coupling partners,[11] they are known to participate in site-selective, double as well as alkynylative cross-coupling reactions. This last mode strongly depends on the nature of the halogen atom, on the polarity of the solvent and on the nature of the ligands and bases utilized.[18] With a proper selection of these parameters, we should be able to block the undesired alkynylative coupling to **D**.

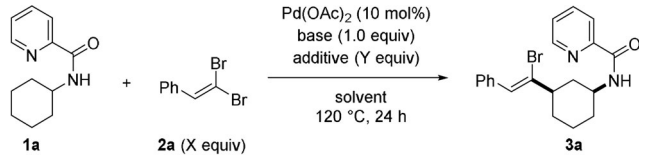
Results and Discussion

Initially, we focused on the γ-C-H-haloalkenylation. Besides being a challenging remote functionalization, the presence of two halogens in the *gem*-dihalovinyl reactant poses potential selectivity issues.[18,19] To the best of our knowledge only one DG-assisted γ-C(sp^3)-H alkenylation in cyclic systems has been reported. Chen described a Pd-catalyzed directed γ-C(sp^3)-H alkenylation of methyl 1-aminocyclohexane-1-carboxylate equipped with a picolinamide DG (**1b**) with cyclic vinyl iodides of different ring sizes, such as 1-cyclohexenyl iodide (**2aa**) (Supporting Information, Scheme S1).[20] When we applied these conditions for the γ-alkenylation of *N*-cyclohexylpyridine-2-carboxamide (**1a**), lacking the geminal ester making use of the same DG, no reaction was observed with **2aa** and only unreacted **1a** was recovered (Scheme S1A). This indicates that a geminal ester is crucial for the literature protocol. When **1a** was reacted with (2,2-dibromoethenyl)benzene (**2a**), a representative 1,1-dibromo-1-alkene, the desired product **3a** was only

obtained in 16% NMR yield with 84% **1a** recovery (Scheme S2). Clearly new reaction conditions are required for the remote alkenylation of **1a**.

Hence, we started a de novo optimization of the γ-C(sp^3)-H alkenylation reaction of **1a** with **2a** as model substrate. When 10 mol% $Pd(OAc)_2$, 1.5 equiv **2a**, and 1.0 equiv K_2CO_3 in 1,2-dichloroethane (DCE) were stirred at 120°C for 24 h, 52% conversion of **1a** and 48% of the desired product **3a** was obtained (Table 1, entry 1). With 0.4 equiv of PivOH as additive, both the conversion of **1a** and yield of **3a** were increased to 69% and 51%, respectively (Table 1, entry 2). Use of Ag_2CO_3 significantly reduced the yield, while Cs_2CO_3 gave a similar conversion and yield (Table 1, entries 3 and 4). When Rb_2CO_3 was employed, **3a** was formed in a slightly higher yield with a good mass balance (Table 1, entry 5). A number of carboxylic acid additives were subsequently screened (Supporting Information, Table S2). Sterically hindered aliphatic adamantanecarboxylic acid gave similar yields as pivalic acid, but acetic acid decreased both the conversion and product yield (Table 1, entries 6 and 7). To allow a more rigorous stirring, the reaction concentration was reduced to 0.13 M, which increased the yield to 71% (Table 1, entry 8). Solvent screening confirmed DCE to be the best solvent (Table S3; Table 2, entries 9–11). Adding the acid in its carboxylate salt form (PivOK) and using 2.0 equiv of **2a** delivered **3a** in 82% yield (Table 1, entries 12 and 13). Several ligands were also considered, but no improvement was observed (Scheme S5). Interestingly, re-evaluation of

Table 1: Optimization of the Pd-catalyzed γ-C(sp^3)-H alkenylation of **1a** with **2a**.[a]

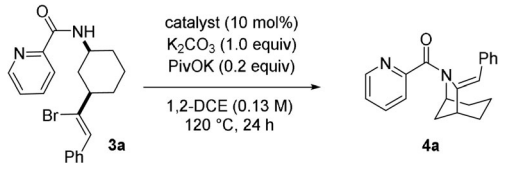


1a **2a** (X equiv) **3a**

Entry	**2a** [X equiv]	Base	Additive [Y equiv]	Solvent (conc.)	Conv. [%][b] **1a**	Yield [%][b] **3a**
1	1.5	K_2CO_3	–	DCE (0.2 M)	52	48
2	1.5	K_2CO_3	PivOH (0.4)	DCE (0.2 M)	69	51
3	1.5	Ag_2CO_3	PivOH (0.4)	DCE (0.2 M)	18	14
4	1.5	Cs_2CO_3	PivOH (0.4)	DCE (0.2 M)	68	54
5	1.5	Rb_2CO_3	PivOH (0.4)	DCE (0.2 M)	68	60
6	1.5	Rb_2CO_3	$AdCO_2H$ (0.4)	DCE (0.2 M)	69	59
7	1.5	Rb_2CO_3	AcOH (0.4)	DCE (0.2 M)	48	28
8	1.5	Rb_2CO_3	PivOH (0.4)	DCE (0.13 M)	77	71
9	1.5	Rb_2CO_3	PivOH (0.4)	1,4-dioxane (0.13 M)	72	59
10	1.5	Rb_2CO_3	PivOH (0.4)	toluene (0.13 M)	71	52
11	1.5	Rb_2CO_3	PivOH (0.4)	*t*BuOH (0.13 M)	14	4
12	1.5	Rb_2CO_3	PivOK (0.4)	DCE (0.13 M)	88	75
13	2.0	Rb_2CO_3	PivOK (0.4)	DCE (0.13 M)	92	82 (73)
14	3.0	Rb_2CO_3	PivOK (0.4)	DCE (0.13 M)	93	83
15	2.0	K_2CO_3	PivOK (0.4)	DCE (0.13 M)	92	81
16	**2.0**	**K_2CO_3**	**PivOK (0.2)**	**DCE (0.13 M)**	**92**	**82 (72)**
17[c]	2.0	K_2CO_3	PivOK (0.2)	DCE (0.13 M)	70	67

[a] Reaction conditions: **1a**, **2a** (1.5–3.0 equiv), $Pd(OAc)_2$ (10 mol%), base (1.0 equiv), additive (0–0.4 equiv), solvent (0.13–0.20 M), 120°C, 24 h, sealed pressure tube. [b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as internal standard (isolated yields in parentheses). [c] H_2O (10 equiv) was added. DCE = 1,2-dichloroethane, $AdCO_2H$ = 1-adamantanecarboxylic acid.

Table 2: Optimization of the Cu-catalyzed intramolecular C-Br amidation of **3a** to **4a**.[a]



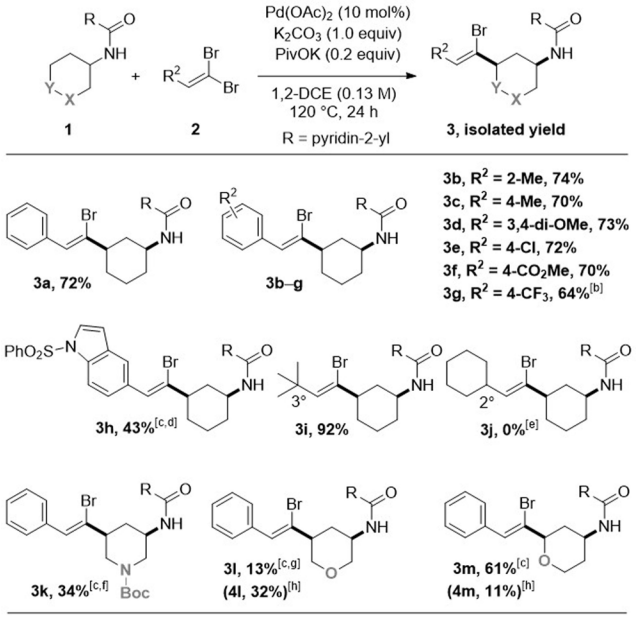
3a **4a**

Entry	Catalyst	Conv. [%][b] **3a**	Yield [%][b] **4a**
1	$Pd(OAc)_2$	14	0
2	$Cu(OAc)_2 \cdot H_2O$	100	87
3	**CuI**	**100**	**88 (85)**

[a] Reaction conditions: **3a**, catalyst (10 mol%), K_2CO_3 (1.0 equiv), PivOK (0.2 equiv), 1,2-DCE (0.13 M), 120°C, 24 h, sealed pressure tube. [b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as internal standard (isolated yields in parentheses).

K_2CO_3 gave the same result and the loading of PivOK could even be further reduced delivering product **3a** in 82% yield (Table 1, entries 15 and 16). The C(sp^3)-H alkenylation reaction proved fully site- (γ) and diastereoselective (*Z* alkene, *cis* cyclohexane). The robustness versus water was also studied. When 10 equiv H_2O were added the desired product **3a** was also formed, albeit in a slightly lower yield (67%) and unreacted **1a** was recovered in 30% (Table 1, entry 17).

With the optimized reaction conditions identified, we evaluated the scope of the γ-C(sp^3)-H alkenylation reaction protocol with other 1,1-dibromo-1-alkene coupling partners (**2**) with **1a** (Scheme 1). When 1-(2,2-dibromoethenyl)arenes (**2b**–**g**), bearing different substituents at the 2-, 3- and 4-positions of the phenyl ring were used, the reaction condition proved to be suitable giving the desired products **3b**–**g** in good to high yields (64–74%). The incorporation of electron-donating (**3b**–**d**) as well as electron-withdrawing (**3e**–**g**) substituents proved to be compatible with the developed protocol. The presence of an *ortho*-methyl group did not hamper the reaction, delivering **3b** in 74% yield. The chloro functionality was well tolerated, allowing post-derivatizing of **3e** at the arene moiety. Only when a CF_3 moiety was introduced with **2g**, no full conversion (85%) and consequently a lower product yield **3g** (64%) was observed. The application of a very challenging heteroarene coupling partner bearing a protected indole (**2h**) was also evaluated. Unfortunately, even with a double amount of **2h**, an incomplete conversion was achieved (33% recov-



Scheme 1. Scope of the Pd-catalyzed directed γ-alkenylation of **1** with **2**.[a] [a] Reaction conditions: **1**, **2** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PivOK (0.2 equiv), K_2CO_3 (1.0 equiv), 1,2-DCE (0.13 M), 120°C, 24 h, sealed pressure tube. Less than 10% of **1** recovered unless otherwise mentioned. [b] 15% **1a** recovered. [c] 4.0 equiv **2** used. [d] 33% **1a** recovered. [e] 87% **1a** recovered. [f] 17% **1c** recovered. [g] 35% **1d** recovered. [h] Product of auto tandem catalysis (see Scheme 2).

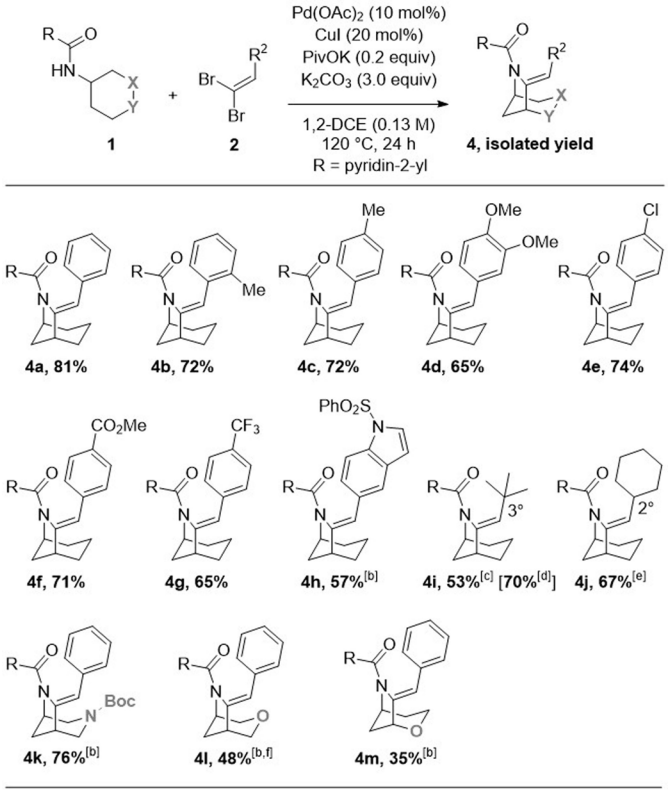
ery of **1a**), delivering reaction product **3h** in 43% yield. Gratifyingly, 73–90% of the excess coupling partner **2a–f,h** was easily recovered upon chromatographic purification of the reaction product **3**, implying that only 1.15 to 1.38 equiv were effectively consumed in the direct alkenylation reaction. The only exception are volatile 1,1-dibromo-1-alkenes **2**, such as **2g**, which are lost during work-up. Subsequently, aliphatic alkenes were studied as reactants. Reaction of 1,1-dibromo-3,3-dimethylbut-1-ene (**2i**) with **1a** delivered product **3i** in 92% yield with full conversion of **1a**. Remarkably, the use of (2,2-dibromoethenyl)cyclohexane (**2j**), failed to deliver the desired product **3j**, with 87% recovery of **1a** (vide infra). While Pd-catalyzed cross-coupling reactions of *gem*-dihalovinyl systems with organometallics are known to provide three products, that is, mono and double C-X functionalized as well as alkynylated product,[18,19] we only obtain a single compound **3** with *Z* configuration in our remote C-H functionalization.

Next, we evaluated challenging saturated heterocyclic substrates (Scheme 1). Commercially available 3-amino-1-Boc-piperidine, tetrahydro-2*H*-pyran-3-amine and tetrahydro-2*H*-pyran-4-amine were transformed into the corresponding picolinamides and subjected to the optimal alkenylation reaction conditions. With piperidine substrate **1c**, 66% conversion was achieved using standard conditions. With 4.0 equiv **2a** loading, an improved conversion was achieved (75%) and the desired product **3k** was obtained in 34% isolated yield. The pyran substrates (**1d** and **1e**) afforded the desired products **3l** and **3m** in 13% and 61%, respectively. Interestingly, **3l** and **3m** further reacted in an intramolecular amidation additionally delivering the normorphans, **4l** and **4m** in 32% and 11%. Although, this auto tandem Pd catalysis was only observed with the tetrahydro-2*H*-pyranamine ring system, it supported the feasibility of our goal. The observation that two of the three heterocyclic substrates, **1c** and **1d**, did not give full conversion of substrate, points to complexation of the additional heteroatoms with the catalyst, hereby inhibiting the catalytic activity. Clearly, there is a spatial effect as these are γ versus the amino group, while this is δ in substrate **1e** providing full conversion. As observed on the cyclohexanes, the excess **2a** (up to 81%) was easily recovered.

As the auto tandem γ-C(sp^3)-H alkenylation and C-Br amidation on our model reaction of **1a** with **2a** was not observed under Pd catalysis, we further investigated the subsequent cyclization of intermediate **3a** into normorphan **4a** (Table 2). Interestingly, when $Cu(OAc)_2{\cdot}H_2O$ was used, full conversion of **3a** was observed and the desired product 7-benzylidinenormorphan (**4a**) was obtained in 87% NMR yield (Table 2, entry 2). The use of cheaper CuI proved equally effective providing **4a** in 85% isolated yield (Table 2, entry 3). The bicyclic core structure and exclusive *Z*-alkene configuration of **4a** were unambiguously confirmed by 2D NMR analysis (Supporting Information).

Considering our "one pot" goal, CuI and additional K_2CO_3 were subsequently added to the optimal Pd-catalyzed γ-C(sp^3)-H alkenylation reaction conditions of the model reaction. Heating **1a** with 2.0 equiv of **2a**, 10 mol% of $Pd(OAc)_2$, 10 mol% CuI, 2.0 equiv of K_2CO_3 and 0.2 equiv of PivOK in 1,2-DCE at 120°C for 24 h gave **4a** in 76% NMR yield. In order to maximize the yield of the tandem reaction, the loading of CuI and K_2CO_3 were further fine-tuned resulting in a rewarding 87% NMR yield (81% isolated yield) of **4a** (Scheme 2). Interestingly, the excess **2a** was recovered in 91% yield and no intermediate **3a** was observed. The result is quite remarkable considering the overall yield of **4a** is higher in comparison to the two-step process starting from **1a** (61% overall: 72% of **3a** from **1a** and 85% of **4a** from **3a**) (Scheme 1 and Table 2, entry 3). This supports the efficiency of our tandem protocol towards synthesizing our target normorphans beyond a step-economic way. The robustness of the tandem one pot reaction in the presence of water was also evaluated. When 10 equiv H_2O were added, the desired product **4a** was also formed, albeit in a slightly lower yield (67%) and unreacted **1a** was recovered in 30%.

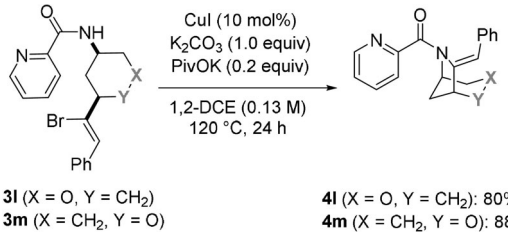
With the optimized reaction condition for the tandem process identified, the scope with respect to 1,1-dibromo-1-alkenes (**2**) was evaluated. First, the same 1-(2,2-dibromoethenyl)arenes (**2b–g**) as used in Scheme 1 were reacted with **1a** using the optimal tandem reaction conditions. The incorporation of electron-donating and electron-withdrawing substituents proved to be compatible as good to high yields of bicyclic products **4a–g** (65–74%) were obtained, considering two reactions occur in one step. Even the use of heterocyclic 1-(benzenesulfonyl)-5-(2,2-dibromoethenyl)-1*H*-indole (**2h**) delivered **4h** in 57% yield with no **1a** remaining. In all examples, excess **2** was recovered (35–64%). Interestingly, while **2g** and **2h** gave full conversion of **1a** in the orthogonal tandem reaction, the corresponding Pd-catalyzed γ-C(sp^3)-H alkenylation with these aromatic 1,1-dibromoalkenes did not



Scheme 2. Scope of the orthogonal tandem reaction of **1** with **2**.[a] [a] Reaction conditions: **1**, **2** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), CuI (20 mol%), PivOK (0.2 equiv), K_2CO_3 (3.0 equiv), 1,2-DCE (0.13 M), 120°C, 24 h, sealed pressure tube. Less than 10% of **1** was recovered unless otherwise mentioned. [b] 4.0 equiv **2** used. [c] 28% **1a** recovered. [d] PivOH (0.2 equiv) was used instead of PivOK. [e] 18% **1a** recovered. [f] 26% **1d** recovered.

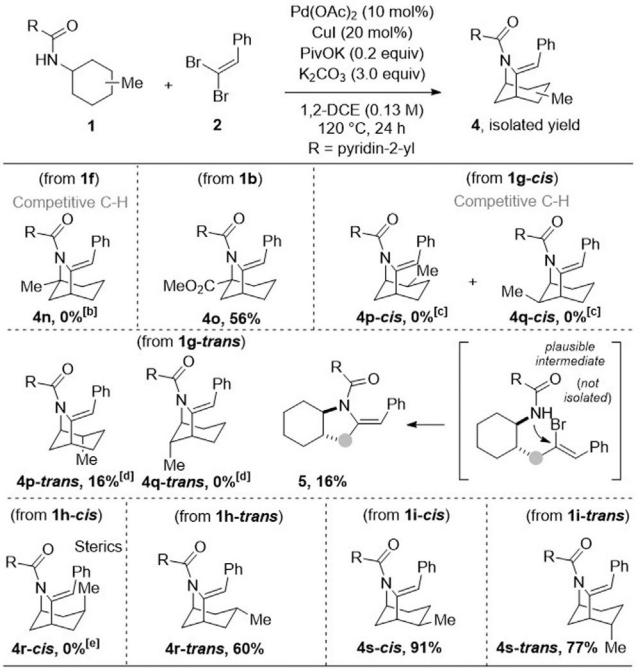
(benzotrifluoride **2g**: 15% **1a**) (1*H*-indole **2h**: 33% **1a**). Next, we used the aliphatic coupling partners bearing a *tert*-butyl (**2i**) and cyclohexyl (**2j**) group. When **2i** was used, the product **4i** was obtained in a moderate yield (53%) with 28% of **1a** recovered using standard reaction conditions. To our delight, the conversion and yield was improved significantly when PivOH was used instead of PivOK, resulting in full conversion and 70% isolated yield of **4i**. Remarkably **2j**, which did not work in the Pd-catalyzed γ-alkenylation reaction (Scheme 1), surprisingly reacted well in the tandem reaction, delivering 67% of **4j**. The use of PivOH in this case did not affect the yield.

Subsequently, challenging heterocyclic amine substrates **1c–e** were studied in the tandem protocol, potentially allowing one to directly access aza- and oxa-analogues of normorphan (Scheme 2, **4k–4m**). Gratifyingly, piperidine-3-amine (**1c**) delivered **4k** in 76% yield. This outcome is surprising as the corresponding Pd-catalyzed γ-(sp^3)-H alkenylation of **1c** suffered from an incomplete conversion (17% **1c** recovery) and low yield (34% **3k**) (Scheme 1). Subsequently, regioisomeric tetrahydro-2*H*-pyranamines equipped with picolinamide DG (**1d**,**e**) were used. These substrates afforded the desired products **4l** and **4m** in 48% and 35% yields, respectively. In case of **4l**, an incomplete conversion was observed as 26% of **1d** was recovered. In case of **4m**, the substrate **1e** was consumed completely. An attempt to obtain a higher yield of **4l** and **4m** by using PivOH (instead of PivOK), was unsuccessful. When the CuI amidation reaction was performed with isolated **3l** and **3m**, the expected product **4l** and **4m** were obtained in 87% and 95% yield, respectively (Scheme 3). Clearly, for substrates allowing auto tandem catalysis the combination of Pd and Cu is less efficient.

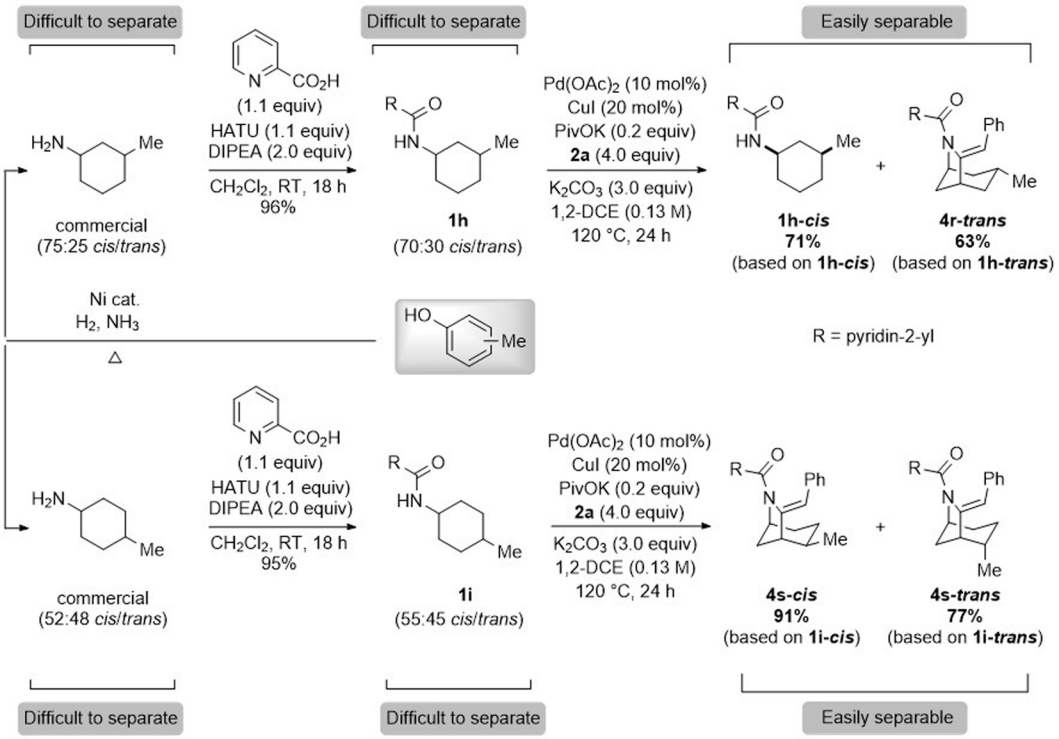


Scheme 3. Cu-catalyzed intramolecular C-Br amidation of **3l** and **3m**.

As a next phase, we applied the tandem reaction protocol on DG equipped C-substituted cyclohexanamines **1**. Cyclohexanamines **B** are either commercially available or readily prepared in one step from (renewable) phenols **A** by reductive amination (Figure 2B).[21] A methyl group was selected for this purpose in a reaction with **2a** (Scheme 4). Methyl substitution at each position of the cyclohexanamine



Scheme 4. Orthogonal tandem reaction with *cis* and *trans* methyl-substituted cyclohexanamines **1**.[a] [a] Reaction conditions: **1**, **2** (4.0 equiv), $Pd(OAc)_2$ (10 mol%), CuI (20 mol%), PivOK (0.2 equiv), K_2CO_3 (3.0 equiv), 1,2-DCE (0.13 M), 120°C, 24 h, sealed pressure tube. Less than 10% of **1** recovered unless otherwise mentioned. [b] 83% unreacted **1f** (NMR yield). [c] 95% unreacted **1g-*cis*** (NMR yield). [d] 24% **1g-*trans*** recovered. [e] 67% unreacted **1h-*cis*** (NMR yield).

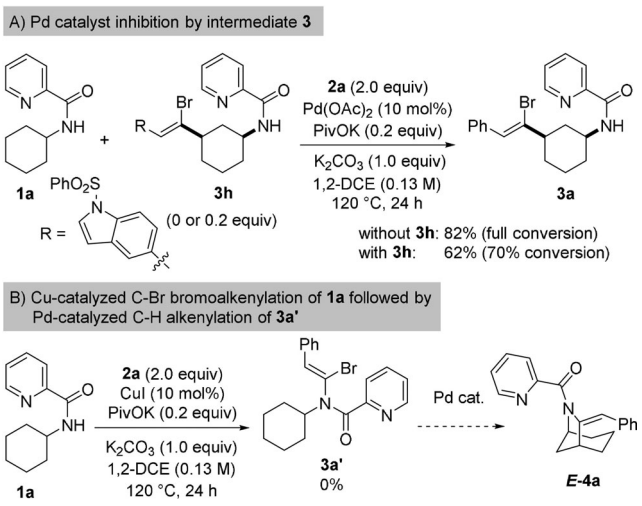


Scheme 5. Orthogonal tandem reaction with diastereomeric mixtures of methyl-substituted cyclohexanamines **1**.

ring was considered. The corresponding *cis*- and *trans*-diastereoisomers of 2-, 3- and 4-methylcyclohexanamine regioisomers were either commercially available or synthesized from the corresponding methylcyclohexanol (Supporting Information). Tandem reaction with 1-methyl substrate **1f** did not deliver the desired product **4n**, only starting material was recovered. This seems to be related to the methyl as when another substituent was used, that is, 1-CO_2Me analogue **1b**, the desired bicyclic product **4o** was obtained in 56% isolated yield with complete conversion. Reaction with *cis*-2-Me (**1g-*cis***) could generate two regioisomeric products (**4p-*cis*** and **4q-*cis***), however no reaction was observed and 95% **1g-*cis*** was recovered. *Trans*-2-Me substrate **1g-*trans*** could deliver two regioisomers (**4p-*trans*** and **4q-*trans***) and the expected **4p-*trans*** product was formed in 16% yield. Regioisomeric **4q-*trans*** was not observed. Instead 2-((*Z*)-benzylidene)octahydro-1*H*-indole **5** was isolated, formed via C-H activation on the 2-Me. We assume that also in substrates **1g-*cis*** and **1f**, competitive C-H activation on the methyl is occurring but it does not lead to functionalization. When 3-methyl substrate was used, *cis*-isomer **1h-*cis*** did not react, but *trans*-isomer **1h-*trans*** transformed smoothly delivering **4r-*trans*** in 60% yield with complete conversion. The former *cis*-3-Me **1h-*cis*** needs to adapt an energetically unfavorable conformation featuring a 1,3-diaxial interaction between DG and Me, rationalizing why it does not allow C-H activation. With 4-methyl substitution, both diastereomeric substrates (**1i-*cis*** and **1i-*trans***) reacted smoothly delivering 91% and 77% isolated yields of **4s-*cis*** and **4s-*trans***, respectively.

Next, we tested whether mixtures of DG equipped *cis*- and *trans*-diastereoisomers of methylcyclohexanamines **1** could be used in our orthogonal tandem protocol (Scheme 5). Reductive amination of methylphenols[21] gives a mixture of diastereoisomers, which are inseparable using classical separation on silica gel. However, the product mixtures of the orthogonal tandem catalysis are expected to not feature this problem, which rationalizes why starting from these mixtures is an advantage. When a mixture of **1h-*cis*** and **-*trans*** was used (70:30 cis/trans), only **1h-*trans*** reacted in accordance with the experiments performed on the pure diastereoisomers. Unreacted *cis*-3-Me (**1h-*cis***) was easily separated from target product **4r-*trans***. Orthogonal tandem catalysis on the diastereomeric mixture of **1i-*cis*** and **-*trans*** (55:45 cis/trans) gave a mixture of normorphans, that is, **4s-*cis*** and **4s-*trans***, which were easily purified by silica chromatography.

Several examples of the 1,1-dibromo-1-alkene (**2**) scope showed that the orthogonal tandem reaction worked better than the corresponding Pd-catalyzed γ-alkenylation reaction alone on **1a**. This interestingly points to the Cu^I influencing the conversion of the γ-functionalization reaction in the tandem process. Pd^{II} coordinates with the picolinamide DG and the alkene moiety in the intermediate **3** in an η^2 manner.[22] If this coordination is strong it will inhibit catalysis by scavenging the Pd^{II} catalyst and Cu^I catalyst can help to release Pd^{II} from **3**. This rationalizes the experiments with electron rich alkenes **2h** and **2j** with substantial amounts of substrate remaining in the γ-alkenylation, respectively 33% and 87% of **1a**. Though **2i** is an aliphatic and therefore also electron rich alkene, the sterically hindered *t*-Bu group hampers η^2 coordination, explaining efficient reactions that were observed in both protocols. To experimentally support our hypothesis of catalyst inhibition by intermediate **3** during the reaction, we performed the standard reaction (**1a** to **3a**) in



Scheme 6. Control experiments.

the presence of 0.2 equiv of **3h** featuring an electron rich double bond (Scheme 6A). Conversion clearly reduced (only 70% compared to full in absence of **3h**) and **3a** was formed in only 62% (compared to 82% in absence of **3h**).

Figure 3 shows the proposed concomitant catalytic cycles for the formation of **4** from **1** via **3**. At first, a bidentate palladium complex **I-1** is formed upon coordination of **1** with $Pd^{II}L_2$ in the presence of base. Subsequent γ-C(sp^3)-H activation via a concerted metalation-deprotonation (CMD) pathway generates complex **I-2**. Next, the 1,1-dibromoalkenyl coupling partner **2** site-selectively oxidatively adds to the metal center, forming a Pd^{IV} complex (**I-3**). Reductive elimination of alkenylated product **3** from **I-3** regenerates $Pd^{II}L_2$. Compound **3** is capable of scavenging $Pd^{II}L_2$ by forming a η^2-coordination complex **I-4**, which can result in incomplete conversion of substrate **1** in Pd-catalyzed γ-alkenylations. In the presence of $Cu^{I}X$ and additional base, compound **3** enters into the second catalytic cycle and releases $Pd^{II}L_2$ from complex **I-4**. The amidation cycle starts with an initial coordination of the amide moiety of **3** to $Cu^{I}X$, forming **I-5**. The resulting copper-amide complex then undergoes an intramolecular oxidative addition generating **I-6**, which allows for a subsequent C(sp^2)–N bond formation by reductive elimination of the desired product **4**.[23] An alternative to this mechanism would involve a Cu-catalyzed intermolecular bromoalkenylation of the amide of **1a**,[24] followed by an intramolecular Pd-catalyzed C-H alkenylation. This is however unlikely, considering acyclic secondary amides are poor substrates in intermolecular Ullmann-Goldberg cross-coupling reactions and the *E* isomer of 7-alkylidenenormorphan **4a** is expected. In accordance with this reaction of **1a** with **2a** under Cu catalysis proved unsuccessful (Scheme 6B).

The enamides **4** are interesting products for further post transformations.[15] In the framework of this work, the double bond was selectively transformed into imide **6** by a Ru^{III}-catalyzed oxidative cleavage (Scheme 7).[25] Both aryl and alkyl substituents on the enamide allowed this transformation as exemplified by a reaction with **4a** and **4j**. The aza normorphan **4k** also reacted under the same reaction conditions delivering 43% **6b**. Subsequent cleavage of the imide in **6** by basic hydrolysis furnished the corresponding lactams **7a**,**b**. These possess interesting synthetic potential via for example, reductive functionalization of amides into α-branched alkanamines.[26]

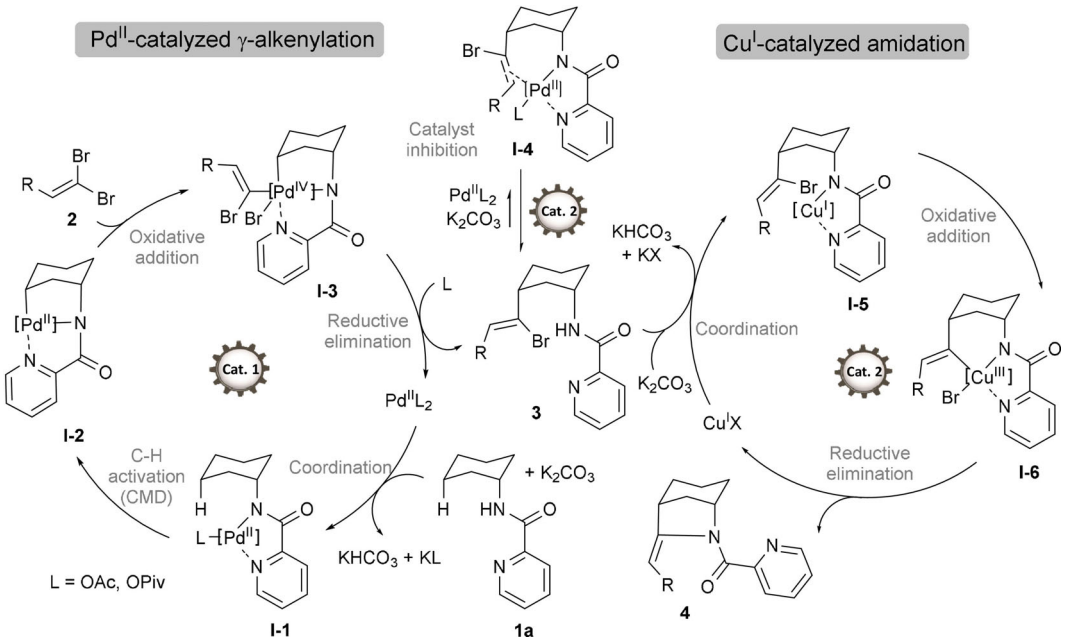
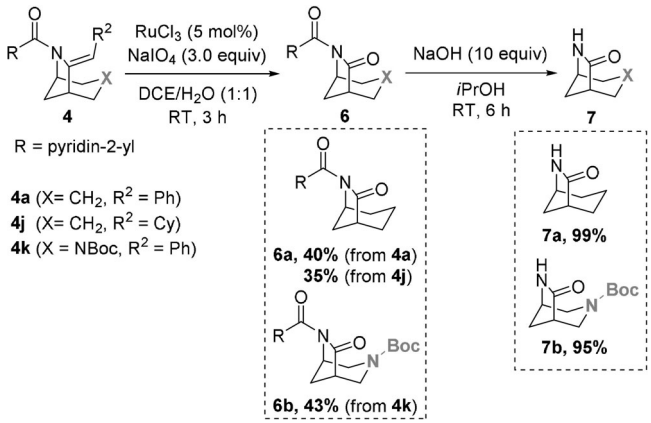


Figure 3. Proposed mechanism of orthogonal tandem catalysis involving Pd^{II}-catalyzed γ-alkenylation of **1** and subsequent Cu^{I}-catalyzed amidation of **3**.



Scheme 7. Post-functionalization: lactam **7** synthesis.

Conclusion

In summary, valuable 7-alkylidenenormorphans have been obtained in a step-economic and efficient way via selective orthogonal tandem catalysis. The "one pot" process involves a remote intermolecular Pd-catalyzed γ-C(sp^3)-H alkenylation on commercial cyclohexanamine, equipped with a picolinamide directing group, with readily available 1,1-dibromo-1-alkenes followed by a Cu-catalyzed C(sp^2)-Br amidation reaction on the 3-(1-bromo-1-alkenyl)cyclohexan-1-amine intermediate. Selectivity obtained includes site (C-H in **1**, C-Br in **2**), diastereoselectivity (*cis*-alkenylation, *Z*-alkene), as well as product selectivity [**3** (C–C bond) versus **C** (C–N bond), **4** (amidation) versus **D** (elimination)]. Diastereomeric mixtures of substituted cyclohexanamines can be directly applied in our protocol providing easily separable reaction mixtures, as exemplified for methylcyclohexanamines. Considering these diastereoisomers are obtained via reductive amination of the corresponding phenols and are generally inseparable, this offers ample application potential for chemical libraries synthesis. The protocol can also be applied on commercial aminoheterocycles immediately providing access to the corresponding aza- and oxa-analogues of 7-alkylidenenormorphans. Besides acting as a directing group, the amide directing group stabilizes the enamine in the reaction product as its enamide. Enamides are valuable entities in organic synthesis which can provide access to various C7-derived normorphans. This is exemplified by oxidation of the products into the corresponding lactams. When only Pd catalyst is used, γ-C(sp^3)-H olefination is occurring, providing the intermediate 3-(1-bromo-1-alkenyl)-cyclohexan-1-amines of the tandem protocol as a single regio- and diastereoisomer (*Z* alkene, *cis*-cyclohexane). These novel alkenylated products are synthetically useful precursors for further transformations and the subject of further studies in our laboratories. Remarkably, when electron rich and non-sterically hindered alkenes are used, the tandem protocol actually works better than the γ-C(sp^3)-H alkenylation. Our results show this is due to off-cycle scavenging of Pd catalyst by the alkene moiety of the 3-(1-bromo-1-alkenyl)cyclohexan-1-amine, which is released by Cu catalyst present in the tandem protocol, rationalizing the better conversion observed. The synthesis of other bridged nitrogen bicyclic skeletons via the new strategy disclosed, as well as the generality of the copper effect for other vinylation reactions, is under study in our laboratories.

Acknowledgements

The research was funded by FWO-Flanders (Research project Grant No. G0A2820N and WOG), the Federal Excellence of Science (EoS) program (BIOFACT, Grant No. 30902231), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Actions (Grant No. 837718), and the Hercules Foundation. B.U.W.M. acknowledges the Francqui Foundation for an appointment as Collen-Francqui professor. All authors thank G. Van Haesendonck, Prof. F. Lemière, and Dr. D. Buyst for analytical support and, D. De Vos for the synthesis of some starting materials.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkenylation · bridged bicyclic nitrogen scaffolds · normorphan · remote functionalization · tandem catalysis

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Manuscript received: May 19, 2021
Accepted manuscript online: June 18, 2021
Version of record online: ■■ ■■, ■■■■

Research Articles

C–H Functionalization

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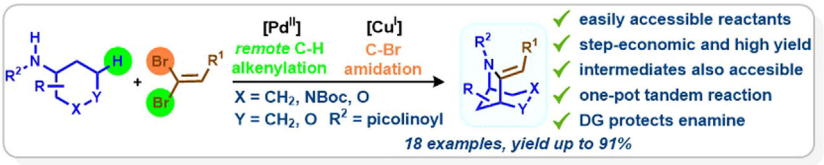

Expedient Synthesis of Bridged Bicyclic Nitrogen Scaffolds via Orthogonal Tandem Catalysis

Bridged bicyclic nitrogen scaffolds are conformational restricted analogues of important aminocarbo- and amino-heterocycles. Fixation of functional groups in a biologically active conformation provides efficient and selective ligands for various targets, featuring improved ADME parameters. Long synthetic sequences relying on traditional organic chemistry currently limit the drug discovery process. New step-economic synthetic procedures are therefore highly sought after.