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Communication

Nickel-catalyzed asymmetric arylative cyclization of *N*-alkynones: Efficient access to 1,2,3,6-tetrahydropyridines with a tertiary alcohol

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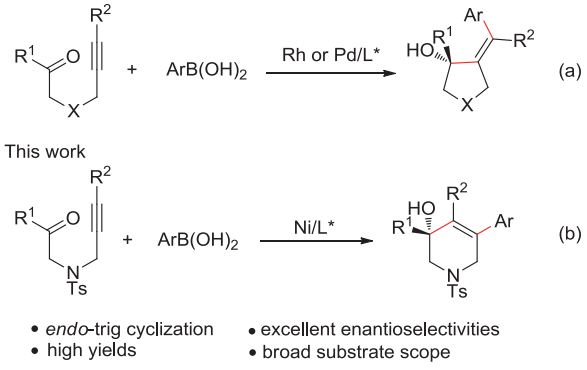
ABSTRACT

Nickel/(*S*)-*t*-Bu-PHOX complex catalyzed asymmetric arylative cyclization of *N*-alkynones has been achieved, delivering 1,2,3,6-tetrahydropyridines containing a chiral tertiary alcohol in high yields and excellent enantioselectivities, which provides efficient access to chiral tetrahydropyridine and piperidine analogues.

Enantioselective construction of high valuable chiral heterocycles in an atom economy and step economy manner is one of the most important goals of chemists pursued [1,2]. To this end, the transition-metal-catalyzed intramolecular cyclization of alkynals/alkynones, one of the most straightforward methods for the efficient construction of five- to six-membered heterocycles bearing a tertiary alcohol, has been widely investigated [3-5]. As a result, cyclization of alkynals/alkynones has been achieved by various kinds of transition-metal catalysts, such as rhodium [6-15], ruthenium [16], nickel [17-23] or palladium complexes [24-28], which greatly promoted the development of intramolecular cyclization of alkynals/alkynones. However, most of these approaches involved an *exo*-trig pathway, affording five-membered heterocycles containing an exocyclic olefin (Scheme 1a) [29-31]. By comparison, the *endo*-trig cyclization of alkynals/alkyones to generate endocyclic alkenes was rarely reported, although it provides concise access to some valuable molecules. In 2016, Lam group reported their pioneer work on Ni-catalyzed desymmetrization of 1,3-diketones, which achieved *endo*-trig cyclization of alkynones, giving fused bicycles efficiently [32]. Nevertheless, only cyclic 1,3-diketones with relatively high activity could be tolerated in this transformation, which limited its applications in construction of chiral heterocycles. Thus, it is highly desirable to develop new methodology to expand the generality of *endo*-trig cyclization of alkynones [33].



Scheme 1. Transition metal catalyzed arylative cyclization of alkynones.

In the past decades, nickel catalyzed asymmetric reactions has emerged as a powerful strategy for construction of chiral molecules [34-38]. In this context, our group reported nickel-catalyzed intramolecular asymmetric reductive cyclization of aryl halides with unactivated ketones through the addition of aryl nickel species to carbonyl group [39]. Inspired by this result, we envision that the vinyl nickel species may also react with unactivated ketones to generate chiral heterocycles efficiently. Herein, we report a highly enantioselective intramolecular arylative cyclization of *N*-alkynones to furnish chiral tetrahydropyridines containing a tertiary allylic alcohol in high yields and excellent enantioselectivities (Scheme 1b),

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which are important structural motifs widely existed in natural products and biologically active compounds [40-42].

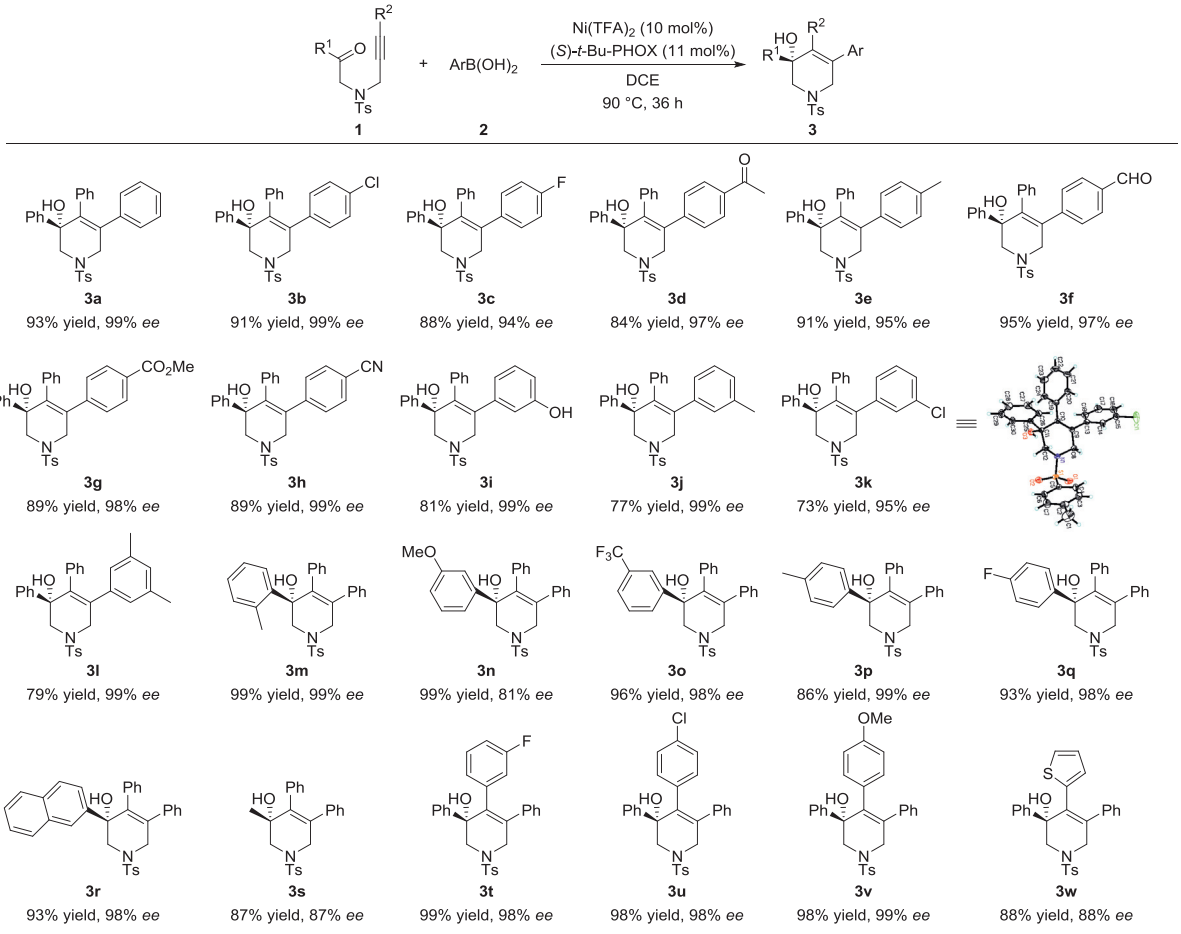
Our initial study began with nickel-catalyzed arylative cyclization of *N*-alkynone (**1a**) with phenylboronic acid (**2a**) in the presence of 10 mol% $Ni(OAc)_2$•$4H_2O$ in DCE. Firstly, a series of commercial available chiral oxazoline ligands were evaluated. As shown in Table 1, Pybox (**L1**), Pyox (**L2**), and Box (**L3**) did not exhibit any catalytic activity in this transformation (entries 1–3). When phosphine-oxazoline ligand **L4** was employed, it delivered target product in 50% yield with 14% *ee* (entry 4). Increasing the steric hindrance of oxazoline, the enantioselectivity was greatly proved, but the yield was decreased gradually (entries 5 and 6). Considering the excellent enantiocontrol ability of (*S*)-*t*-Bu-PHOX, it was chosen as the best ligand for further optimization. Subsequently, the solvent effects were investigated, and the results disclosed that toluene and methanol were detrimental to the conversion, which lead to a totally inhibition of this transformation. The yields increased when 1,4-dioxane, CH_3CN and 2-methyltetrahydrofuran (2-MeTHF) were used as solvent, while the enantioselectivities decreased to some extent (entries 7–11). Interestingly, a little water can improve the yield and has little impact on the enantioselectivity (entry 12). To our delight, the yield was increased to 95% when $Ni(TFA)_2$ was used as metal precursor in presence of 2 equiv. water (entry 13). Increasing the temperature to 90 °C, a full conversion was obtained, affording target product **3a** in 99% yield with 99% *ee* (entry 14).

With the optimal conditions in hand, we surveyed the generality of nickel-catalyzed arylative cyclization of *N*-alkynones. Generally, the reaction had a broad substrate scope and exhibited good tolerance to various substituted arylboronic acids and *N*-alkynones. As shown in Scheme 2, different kinds of arylboronic acids, no matter the position and the electronic nature of substituent, are well tolerated in this transformation, giving target products in high

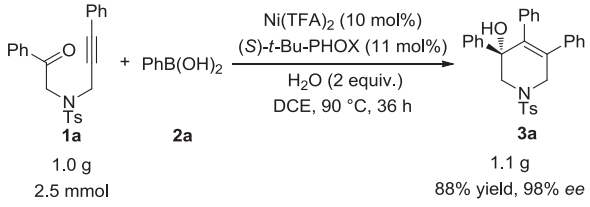
Table 1
Optimization for nickel-catalyzed arylative cyclization of **1a** and **2a**.[a]

Entry	L	Solvent	Metal salt	Yield (%)[b]	*ee* (%)[c]
1	**L1**	DCE	$Ni(OAc)_2$•$4H_2O$	NR	NA
2	**L2**	DCE	$Ni(OAc)_2$•$4H_2O$	NR	NA
3	**L3**	DCE	$Ni(OAc)_2$•$4H_2O$	NR	NA
4	**L4**	DCE	$Ni(OAc)_2$•$4H_2O$	50	14
5	**L5**	DCE	$Ni(OAc)_2$•$4H_2O$	29	84
6	**L6**	DCE	$Ni(OAc)_2$•$4H_2O$	19	99
7	**L6**	1,4-Dioxane	$Ni(OAc)_2$•$4H_2O$	68	86
8	**L6**	Toluene	$Ni(OAc)_2$•$4H_2O$	trace	NA
9	**L6**	MeOH	$Ni(OAc)_2$•$4H_2O$	trace	NA
10	**L6**	CH_3CN	$Ni(OAc)_2$•$4H_2O$	52	83
11	**L6**	2-MeTHF	$Ni(OAc)_2$•$4H_2O$	44	88
12[d]	**L6**	DCE	$Ni(OAc)_2$•$4H_2O$	31	99
13[d]	**L6**	DCE	$Ni(TFA)_2$	95	99
14[d, e]	**L6**	DCE	$Ni(TFA)_2$	99 (93)[f]	99

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.15 mmol), nickel salt (10 mol%), ligand (11 mol%), solvent (1 mL), 80 °C, under Ar atmosphere.
[b] Determined by ^1H NMR using 3,5-dimethylpyrazole as internal standard.
[c] Determined by chiral HPLC.
[d] H_2O (0.10 mmol).
[e] The reaction was performed at 90 °C.
[f] The isolated yield.



Scheme 2. Substrate scope. Unless otherwise noted, the reactions were performed with **1** (0.1 mmol), **2** (0.3 mmol), $Ni(TFA)_2$ (10 mol%), (*S*)-*t*-Bu-PHOX (11 mol%) and H_2O (0.2 mmol, 5.5 mol/L in dioxane) in DCE (2 mL) at 90 °C for 36 h under Ar atmosphere. Yields of isolated product **3**. Enantiomeric excess was determined by chiral HPLC. The absolute configuration of **3k** was confirmed to be R by X-ray, the other configurations follows that of **3k**.



Scheme 3. Gram scale reaction.

yields and excellent enantioselectivities (**3a**-**3l**). Notably, the reaction shows excellent compatibility to a series of functional groups, such as aldehyde (**3f**), ester (**3g**), cyano group (**3h**), hydroxyl group (**3i**), and there was no significant impact on the yield and enantioselectivity. When R^1 is substituted aryl group or naphthyl group, the reaction proceeded very smoothly, delivering desired products **3m**-**3r** with high yields and excellent enantioselectivities. It is worth noting that the reaction was also compatible with alkyl substituted *N*-alkynone, furnishing **3s** in 87% yield with 87% *ee*. When R^2 is substituted benzene group, it afforded target products with high yields and excellent *ee* values (**3t**-**3v**). Replacing R^2 by a heteroaryl, the yield and enantioselectivity decreased to some extent (**3w**). The ether-tethered substrate was also tolerated, but the ee value dropped dramatically (88% yield and 66% *ee*, see Supporting information).

To demonstrate the synthetic utility of the current methodology, a gram-scale reaction was conducted under the standard condition, affording desired product **3a** in 88% yield with 98% *ee*, which indicated that the method has a potential application in construction of chiral molecules with a tetrahydropyridine motif.

In conclusion, nickel-catalyzed asymmetric cyclization of *N*-alkynones with arylboronic acids has been achieved, offering 1,2,3,6-tetrahydropyridines bearing a chiral tertiary alcohol in excellent yields with excellent enantioselectivities (up to 99% yield, up to 99% *ee*). This reaction proceeded through an *endo*-trig pathway, which provides efficient access to heterocycles with an endocyclic allylic alcohol. Moreover, the potential utility of this method was demonstrated by a gram-scale reaction without loss of yield and enantioselectivity. Further development and application of this reaction is underway in our laboratories.

Declaration of competing interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.06.006.

References

[1] M.G. Vinogradov, O.V. Turova, S.G. Zlotin, Adv. Synth. Catal. 363 (2021) 1466–1526.
[2] R.M. Philip, S. Radhika, P.V. Saranya, G. Anilkumar, RSC Adv. 10 (2020) 42441–42456.
[3] I. Ojima, M. Tzamarioudaki, Z. Li, R.J. Donovan, Chem. Rev. 96 (1996) 635–662.
[4] J. Montgomery, Acc. Chem. Res. 33 (2000) 467–473.
[5] W.W. Chen, M.H. Xu, Org. Biomol. Chem. 15 (2017) 1029–1050.
[6] I. Ojima, M. Tzamarioudaki, C.Y. Tsai, J. Am. Chem. Soc. 116 (1994) 3643–3644.
[7] B. Bennacer, M. Fujiwara, S.Y. Lee, I. Ojima, J. Am. Chem. Soc. 127 (2005) 17756–17767.
[8] R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama, T. Hayashi, J. Am. Chem. Soc. 127 (2005) 54–55.
[9] J.U. Rhee, M.J. Krische, J. Am. Chem. Soc. 128 (2006) 10674–10675.
[10] X. Fang, C. Li, X. Tong, Chem. Commun. (2009) 5311–5313.
[11] R. Tanaka, K. Noguchi, K. Tanaka, J. Am. Chem. Soc. 132 (2010) 1238–1239.
[12] K. Masuda, N. Sakiyama, R. Tanaka, K. Noguchi, K. Tanaka, J. Am. Chem. Soc. 133 (2011) 6918–6921.
[13] J. Keilitz, S.G. Newman, M. Lautens, Org. Lett. 15 (2013) 1148–1151.
[14] F. Serpier, J.L. Brayer, B. Folléas, S. Darses, Org. Lett. 17 (2015) 5496–5499.
[15] A. Selmani, S. Darses, Org. Lett. 22 (2020) 2681–2686.
[16] A. Saxena, F. Perez, M.J. Krische, Angew. Chem. Int. Ed. 55 (2016) 1493–1497.
[17] X.Q. Tang, J. Montgomery, J. Am. Chem. Soc. 121 (1999) 6098–6099.
[18] Y. Ni, K.K.D. Amarasinghe, J. Montgomery, Org. Lett. 4 (2002) 1743–1745.
[19] R.D. Baxter, J. Montgomery, J. Am. Chem. Soc. 133 (2011) 5728–5731.
[20] A.D. Jenkins, A. Herath, M. Song, J. Montgomery, J. Am. Chem. Soc. 133 (2011) 14460–14466.
[21] M.T. Haynes, P. Liu, R.D. Baxter, et al., J. Am. Chem. Soc. 136 (2014) 17495–17504.
[22] H. Wang, S. Negretti, A.R. Knauff, J. Montgomery, Org. Lett. 17 (2015) 1493–1496.
[23] Z. Zhou, W. Liu, W. Kong, Org. Lett. 22 (2020) 6982–6987.
[24] K. Shen, X. Han, X. Lu, Org. Lett. 15 (2013) 1732–1735.
[25] J. Song, Q. Shen, F. Xu, X. Lu, Org. Lett. 9 (2007) 2947–2950.
[26] L. Zhao, X. Lu, Angew. Chem. Int. Ed. 41 (2002) 4343–4345.
[27] H. Wang, X. Han, X. Lu, Tetrahedron 66 (2010) 9129–9134.
[28] X. Han, X. Lu, Org. Lett. 12 (2010) 108–111.
[29] Y. Li, M.H. Xu, Org. Lett. 16 (2014) 2712–2715.
[30] W. Fu, M. Nie, A. Wang, Z. Cao, W. Tang, Angew. Chem. Int. Ed. 54 (2015) 2520–2524.
[31] G. Liu, W. Fu, X. Mu, et al., Commun. Chem. 1 (2018) 90.
[32] C. Clarke, C.A. Incerti-Pradillos, H.W. Lam, J. Am. Chem. Soc. 138 (2016) 8068–8071.
[33] H. Green, S.P. Argent, H.W. Lam, Chem. Eur. J. (2021), doi:10.1002/chem.202100143.
[34] Z. Lu, X.D. Hu, H. Zhang, et al., J. Am. Chem. Soc. 142 (2020) 7328–7333.
[35] W. Wang, C. Ding, G. Yin, Nat. Catal. 3 (2020) 951–958.
[36] Y. Cai, L.X. Ruan, A. Rahman, S.L. Shi, Angew. Chem. Int. Ed. 60 (2021) 5262–5267.
[37] Y.Q. Li, G. Chen, S.L. Shi, Org. Lett. 23 (2021) 2571–2577.
[38] P. Ye, X. Liu, G. Wang, L. Liu, Chin. Chem. Lett. 32 (2021) 1237–1240.
[39] Y. Li, W. Li, J. Tian, G. Huang, H. Lv, Org. Lett. 22 (2020) 5353–5357.
[40] M.M. Khan, S. Khan, S. Saigal, Iqbal, RSC Adv. 6 (2016) 42045–42061.
[41] S. Hanessian, A.K. Chattopadhyay, Org. Lett. 16 (2014) 232–235.
[42] O.G. Mancheño, R. Gómez Arrayás, J. Adrio, J.C. Carretero, J. Org. Chem. 72 (2007) 10294–10297.