A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Modular One-Step Three-Component Synthesis of Tetrahydroisoquinolines via a Catellani Strategy

Authors: Qianghui Zhou, Guangyin Qian, Miao Bai, Shijun Gao, Han Chen, Siwei Zhou, Hong-Gang Cheng, and Wei Yan

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201806780
Angew. Chem. 10.1002/ange.201806780

Link to VoR: http://dx.doi.org/10.1002/anie.201806780
http://dx.doi.org/10.1002/ange.201806780

WILEY-VCH

10.1002/anie.201806780

WILEY-VCH

COMMUNICATION

Modular One-Step Three-Component Synthesis of Tetrahydroisoquinolines via a Catellani Strategy

Guangyin Qian, Miao Bai, Shijun Gao, Han Chen, Siwei Zhou, Hong-Gang Cheng*, Wei Yan and Qianghui Zhou*

Dedicated to Prof. E. J. Corey on the occasion of his 90th birthday

Abstract: Reported is a modular one-step three-component synthesis of tetrahydroisoquinolines via a Catellani strategy. This process exploits aziridines as the alkylating reagents through palladium/norbornene cooperative catalysis to enable a Catellani/Heck/aza-Michael addition cascade. This mild, chemoselective, and scalable protocol has broad substrate scope (43 examples, up to 90% yield). The most striking feature of this protocol is the excellent regioselectivity and diastereoselectivity observed for 2-alkyl and 2-aryl substituted aziridines to access 1,3-*cis*-substituted and 1,4-*cis*-substituted tetrahydroisoquinolines respectively. Moreover, this is a versatile process with high step- and atom-economy.

The 1,2,3,4-tetrahydroisoquinoline core[1] is widely studied as a privileged scaffold for the preparation of therapeutically active compounds.[2] This heterocycle scaffold is prevalent in bioactive natural products[1a,3] and therapeutic agents,[2,4-5] for instance, the potent antitumor alkaloid (-)-quinocarcin,[3] the antimuscarinic drug solifenacin (astellas),[4] and the antichorea drug tetrabenazine[5] (Figure 1A). As such, a growing effort has been directed toward the efficient preparation of this valuable scaffold. The traditional methods[6] (Pomeranz-Fritsch, Bischler-Napieralsky, Pictet-Spengler,[6c] and intramolecular Friedel-Crafts[7]) really work well only with electron-rich systems. Other methods also have been developed that do not rely on the electronic characteristics of the aromatic ring.[8] For example, transition metal catalyzed hydrogenation[9] or nucleophilic addition[10] to 3,4-dihydroisoquinolines, or intramolecular Heck reaction[11] *etc* (Figure 1B).[12] However, these methods generally require specially functionalized substrates or harsh reaction conditions, significantly limiting their scopes. Therefore, development of general and efficient approaches for the direct synthesis of tetrahydroisoquinolines from readily available starting materials would be a highly desirable yet challenging subject.[8]

The Catellani reaction, firstly introducted by Prof. Catellani,[13] utilizes the palladium/norbornene (NBE) cooperative catalysis to facilitate sequential *ortho* C–H bond activation and *ipso* coupling of aryl iodide, thereby allowing the precise functionalization of *ortho* and *ipso* positions simultaneously.[14-15] Through twenty years of development, this reaction has become a powerful tool

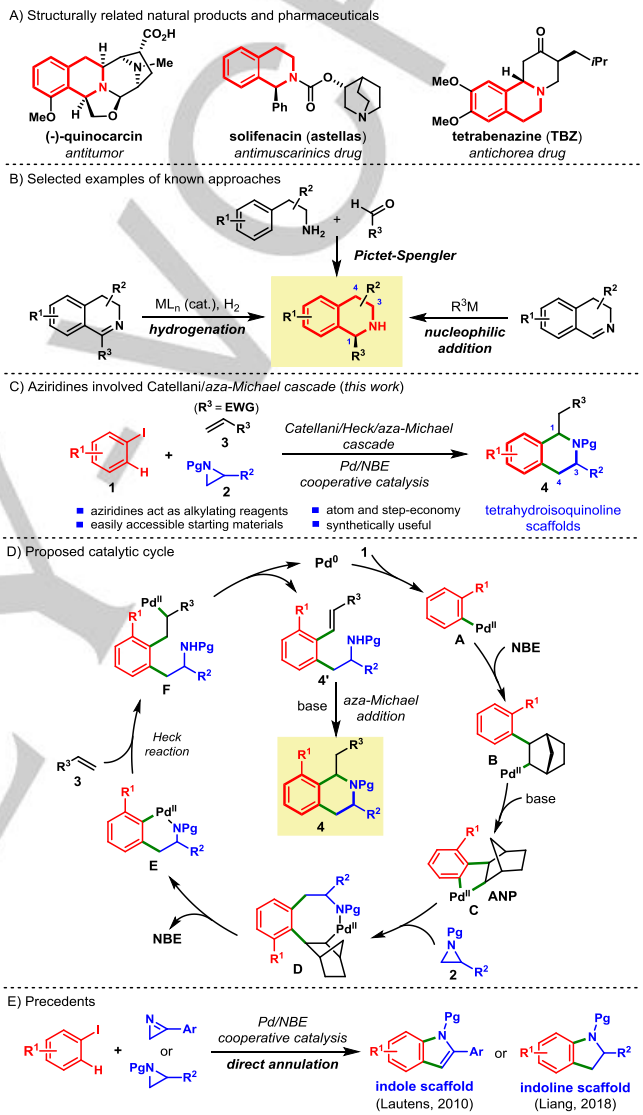


Figure 1. Approaches to access tetrahydroisoquinolines

for the synthesis of highly substituted arenes. Notably, Lautens, Catellani and others have developed a gamut of elegant Catellani-type annulations to access diversified benzo-fused rings.[16] Recently, our group identified that epoxides could act as alkylating reagents for the Catellani reaction, providing an efficient strategy for the synthesis of isochromans.[16j] Inspired by this discovery, we envisaged that the readily available aziridines[17] might also act as alkylating reagents to enable a Catellani/Heck/aza-Michael addition cascade[18] for the direct synthesis of tetrahydroisoquinolines, as depicted in Figure 1C. Prior to the start of this project, applying aziridines as the alkylating reagents in Catellani reaction had not been reported.[19] Until recently, the Liang group reported an elegant related research (Figure 1E).[20] Based on the

[*] G. Qian, M. Bai, S. Gao, H. Chen, S. Zhou, Dr. H.-G. Cheng, W. Yan, Prof. Dr. Q. Zhou
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072 (China)
E-mail: hgcheng@whu.edu.cn, qhzhou@whu.edu.cn
Homepage: http://qhzhou.whu.edu.cn/
Prof. Dr. Q. Zhou
The Institute for Advanced Studies, Wuhan University, Wuhan, 430072 (China)
Supplementary information for this article is given via a link at the end of the document.

10.1002/anie.201806780

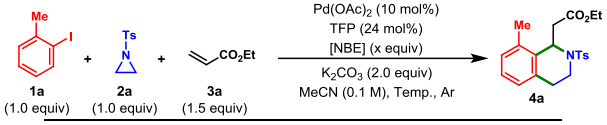
WILEY-VCH

COMMUNICATION

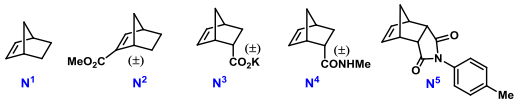
previous mechanistic studies,[15] we surmised that, just like epoxides, aziridines **2** might react with the key **ANP** intermediate **C** to form intermediate **D**, which would lead to palladium circle **E** after the extrusion of NBE. Then, **E** reacted with olefin **3** via a Heck reaction to afford uncyclized product **4'** and regenerated the Pd(0) catalyst. Finally, **4'** would be readily transformed to tetrahydroisoquinoline **4** through a base promoted aza-Michael addition (Figure 1D). Such a sequence would enable the formation of one C-N bond and two C-C bonds, the creation of a benzylic stereogenic center, and direct construction of the tetrahydroisoquinoline scaffold in a single operation, representing a versatile step- and atom-economic process.[21,22] Nevertheless, we speculated the innate challenges for this process would include: a proper *N*-substitution might be needed to ensure the reactivity of the aziridines; the tuning of the regioselectivity of the aziridine ring cleavage and the diastereoselectivity of the intramolecular aza-Michael addition.

To probe this intriguing process, our efforts commenced with the model reaction using readily available 2-iodotoluene (**1a**, 1.0 equiv), 1-tosylaziridine (**2a**, 1.0 equiv) and ethyl acrylate (**3a**, 1.5 equiv) as the reactants (Table 1). Initially, $Pd(OAc)_2$ was chosen as the catalyst (10 mol%), norbornene as the mediator (3.0 equiv), K_2CO_3 as the base (2.0 equiv), MeCN as the solvent (0.1 M), and tri-2-furanylphosphine as the ligand. To our delight, when the reaction was run at 80 °C under argon, the desired product **4a** was indeed obtained in 67% yield (entry 1). Lowering the reaction temperature from 80 °C to 70 °C led to a cleaner reaction, which improved the yield to 87% (entry 2). Following studies focused on identifing the optimal mediator. Various readily available norbornene derivatives were then examined, including the Yu mediator (**N²**)[23], the potassium salf of 5-norbornene-2-carboxylic acid (**N³**)[16j], and the Dong mediator (**N⁴**)[24] (entries 4-6). Switched to a 50 mol% loading of the mediator, the yield of **4a** dropped dramatically to 39% for **N¹** (entry 3), while only a trace amount of **4a** was obtained for **N²** (entry 4). In contrast, **N³** and **N⁴** could provide significantly increased yields (entries 5-6). Gratifyingly, the readily available NBE derivative **N⁵** was among the best,[25] affording **4a** in the highest yield (85%) (entry 7). Further reducing the loading of **N⁵** to 20 mol% led to a slightly lower yield (79%, entry 8). Additional optimization of the base, the ligand and the palladium catalyst did not provide obvious improvement in the efficiency (see the Supplementary Information (SI) for details). Finally, the optimal conditions involved the increase of **1a** to 1.2 equiv and the concentration to 0.2 M, which furnished **4a** in 82% yield (81% isolated yield) (entry 10). It is worth mentioning that the current transformation is advantageous, not only for its high atom economy–since aziridine **2a** and olefin **3a** can be incorporated into the product **4a** in its entirety, but also for its high step economy–the tetrahydroisoquinoline motif can be built in just one step from three types of substrates. In addition, the identification of **N⁵** as a catalytic mediator is another striking feature.

Table 1. Optimization of reaction conditions.[a]



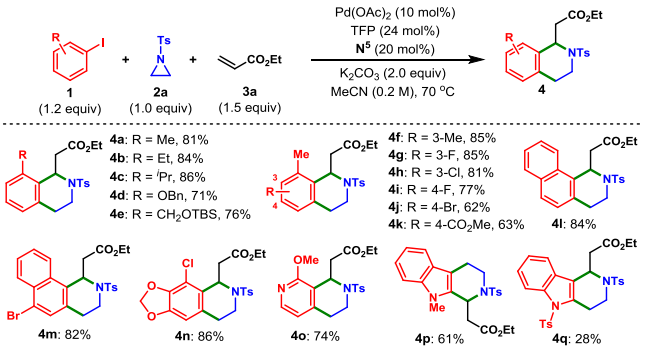
Entry	[NBE]	x	Temp. (°C)	Yield (%)[b]
1	**N¹**	3.0	80	67
2	**N¹**	3.0	70	87 (85)[c]
3	**N¹**	0.5	70	39
4	**N²**	0.5	70	7
5	**N³**	0.5	70	57
6	**N⁴**	0.5	70	74
7	**N⁵**	0.5	70	85
8	**N⁵**	0.2	70	79
9[d]	**N⁵**	0.2	70	81
10[d,e]	**N⁵**	0.2	70	82 (81)[c]



[a] All reactions were performed on a 0.1 mmol scale. [b] GC yield with biphenyl as an internal standard. [c] Isolated yield in parentheses. [d] 1.2 equiv of **1a** was used. [e] The reaction was performed in 0.2 M solution. Ts = *p*-toluenesulfonyl, TFP = tri-2-furanylphosphine.

With the above optimal conditions identified, we first examined the scope of aryl iodides, with aziridine **2a** and olefin **3a** as the reaction partners (Table 2). Gratifyingly, aryl iodides containing electron-donating and electron-withdrawing groups all proved to be competent substrates, providing the desired products in 62–86% yield. The reaction system also exhibited high chemoselectivity: various functional groups were tolerated including benzyloxy (product **4d**), methoxy (product **4o**), TBS-protected hydroxymethyl (product **4e**), fluoride (products **4g** and **4i**), chloride (products **4h** and **4n**), bromide (products **4j** and **4m**), and methyl ester (product **4k**), providing handles for further product diversification. Importantly, heteroaryl iodides (**1o**-**q**) were also demonstrated to be suitable substrates, wherein their reaction with **2a** and **3a** afforded products **4o**-**q** in 28-74% yield.

Table 2. Reaction scope with respect to the aryl iodide.[a]



[a] All reactions were performed on a 0.2 mmol scale. Reported yields are for the isolated products. TBS = *t*-butyldimethylsilyl, Bn = benzyl.

Then, the scope of olefin **3** was explored (Table 3A). An array of *mono*-substituted olefins with electron-withdrawing groups are suitable substrates (**3a**-**i**), including acrylates (**3a**-**d**),[26-27] the Weinreib amide of acylic acid (**3e**), as well as alkyl vinyl ketones (**3f**-**h**), providing the desired products in good to excellent yields. Notably, for phenylvinylketone (**3i**), the ligand should be switched to DavePhos to obtain a good yield.

Next, the scope of *N*-substitution of aziridine **2** was examined (Table 3B). Besides 4-toluenesulfonyl (Ts), benzenesulfonyl (Bs) (**2b**) and 4-nitro-benzenesulfonyl (Ns) (**2c**) were also compatible, but the latter delivered the corresponding product in a much lower yield. Interestingly, *N*-benzyloxycarbonyl (*N*-Cbz) and *N*-*t*-butoxycarbonyl substitution (*N*-Boc) substituted aziridines (**2d** and **2e**) were competent substrates to deliver the corresponding uncyclized products **4ad** and **4ae** solely (see the SI). As to the *N*-

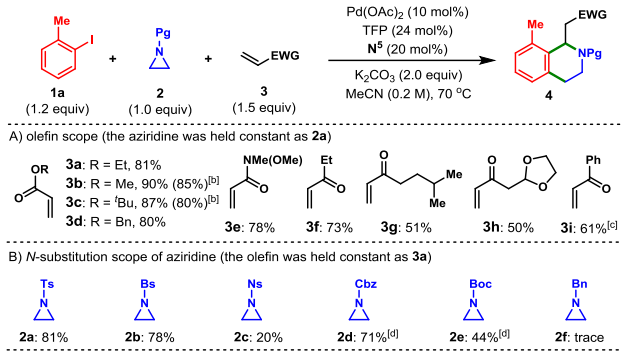
10.1002/anie.201806780

WILEY-VCH

COMMUNICATION

benzyl substituted aziridine **2f**, only a trace amount of the product was detected, which indicates that an electron-withdrawing *N*-substitution of aziridine is necessary to ensure enough reactivity.

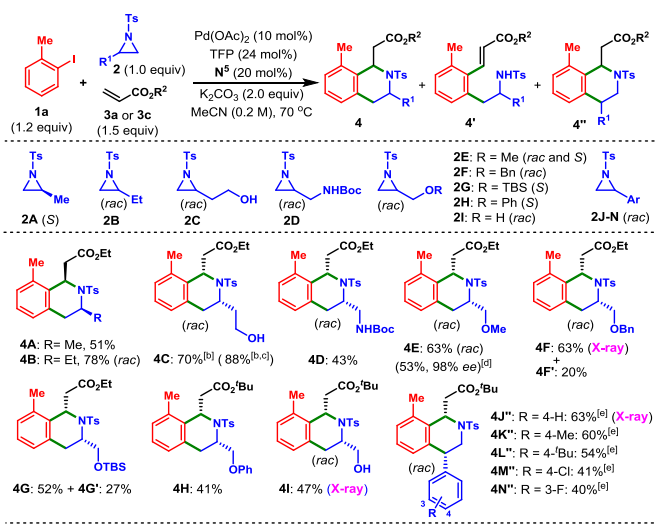
Table 3. Reaction scope with olefin and *N*-substitution of aziridine.[a]



[a] All reactions were performed on a 0.2 mmol scale. Reported yields are for the isolated products. [b] On a 4.0 mmol scale. [c] 24 mol% DavePhos was applied instead of TFP. [d] Uncyclized product was obtained. Bs = benzenesulfonyl, Ns = 4-nitro-benzenesulfonyl, Cbz = benzyloxycarbonyl, Boc = *t*-butoxycarbonyl.

To further illustrate the synthetic utility of this protocol, we examined the reaction scope of 2-substituted *N*-Ts-aziridine **2** (Table 4).[28] Reaction with simple *N*-Ts-2-methyl aziridine (**2A**) and *N*-Ts-2-ethyl aziridine (**2B**) gave the 1,3-*cis*-substituted tetrahydroisoquinolines **4A** and **4B** in 51% and 78% yield, respectively. Other *N*-Ts-aziridines with functionalized alkyl substitutions, including 2-hydroxyethyl (**2C**),[29] *N*-Boc-protected aminomethyl (**2D**) and various protected 2-hydroxymethyl (**2E**-**H**), gave the corresponding products **4C**–**H** in moderate to good yields. Interestingly, as to the case of **2F** and **2G**, the uncyclized products **4F'** and **4G'** were also isolated in 20% and 27% yield respectively. Notably, a free hydroxy group (for **2C** and **2I**) was compatible with this protocol. If enantiomerically pure aziridine **2E** was used, the reaction proceeded with stereoretention to afford the corresponding chiral product **4E** with 98% *ee*. The formation of 1,3-*cis*-substituted tetrahydroisoquinolines **4A**-**I** and the stereoretention experiment indicated the C-N bond cleavage specifically took place at the less bulkier site of the aziridine ring

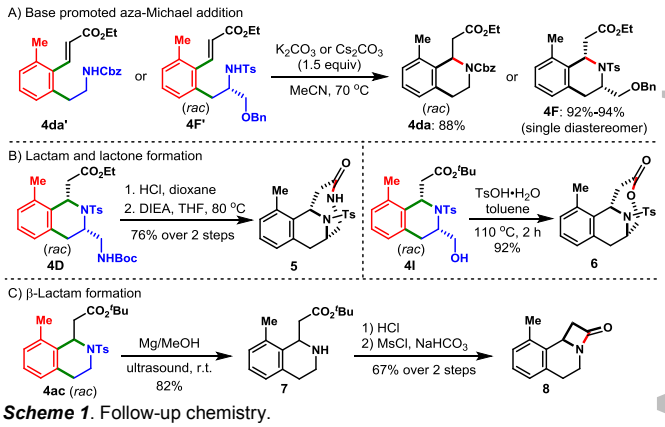
Table 4. Reaction scope with respect to 2-substituted aziridine.[a]



[a] All reactions were performed on a 0.1 mmol scale. Reported yields are for the isolated products. [b] 24 mol% DavePhos was applied instead of TFP. [c] 50 mol% **N**[5] was used. [d] Enantiopure **2E** was applied. [e] The reaction temperature was increased to 80 °C.

for 2-alkyl substituted *N*-Ts-aziridines. Further exploration demonstrated that 2-aryl substituted *N*-Ts-aziridines (**2J**-**N**) were also suitable substrates for this protocol. However, the obtained products were specifically changed to 1,4-*cis*-substituted tetrahydroisoquinolines (**4J''**-**N''**), indicating a totally reversed regioselectivity of the ring cleavage. Importantly, the structure of products **4F**, **4I** and **4J''** were unambiguously assigned by X-ray crystallographic analysis (CCDC 1847841, 1847842 and 1847839) (see the SI for details). The observed two distinct kinds of regioselectivity can be rationalized as follows: the former is controlled by the steric hindrance of the aziridine ring, while the latter is governed by the innate static electronic property of the 2-aryl-substituted aziridine ring.[30]

To demonstrate the synthetic value of the obtained products, we investigated follow-up chemistry. As shown in Scheme 1A, uncyclized products **4da'** and **4F'** underwent facile aza-Michael addition in the presence of base K_2CO_3 or Cs_2CO_3 to provide tetrahydroisoquinolines **4da** and **4F** in excellent yields. The fact that **4F** was obtained as the single diastereomer demonstrates the excellent diastereoselectivity of the aza-Michael addition process,[16h] that is in sharp constrast to the reported oxa-Michael addition process.[16j] As depicted in Scheme 1B, a two-step lactam formation process was developed for **4D** to afford **5**, including acid mediated deprotection of the *N*-Boc and base promoted intramolecular cyclization. Similarly, **4I** can be transformed to **6** through an acid promoted one-step lactone formation process. Meanwhile, the formation of **5** and **6** also indicates that **4D** and **4I** are 1,3-*cis*-substituted tetrahydroisoquinolines. Lastly, the removal of the *N*-Ts group in **4ac** was achieved with the aid of magnesium in methanol under ultrasound[31] to deliver intermediate **7**, which led to β-lactam **8** through a facile two-step process[32] (Scheme 1C). More efforts are underway to utilize this versatile process as the key step for the preparation of complex natural products and therapeutics.



Scheme 1. Follow-up chemistry.

In summary, we have developed a modular one-step three-component synthesis of tetrahydroisoquinolines via a Catellani strategy. This process exploits aziridines as the alkylating reagents through palladium/norbornene cooperative catalysis to enable a Catellani/Heck/aza-Michael addition cascade. This mild, chemo-selective, and scalable protocol is compatible with a range of aryl iodides, aziridines as well as olefins, providing a versatile platform to access diversified tetrahydroisoquinolines. The most striking feature of this process is the excellent regioselectivity and diastereoselectivity observed for 2-alkyl and 2-aryl substituted aziridines to access 1,3-*cis*-substituted and 1,4-*cis*-substituted

tetrahydroisoquinolines respectively. Moreover, this is a process with high step- and atom-economy. Owing to these advantages, we believe this chemistry will be welcomed by synthetic chemists and medicinal chemists.

Acknowledgements

We are grateful to the National Key Research and Development Program of China (No. 2016YFB0101203), the National "1000-Youth Talents Plan", the Innovation Team Program of Wuhan University (Program No. 2042017kf0232) and start-up funding from Wuhan University for financial support. We thank Prof. Wenjing Xiao from CCNU for donating some aziridine substrates, Mr. Chuanxin Du and Ms. Yuanyuan Xia for technical assistance.

Keywords: Catellani reaction • cooperative catalysis • aziridine • tetrahydroisoquinoline • aza-Michael addition

[1] For related reviews, see: a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) V. G. Kartsev, *Med. Chem. Res.* **2004**, *13*, 325; c) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444.

[2] N. Cabedo, I. Berenguer, B. Figadere, D. Cortes, *Curr. Med. Chem.* **2009**, *16*, 2441.

[3] K. Fujimoto, T. Oka, M. Morimoto, *Cancer Res.* **1987**, *47*, 1516.

[4] L. Goldman MD, A. I. Schafer MD, **2011**, *Goldman's Cecil Medicine* (24th ed.). Philadelphia: Elsevier Saunders. ISBN 1437727883.

[5] Z. Yao, X. Wei, X. Wu, J. L. Katz, T. Kopajtic, N. H. Greig, H. Sun, *Eur. J. Med. Chem.* **2011**, *46*, 1841.

[6] For selected reviews on the synthesis of tetrahydroisoquinolines, see: a) M. D. Rozwadowska, *Heterocycles* **1994**, *39*, 903; b) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; c) J. Stçckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538; *Angew. Chem.* **2011**, *123*, 8692.

[7] W. Huang, Q. Shen, J. Wang, X. Zhou, *J. Org. Chem.* **2008**, *73*, 1586.

[8] For a recent review on the synthesis of tetrahydroisoquinolines, see: M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev.* **2016**, *116*, 12369.

[9] J.-H. Xie, P.-C. Yan, Q.-Q. Zhang, K.-X. Yuan, Q.-L. Zhou, *ACS Catal.* **2012**, *2*, 561; b) F. Berhal, Z. Wu, Z. Zhang, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2012**, *14*, 3308.

[10] B. A. Granger, K. Kaneda, S. F. Martin, *Org. Lett.* **2011**, *13*, 4542.

[11] A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 6552.

[12] Other recent elegant examples on the synthesis of tetrahydroisoquinolines, see: a) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 6452; *Angew. Chem.* **2008**, *120*, 6552; b) D. Enders, J. X. Liebich, G. Raabe, *Chem. Eur. J.* **2010**, *16*, 9763; c). H. Zhou, Y. Liu, S. Yang, L. Zhou, M. Chang, *Angew. Chem. Int. Ed.* **2017**, *56*, 2725; *Angew. Chem.* **2017**, *129*, 2769.

[13] M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed.* **1997**, *36*, 119; *Angew. Chem.* **1997**, *109*, 142.

[14] For selected reviews, see: a) M. Lautens, D. Alberico, C. Bressy, Y.-Q. Fang, B. Mariampillai, T. Wilhelm, *Pure Appl. Chem.* **2006**, *78*, 351; b) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1; c) J. Ye, M. Lautens, *Nat. Chem.* **2015**, *7*, 863; d) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389; e) D.-S. Kim, W.-J. Park, C.-H. Jun, *Chem. Rev.* **2017**, *117*, 8977.

[15] For selected mechanistic studies on Catellani-type reactions, see: a) M. Larraufie, G. Maestri, É. Beaume, P. Derat, C. Ollivier, L. Fensterbank, C. Courillon, E. Lacôte, M. Catellani, M. Malacria, *Angew. Chem. Int. Ed.* **2011**, *50*, 12253; *Angew. Chem.* **2011**, *123*, 12461; b) G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat, M. Catellani, *J. Am. Chem. Soc.* **2011**, *133*, 8574; c) D. I. Chai, P. Thansandote, M. Lautens, *Chem. Eur. J.* **2011**, *17*, 8175.

[16] For selected works, see: a) M. Lautens, S. Piguel, *Angew. Chem. Int. Ed.* **2000**, *39*, 1045; *Angew. Chem.* **2000**, *112*, 1087; b) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148; c) D. A. Candito, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 6713; *Angew. Chem.* **2009**, *121*, 6841; d) H. Liu, M. El-Salfiti, M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 9846; *Angew. Chem.* **2012**, *124*, 9984; e) R. Ferraccioli, D. Carenzi, O. Rombola, M. Catellani, *Org. Lett.* **2004**, *6*, 4759; f) N. D. Ca', E. Motti, M. Catellani, *Adv. Synth. Catal.* **2008**, *350*, 2513; g) E. Motti, N. D. Ca', D. Xu, A. Piersimoni, E. Bedogni, Z.-M. Zhou, M. Catellani, *Org. Lett.* **2012**, *14*, 5792; h) V. Narbonne, P. Retailleau, G. Maestri, M. Malacria, *Org. Lett.* **2014**, *16*, 628; i) R. Li, G. Dong, *Angew. Chem. Int. Ed.* **2018**, *57*, 1697; *Angew. Chem.* **2018**, *130*, 1713; j) H.-G. Cheng, C. Wu, H. Chen, R. Chen, G. Qian, Z. Geng, Q. Wei, Y. Xia, J. Zhang, Y. Zhang, Q. Zhou, *Angew. Chem. Int. Ed.* **2018**, *57*, 3444; *Angew. Chem.* **2018**, *130*, 3502; k) C. Liu, Y. Liang, N. Zheng, B.-S. Zhang, Y. Feng, S. Bi, Y.-M. Liang, *Chem. Commun.* **2018**, *54*, 3407; l) Z.-S. Liu, G. Qian, Q. Gao, P. Wang, H.-G. Cheng, Q. Wei, Q. Liu, Q. Zhou, *ACS Catal.* **2018**, *8*, 4783; m) C. Wu, H.-G. Cheng, R. Chen, H. Chen, Z.-S. Liu, J. Zhang, Y. Zhang, Y. Zhu, Z. Geng, Q. Zhou, *Org. Chem. Front.* **2018**, DOI:10.1039/C8QO00348C.

[17] Aziridines are prepared in a few steps from olefins or substituted 2-amino-1-ol, see: a) J. L. Jat, M. P. Paudyal, H. Gao, Q.-L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürti, J. R. Falck, *Science* **2014**, *343*, 61; b) Z. Ma, Z. Zhou, L. Kürti, *Angew. Chem. Int. Ed.* **2017**, *56*, 9886; *Angew. Chem.* **2017**, *129*,10018; c) F. Beltran, I. Fabre, I. Ciofini, L. Miesch, *Org. Lett.* **2017**, *19*, 5042.

[18] Aza-Michael addition was previously reported to couple with Catellani reaction, see: Refs [16f,h] and N. Della Ca', E. Motti, A. Mega, M. Catellani, *Adv. Synth. Catal.* **2010**, *352*, 1451.

[19] A related work regarding the use of the strained azirines in Catellani reaction was firstly reported by the Lautens group (Figure 1E), see: D. A. Candito, M. Lautens, *Org. Lett.* **2010**, *12*, 3312.

[20] While this study was in progress, an elegant related transformation was reported by the Liang group, see Ref. [16k].

[21] P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197.

[22] B. M. Trost, *Science* **1991**, *254*, 1471.

[23] P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574.

[24] Z. Dong, J. Wang, Z. Ren, G. Dong, *Angew. Chem. Int. Ed.* **2015**, *54*, 12664; *Angew. Chem.* **2015**, *127*, 12855.

[25] **N^5** is prepared just one-step from inexpensive reagent himic anhydride, and was firstly introduced as mediator in Catellani reaction by the Zhou group, see Ref. [16l].

[26] Both product **4ab** and **4ac** (from olefin **3b** and **3c** respectively) were successfully prepared on a gram scale, and the yields are slightly lower than the small scale (0.2 mmol) (See SI, part 9).

[27] The structure of product **4ab** was unambiguously assigned by X-ray crystallographic analysis. CCDC 1847835 contains the supplementary crystallographic data for this paper.

[28] Reactions with disubstituted *N*-Ts-aziridines suffered from low yields, while trisubstituted *N*-Ts-aziridines were not reactive under the current conditions.

[29] For **2C**, DavePhos was used as the ligand to obtain a good yield (70%). The yield could be further increased to 88% if 50 mol% of **N^5** was used.

[30] The excellent regioselectivities in palladium and Ni catalyzed aziridine cleavage were documented. For 2-alkyl substituted aziridines, see: a) M. L. Duda, F. E. Michael, *J. Am. Chem. Soc.* **2013**, *135*, 18347; b) J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.* **2006**, *128*, 15415; and Ref. [16k]. For 2-aryl substituted aziridines, see: c) Y. Takeda, Y. Ikeda, A. Kuroda, S. Tanaka, S. Minakata, *J. Am. Chem. Soc.* **2014**, *136*, 8544; d) B. P. Woods, M. Orlandi, C.-Y. Huang, M. S. Sigman, A. G. Doyle, *J. Am. Chem. Soc.* **2017**, *139*, 5688; e) X.-Y. Yu, Q.-Q. Zhou, P.-Z. Wang, C.-M. Liao, J.-R. Chen, W.-J. Xiao, *Org. Lett.* **2018**, *20*, 421. Interestingly, the Liang group only observed a moderate regioselectivity for 2-aryl substituted aziridines as described in Ref. [16k].

[31] F. Serpier, J.-L. Brayer, B. Folléas, S. Darses, *Org. Lett.* **2015**, *17*, 5496.

[32] T. L. Gilchrist, A. Rahman, *J. Chem. Soc., Perkin Trans.1* **1998**, 1203.

.

10.1002/anie.201806780

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

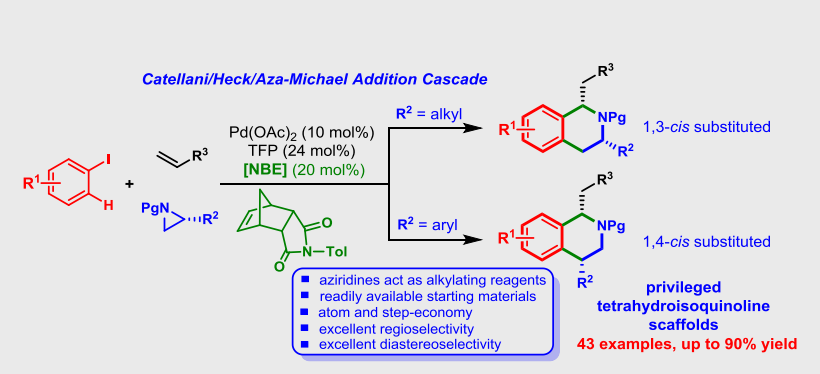
*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

COMMUNICATION



Guangyin Qian, Miao Bai, Shijun Gao, Han Chen, Siwei Zhou, Hong-Gang Cheng, Wei Yan and Qianghui Zhou**

Page No. – Page No.

Modular One-Step Three-Component Synthesis of Tetrahydroisoquinolines via a Catellani Strategy

A modular one-step, three-component synthesis of tetrahydroisoquinolines via a Catellani strategy was developed. In this process, aziridines act as the alkylating reagents to enable a Catellani/Heck/aza-Michael addition cascade through palladium/norbornene cooperative catalysis. This mild, chemo-selective, and scalable protocol is compatible with a wide range of readily available aryl iodides, aziridines as well as olefins (43 examples, up to 90% yield). The most striking feature of this process is the excellent regioselectivity and diastereoselectivity observed for 2-alkyl and 2-aryl substituted aziridines to access 1,3-*cis*-substituted and 1,4-*cis*-substituted tetrahydroisoquinolines respectively. Moreover, this is a versatile process with high step- and atom-economy.

10.1002/anie.201806780

WILEY-VCH

COMMUNICATION