Gold-Catalyzed Stereoselective Domino Cyclization/Alkynylation of N-Propargylcarboxamides with Benziodoxole Reagents for the Synthesis of Alkynyloxazolines

Zhao, Ximei; Tian, Bing; Yang, Yangyang; Si, Xiaojia; Mulks, Florian F.; Rudolph, Matthias; Rominger, Frank; Hashmi, A. Stephen K.

Published in:
Advanced Synthesis & Catalysis

DOI:
10.1002/adsc.201900264

FULL PAPER DOI: 10.1002/adsc.201900264 Advanced Synthesis & Catalysis

Gold-Catalyzed Stereoselective Domino Cyclization/Alkynylation of *N*-Propargylcarboxamides with Benziodoxole Reagents for the Synthesis of Alkynyloxazolines

Ximei Zhao,[a] Bing Tian,[a] Yangyang Yang,[a] Xiaojia Si,[a] Florian F. Mulks,[a, b] Matthias Rudolph,[a] Frank Rominger,[a] and A. Stephen K. Hashmi[a, c,*]

[a] Organisch-Chemisches Institut, Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
E-mail: hashmi@hashmi.de
Homepage: http://www.hashmi.de
[b] Zernike Institute for Advanced Materials, Rijksuniversiteit Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
[c] Affiliation a Chemistry Department, Faculty of Science, King Abdulaziz University (KAU), 21589 Jeddah, Saudi Arabia
Phone: (+49)-(0)6221-54-8413
Fax:(+49)-(0)6221-54-4205

Manuscript received: February 26, 2019; Revised manuscript received: March 28, 2019;
Version of record online: April 29, 2019

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201900264

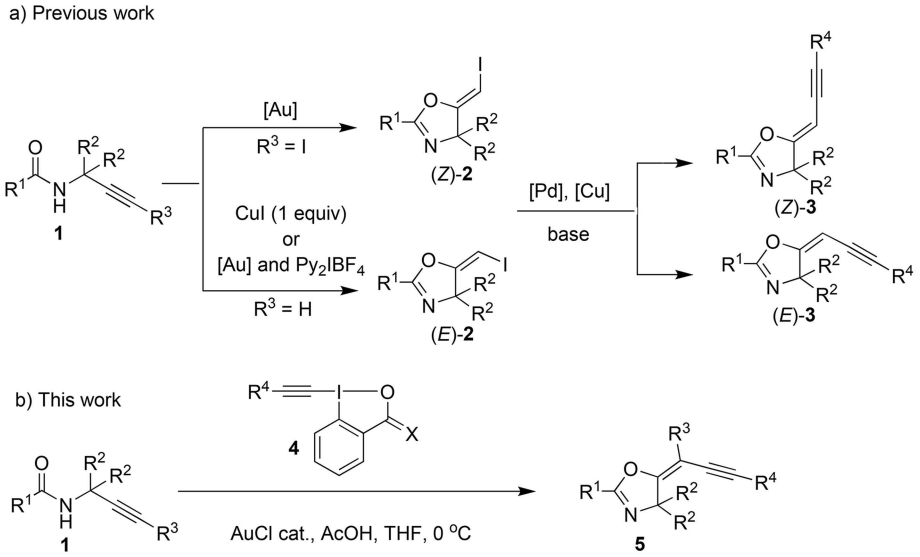
Abstract: A concise and highly stereoselective synthesis of alkynyloxazolines *via* a gold-catalyzed domino cyclization-alkynylation cascade of *N*-propargylcarboxamides with benziodoxole reagents is reported. This new protocol, which represents an attractive alternative to two step sequences based on Sonagashira couplings, offers a broad substrate scope, excellent functional group tolerance, and perfect stereoselectivity. A comparison of the computed energies of the isomers of the product suggests kinetic control as the cause of the observed selectivity.

Keywords: benziodoxole; gold catalysis; oxazolines; oxidative alkynylation; propargylamides

Introduction

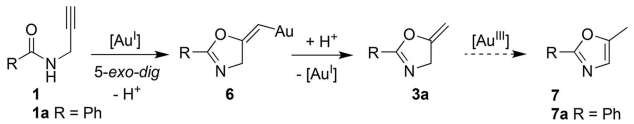
Oxazolines are important heterocycles ubiquitous in bioactive natural products and pharmaceuticals.[1] In addition, they also function as useful synthetic intermediates,[2] protecting groups,[3] as well as valuable ligands[4] in synthetic and catalytic chemistry. Therefore, effective ways to synthesize and functionalize oxazolines are highly desirable. Traditional methods for accessing these heterocycles start from carboxylic acids, esters, nitriles, hydroxyamides, aldehydes and olefins.[1c] Another versatile and effective way is the transition metal-catalyzed cyclization of *N*-propargylcarboxamides,[5] with Brønsted acids,[6] or under strong basic conditions.[7] Among these *N,O*-heterocycles, alkynyl-substituted oxazolines represent a highly interesting class of functionalized building blocks for synthetic chemistry, a fruitful follow-up chemistry is enabled by the subsequent functionalization of the alkynyl groups.[8] Traditionally, these compounds are synthesized by Sonogashira cross coupling reactions.[9] But this transformation is based on the availability of the corresponding halogenated oxazolines, which are usually accessed through the cyclization-halogenation reaction of propargylamides (Scheme 1a).[10] This two-step strategy requires isolation and purification of the sensitive[5h] halogenated oxazoline intermediates, which inevitably consumes additional time, labour, and resources. In addition, this method cannot provide access to products bearing reactive halogen substituents like bromides or iodides for further subsequent functionalization, as these also will react under the palladium-catalyzed conditions of the Sonogashira coupling. Hence, a cyclization/alkynylation process that can be carried out in a domino procedure would be advantageous to the existing strategies.

Alkynyl-substituted hypervalent iodine compounds are powerful reagents for the formation of new C-alkynyl bonds by electrophilic alkynylation reactions.[11] In 2009, Waser and co-workers reported the first direct C–H alkynylation of pyrroles and indoles by using [(triisopropylsilyl)ethynyl]benziodoxolone (TIPS-EBX (**4a**)) in combination with AuCl



Scheme 1. Previous synthesis of alkynyl-substituted alkylidenoxazolines and gold-catalyzed domino cyclization/alkynylation process.

as catalyst.[12] Since then, the use of TIPS-EBX for a direct ethynyl transfer reactions has been extensively exploited.[11a,b] For instance, a Pd-catalyzed cyclization-alkynylation cascade of olefins with TIPS-EBX reported by Waser *et al.* lead to oxyalkynylation products of alkenes.[13] Patil's group has addressed a gold-catalyzed aminoalkynylation of alkynes by using TIPS-EBX to access alkynylated quinalizinones.[14] In 2013, a modified ethynylbenziodoxole reagent (TIPS-EBX* (**4b**)) was developed by Waser *et al.*, this reagent was exceptionally efficient for a domino cyclization-alkynylation process of allenyl ketones to access C3-alkynylated furans.[15] In addition, it also acted effectivly in the gold-catalyzed C(*sp*)–C(*sp*) cross-coupling reaction of terminal alkynes with alkynyl-substituted hypervalent iodine reagents for the synthesis of unsymmetrical 1,3-diynes.[16] Inspired by this, we envisaged a domino process (Scheme 1b) on the basis of our previous studies on the gold-catalyzed cyclization of propargylamides (Scheme 2)[5g] and one-pot strategies based on this reactivity.[17]



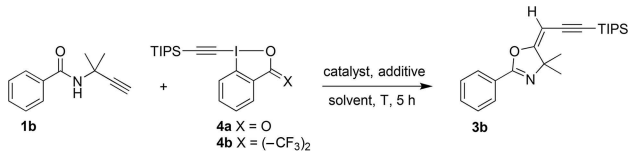
Scheme 2. Gold-catalyzed cyclization of propargylamides.

Results and Discussion

First we used propargylamide **1a** as the test substrate with EBX* derivative **4b** in the presence of AuCl (10 mol%) in Et_2O. To our disappointment, only trace amounts of the desired product could be detected by ^1H NMR, together with a large amount of oxazole **7a**. This is in line with our previous work, which showed that in the presence of Au^{III}, the oxazolines **3** readily aromatize to oxazoles **7**.[5c] This seems to be initiated by the oxidation of Au^I to Au^{III} in the presence of **4b**. To prevent this isomerisation, compounds **1** with tertiary propargylic substituents were used for the subsequent conversions.

Thus *N*-propargylamide **1b** and TIPS-EBX* **4b** were used as the model substrates to optimize the reaction conditions (Table 1). Preliminary results showed the desired transformation, 9% of the product **3b** were detected (10 mol% AuCl, Et_2O, RT; entry 1), but this would be stoichiometric in gold. Other gold catalysts with ligands like IPrAuCl or PPh_3AuCl did not afford **3b** (entry 2 and 3). Changing the solvent to THF gave a positive result, affording **3b** in 23% yield (entry 4). Other screened solvents, DCM, CH_3CN, and ^{i}PrOH, generated **3b** in much lower yields (entry 5–7). By decreasing the reaction temperature to 0 °C, the yield increased to 36% (entry 9), while at 50 °C and −20 °C the coupling was less efficient (entry 8 and 10). Adding 0.5 equiv. of AcOH again improved the reaction, yielding 48% of **3b** (entry 11). The yield could be further increased to 67% by raising the amount of AuCl to 15 mol% (entry 12). Among the screened amounts of AcOH, 0.2, 0.8, and 1.0 equiv. were less efficient, affording **3b** in lower yields (entry 13–15). Changing the additive to $Zn(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_2$, NaOAc, or Na_2CO_3, and 2-picolinic acid significantly decreased the yield (entry 16–21). Another EBX derivative (**4a**) did also afford **3b**, but in

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	T [°C]	Additive	Yield (%)[b]
1	AuCl	Et_2O	RT	–	9
2	IPrAuCl	Et_2O	RT	–	ND
3	PPh_3AuCl	Et_2O	RT	–	ND
4	AuCl	THF	RT	–	23
5	AuCl	DCM	RT	–	8
6	AuCl	CH_3CN	RT	–	8
7	AuCl	^{i}PrOH	RT	–	trace
8	AuCl	THF	50	–	10
9	AuCl	THF	0	–	36
10	AuCl	THF	−20	–	4
11	AuCl	THF	0	AcOH (0.5 eq.)	48
12	**AuCl**	**THF**	**0**	**AcOH (0.5 eq.)**	**67(64)**[c]
13	AuCl	THF	0	AcOH (0.2 eq.)	46
14	AuCl	THF	0	AcOH (0.8 eq.)	61
15	AuCl	THF	0	AcOH (1.0 eq.)	54
16	AuCl	THF	0	$Zn(OTf)_2$ (0.15 eq.)	10
17	AuCl	THF	0	$Yb(OTf)_3$ (0.15 eq.)	48
18	AuCl	THF	0	$Sc(OTf)_2$ (0.15 eq.)	26
19	AuCl	THF	0	NaOAc (1.0 eq.)	trace
20	AuCl	THF	0	Na_2CO_3 (1.0 eq.)	trace
21	AuCl	THF	0	2-Picolinic acid (1.0 eq.)	20
22	AuCl	THF	0	AcOH (0.5 eq.)	20[d]
23	None	THF	0	AcOH (0.5 eq.)	ND[e]

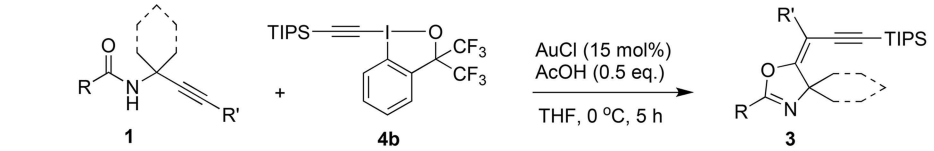
[a] Reaction conditions: entries 1–11, **1b** (0.1 mmol), **4b** (0.12 mmol), catalyst (10 mol%), and additive in 2 mL of solvent; entries 12–21, **1b** (0.1 mmol), **4b** (0.12 mmol), catalyst (15 mol%), and additive in 2 mL of solvent.
[b] Measured by ^{1}H NMR with dibromomethane as the internal standard.
[c] Yield of isolated product.
[d] Reaction conditions: **1b** (0.1 mmol), **4a** (0.12 mmol), catalyst (15 mol%), and additive reacted in 2 mL of solvent.
[e] Reaction conditions: **1b** (0.1 mmol), **4b** (0.12 mmol), and additive reacted in 2 mL of solvent.

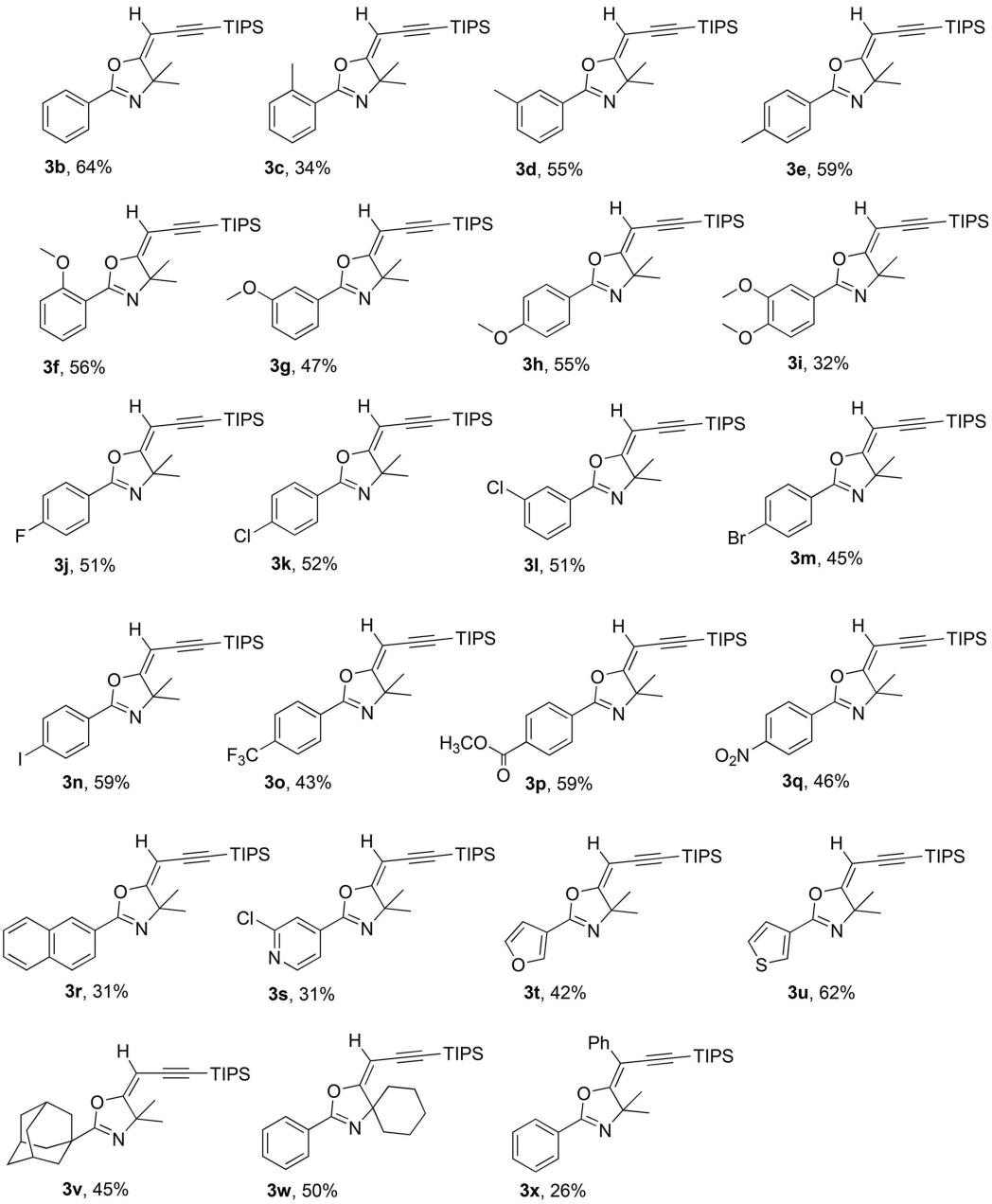
much lower yield (entry 22). Control experiments without catalyst showed no reaction (entry 23).

Under the optimized conditions (1.2 equiv. of ethynylbenziodoxole **4b**, 15 mol% AuCl, 0.5 equiv. of AcOH, THF, 0 °C), the scope with respect to the *N*-propargylcarboxamides **1** was then investigated (Table 2). A wide range of substituents at the phenyl group were compatible, giving the desired products in good to moderate yields (**3b–q**). With regard to methyl-substituted amides, substituents at *m*- and *p*-positions of the phenyl group gave the corresponding products in much higher yields (**3d**, **3e**) than *o*-aryl-substituted amide (**3c**), probably due to the steric hindrance. Amides bearing methoxyl groups at the aromatic rings, no matter at *o*-, *m*, or *p*-positions produced products **3f–h** in moderate yields, while a two-fold methoxy-substituted amide afforded **3i** in 32% yield. Importantly, substrates with electron-withdrawing groups including fluoride (**3j**), chloride (**3k**, **3l**), bromide (**3m**), iodide (**3n**), trifluoromethyl (**3o**), ester (**3p**), and nitro functionalities (**3q**) all turned out to be tolerated and afforded the corresponding products in 45–59% yields, which opens the door for downstream manipulation at such positions. Besides phenyl amides, a naphthyl amide also gave product **3r** in fair yield (31%). When the phenyl group was changed to heterocycles including pyridine (**3s**), furan (**3t**) and thiophene (**3u**), the yields remained good to moderate (31–62%). In addition to aromatic amides, an aliphatic amide also afforded product **3v** in 45% yield. The phenyl amide bearing a cyclohexyl group instead of a dimethyl group gave product **3w** in moderate yield (50%). Finally, an internal phenyl amide was investigated to give **3x** in 26% yield.

Next, the utility of various EBX* analogues for the gold-catalyzed domino cyclization-alkynylation reac-

Table 2. Scope with regard to the *N*-propargylcarboxamides.

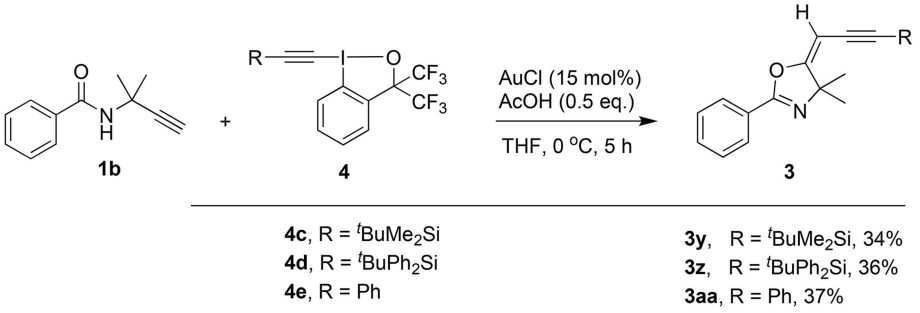


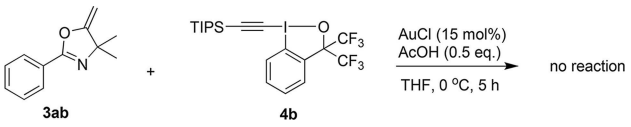


tion was investigated with **1b** as the reaction partner (Table 3). As shown in Table 3, ^{t}BuMe$_2$Si-EBX* (**4c**), ^{t}BuPh$_2$Si-EBX* (**4d**), and Ph-EBX* (**4e**) all worked with the reaction, affording products **3y**, **3z**, and **3aa** in 34%, 36%, and 37% yields, respectively.

In order to gain insight into the reaction mechanism, we performed the experiment with compound **3ab** under the standard conditions (Scheme 3). After stirring at 0 °C for 5 h, still no conversion was observed. This result proves that the gold-catalyzed domino cyclization/alkynylation reaction does not

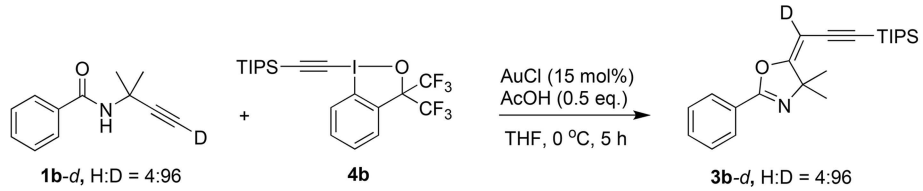
Table 3. Scope with regard to the ethynylbenziodoxoles.



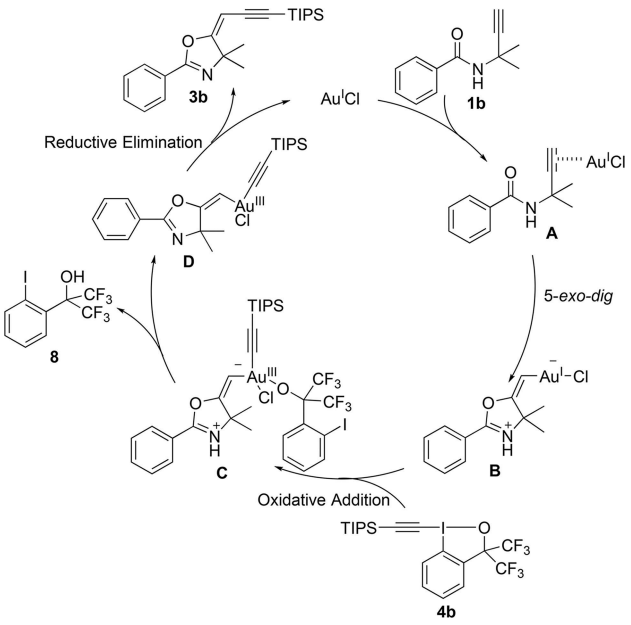


Scheme 3. Reaction of **3 ab** under standard conditions.

proceed *via* **3 ab** as intermediate, followed by the direct sp^2-C–H alkynylation. We also performed a deuterium labeling experiment with deuterated alkyne **1 b**-*d* (H:D = 4:96) under the standard conditions (Scheme 4). Based on the corresponding ^{1}H NMR spectroscopic



Scheme 4. Deuterium labeling experiments.



Scheme 5. Plausible mechanism for the gold-catalyzed domino cyclization-alkynylation reaction.

data, this reaction afforded product **3 b**-*d* with a ratio of H:D of 4:96 at the vinylic position.

From the above experiments and the conclusions from previous reports,[5g,18] a plausible mechanism[19] for the gold-catalyzed domino cyclization/alkynylation reaction is described in Scheme 5. Initially, the carbonyl oxygen atom stereoselectively attacks alkyne, which is π-coordinated to gold, from the backside in an 5-*exo*-*dig* fashion to form vinyl-gold intermediate **B**. After that, the oxidative addition of intermediate **B** (which due to the negatively charged chloride ligand on gold is a locally negatively charged ate-complex of gold(I), and thus easier to oxidize) and compound **4 b** affords intermediate **C**,[20] which then undergoes ligand exchange and reductive elimination to give the active gold(I) catalyst and the final product **3 b**, which is obtained in 100% *trans*-configuration, which is based on the *trans*-selective formation of the vinylgold intermediate. In addition, the increased yield of product **3 b** upon the addition of 0.5 equiv. of acetic acid (Table 1, entry 11) is probably due to the protonation of the alkoxid in complex **C** which assists the formation of **8**, thus accelerating the catalytic cycle and the formation of the desired product.

In order to analyze the relative thermodynamic stability of the two diastereomeric products (*E*)-**3 b** and

(*Z*)-**3 b**, we conducted a computational study. A DFT–D3 analysis (B3LYP-D3(BJ)/6-31G*, CPCM = 8.93)[21] shows that the (*E*)-isomer is thermodynamically favoured by a small margin of ΔG = −1.2 kJ/mol (Zero-point corrected energy difference: ΔE0 = −2.6 kJ/mol, enthalpy difference: ΔH = −2.8 kJ/mol). As Figure 1 shows, due to the slim alkynyl subunit the

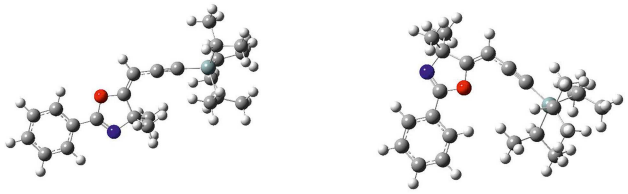


Figure 1. Minimalized structures of the two diastereomeric products (*E*)-**3 b** (left) and (*Z*)-**3 b** (right).

tertiary carbon with the *gem*-dimethyl substitution and the C–C triple bond do not show a strong steric repulsion (Figure 1, left), and thus the energy of the (*E*)-isomer is not increased by such an steric interaction. Taking into account the error margin of the calculations, both structures essentially have almost the same energies, and the experimentally observed selectivity cannot result from thermodynamic control but has to be based on kinetic control.

Finally, we succeeded in growing single crystals of the desilylated derivative **3 q′**. An single crystal X-ray crystal structure analysis of **3 q′**[22] fully confirmed the (*E*)-geometry of the product and thus is in full accord with the mechanistic proposal (Figure 2).

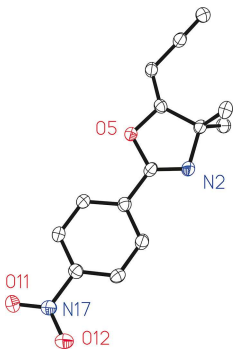


Figure 2. Solid state molecular structure of **3 q'**.

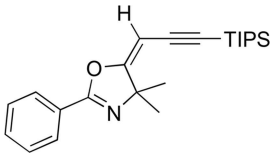
Conclusion

In conclusion, we have developed a novel, concise, efficient, and highly stereoselective synthesis of alkynyloxazolines by the gold-catalyzed domino cyclization/alkynylation of propargylamides with benziodoxole reagents. Simple and mild conditions, broad substrate scope, excellent functional group tolerance, and 100% diastereoselectivity make this new strategy attractive and practical for synthetic chemistry in order to access interesting building blocks.

Experimental Section

General Procedure for the Gold-Catalyzed Stereoselective Domino Cyclization/Alkynylation of *N*-Propargylcarboxamides with Benziodoxole Reagents

A round bottom flask equipped with a magnetic stir bar was charged with AuCl (15.0 μmol, 3.49 mg, 0.15 equiv.), AcOH (2.86 μL, 0.5 equiv.), *N*-propargylcarboxamides **1** (0.10 mmol, 1.0 equiv.), alkynyl hypervalent iodine reagents **4 b** (0.12 mmol, 1.2 equiv.), and THF (2 mL). The mixture was then stirred at 0 °C for 5 h. After reaction, the mixture was extracted with ethyl acetate and concentrated, and the residue was purified by chromatography on silica gel (eluent: PE/EA, or n-hexane/acetone) to give the desired product **3**.



3 b: (*E*)-4,4-Dimethyl-2-Phenyl-5-(3-(Triisopropylsilyl)Prop-2-Ynylidene)-4,5-Dihydrooxazole

According to GP, 18.7 mg (100 μmol) of **1 b**, 66.1 mg (120 μmol) of **4 b**, 3.49 mg (15.0 μmol) of AuCl, and 2.86 μL (50.0 μmol) of AcOH gave 23.5 mg (64.0 μmol) of **3 b** (yield = 64%).

Colorless oil; 1H NMR (500 MHz, CDCl3) δ 7.97 (d, 2H, J = 7.5 Hz), 7.53–7.50 (m, 1H), 7.45–7.42 (m, 2H), 5.48 (s, 1H), 1.71 (s, 6H), 1.11 (s, 21H); 13 C NMR (125 MHz, CDCl3) δ 172.69 (s), 159.12 (s), 131.91 (d), 128.54 (d, 2 C), 128.16 (d, 2 C), 126.36 (s), 100.83 (s), 95.89 (s), 82.50 (d), 71.13 (s), 26.01 (q, 2 C), 18.67 (q, 6 C), 11.49 (s, 3 C); IR (ATR): ν̃ 3062, 2942, 2892, 2865, 2132, 1783, 1672, 1651, 1581, 1462, 1384, 1360, 1319, 1292, 1260, 1181, 1121, 1099, 1046, 1022, 964, 916, 883, 811, 694, 667, 624 cm-1; HRMS (EI) calcd for $[C_{23}H_{34}NOSi]^+$ $(M + H)^+$: 368.2404; found 368.2406.

Acknowledgements

X. Z. is grateful to the CSC (China Scholarship Council) for a Ph.D. fellowship. The authors acknowledge support by the HPC-Europa3 program, funded by the European Commision's Research Infrastructures activity of the Structuring the European Research Area program (contract number 730897) and support by the state of Baden-Württemberg through bwHPC

References

[1] a) J.-P. Genet, S. Thorimbert, A.-M. Touzin, *Tetrahedron Lett.* **1993**, *34*, 1159–1162; b) Q. Li, K. W. Woods, A. Claiborne, S. L. Gwaltney, K. J. Barr, G. Liu, L. Gehrke, R. B. Credo, Y. H. Hui, J. Lee, R. B. Warner, P. Kovar, M. A. Nukkala, N. A. Zielinski, S. K. Tahir, M. Fitzgerald, K. H. Kim, K. Marsh, D. Frost, S.-C. Ng, S. Rosenberg, H. L. Sham, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465–469; c) I. Mohammadpoor-Baltork, A. R. Khosropour, S. F. Hojati, *Synlett* **2005**, 2747–2750.

[2] a) H. H. Wasserman, K. E. McCarthy, K. S. Prowse, *Chem. Rev.* **1986**, *86*, 845–856; b) T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297–2360; c) D. Yang, Y.-C. Yip, X.-C. Wang, *Tetrahedron Lett.* **1997**, *38*, 7083–7086.

[3] H. Vorbrüggen, K. Krolikiewicz, *Tetrahedron* **1993**, *49*, 9353–9372.

[4] a) H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846–848; b) Y. Jiang, Q. Jiang, G. Zhu, X. Zhang, *Tetrahedron Lett.* **1997**, *38*, 215–218; c) H. A. McManus, S. M. Barry, P. G. Andersson, P. J. Guiry, *Tetrahedron* **2004**, *60*, 3405–3416.

[5] a) A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi, F. Marinelli, *Org. Lett.* **2001**, *3*, 2501–2504; b) A. Bacchi, M. Costa, B. Gabriele, G. Pelizzi, G. Salerno, *J. Org. Chem.* **2002**, *67*, 4450–4457; c) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394; d) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, *2006*, 4905–4909; e) C. Jin, J. P. Burgess, J. A. Kepler, C. E. Cook, *Org. Lett.* **2007**, *9*, 1887–1890; f) M. Harmata, C. Huang, *Synlett* **2008**, *2008*, 1399–1401; g) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem. Int. Ed.* **2009**, *48*, 8247–8249; h) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963; i) A. S. K. Hashmi, L. Molinari, F. Rominger, T. Oeser, *Eur. J. Org. Chem.* **2011**, *2011*, 2256–2264; j) X. Meng, S. Kim, *Org. Biomol. Chem.* **2011**, *9*, 4429–4431; k) A. S. Hashmi, M. C. Blanco Jaimes, A. M. Schuster, F. Rominger, *J. Org. Chem.* **2012**, *77*, 6394–6408; l) A. S. K. Hashmi, *Pure Appl. Chem.* **2010**, *82*, 657–668; for the activation of alkynes, see: m) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; n) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 2285–2288; *Angew. Chem.* **2000**, *112*, 2382–2385.

[6] E. Merkul, T. J. J. Müller, *Chem. Commun.* **2006**, 4817–4819.

[7] B. M. Nilsson, H. M. Vargas, B. Ringdahl, U. Hacksell, *J. Med. Chem.* **1992**, *35*, 285–294.

[8] a) A. G. Fallis, *J. Am. Chem. Soc.* **2005**, *127*, 15990–15991; b) P. J. Stang, R. R. Tykwinski, *Acetylene chemistry: chemistry, biology and material science*, John Wiley & Sons, **2006**.

[9] R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[10] a) A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, *2011*, 4595–4602; b) Y. Hu, R. Yi, C. Wang, X. Xin, F. Wu, B. Wan, *J. Org. Chem.* **2014**, *79*, 3052–3059; c) S. Gazzola, E. M. Beccalli, T. Borelli, C. Castellano, M. A. Chiacchio, D. Diamante, G. Broggini, *J. Org. Chem.* **2015**, *80*, 7226–7234; d) S. Zhang, Y. Chen, J. Wang, Y. Pan, Z. Xu, C.-H. Tung, *Org. Chem. Front.* **2015**, *2*, 578–585.

[11] a) J. P. Brand, D. Fernandez Gonzalez, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102–115; b) J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165–4179; c) J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8876–8878; for recent results on alkynylation in gold catalysis, see: d) Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 5129–5133; *Angew. Chem.* **2019**, *131*, 5183–5187..

[12] a) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349; for general reviews on gold catalysis, see: b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; c) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331–1367.

[13] S. Nicolai, S. Erard, D. F. González, J. Waser, *Org. Lett.* **2010**, *12*, 384–387.

[14] P. S. Shinde, A. C. Shaikh, N. T. Patil, *Chem. Commun.* **2016**, *52*, 8152–8155.

[15] Y. Li, J. P. Brand, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 6743–6747.

[16] X. Li, X. Xie, N. Sun, Y. Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 6994–6998.

[17] a) A. S. Hashmi, A. Littmann, *Chem. Asian J.* **2012**, *7*, 1435–1442; b) K. S. Nalivela, M. Rudolph, E. S. Baeissa, B. G. Alhogbi, I. A. I. Mkhalid, A. S. K. Hashmi, *Adv. Synth. Catal.* **2018**, *360*, 2183–2190; for recent results on the synthesis of *N*-heterocycles, see: c) X. Tian, L. Song, M. Rudolph, F. Rominger, T. Oeser, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, *58*, 3589–3593, *Angew. Chem.* **2019**, *131*, 3627–3631; d) X. Tian, L. Song, M. Rudolph, Q. Wang, X. Song, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 1598–1601; e) X. Tian, L. Song, C. Han, C. Zhang, Y. Wu, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 2937–2940.

[18] a) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655–5666; b) H. Ghari, Y. Li, R. Roohzadeh, P. Caramenti, J. Waser, A. Ariafard, *Dalton Trans.* **2017**, *46*, 12257–12262.

[19] A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241.

[20] Y.-Y. Yang, P. Antoni, M. Zimmer, K. Sekine, F. Mulks, L. Hu, L. Zhang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2019**, DOI: 10.1002/anie.201812577R1.

[21] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789; c) S. Grimme, S. Ehrlich, L. Goerigk, *J.*

Comput. Chem. **2011**, *32*, 1456–1465; d) P. C. Hariharan, J. A. Pople, *Theor. Chim. Acta* **1973**, *28*, 213–222; e) M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003**, *24*, 669–681; f) Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Wallingford CT, Gaussian, Inc., **2013**.

[22] CCDC 1905707 (**3q′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

