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Enantioselective nickel-catalyzed alkylative alkyne–aldehyde cross-couplings†

Ming Nie, Wenzhen Fu, Ziping Cao and Wenjun Tang*

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An efficient asymmetric nickel-catalyzed alkylative alkyne–aldehyde cross-coupling is developed by employing a P-chiral monophosphorus ligand BI-DIME, allowing rapid access to a series of chiral tetrasubstituted olefinic allylic alcohols in high yields and good to excellent ees. The three-component reactions enjoy excellent regio- and enantioselectivities, and a broad substrate scope from readily available starting materials.

The development of efficient multicomponent reactions¹ for the rapid construction of molecules with complexity from simple feedstock in high yields and excellent selectivities has become a field of significant interest to synthetic organic chemists. Such reactions are often more environmentally benign, energy-saving, and with high atom and step economy. Chiral tetra-substituted olefinic allylic alcohols² have increasingly become a class of important intermediates in organic synthesis. Their syntheses are often tedious, with the requirement of multiple synthetic steps. The single-step, three-component, nickel-catalyzed alkylative alkyne-aldehyde cross-coupling^{3,4} from readily available starting materials under mild conditions has provided an appealing method for constructing such structures (Fig. 1). Since Montgomery first reported 5 this transformation, enantioselective nickel-catalyzed alkylative alkyne– aldehyde coupling has attracted considerable attention. Due to the lack of efficient chiral nickel catalysts, $6,7$ only a few highly enantioselective examples were reported with limited substrate scope. Excellent enantioselectivities were achieved by Zhou and coworkers^{3f} by employing a chiral 6,6'-disubstituted spiro phosphoramidite ligand on a series of aryl aldehydes as sub-**PUBLISHERT ARTICLE**

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Fig. 1 Nickel-catalyzed alkylative alkyne–aldehyde cross-coupling.

strates. In contrast, only one example with alkyl aldehyde was reported at 10 mol% nickel catalyst loading. We report herein an efficient asymmetric nickel-catalyzed alkylative alkyne–aldehyde coupling that has provided high yields and good to excellent enantioselectivities for a series of chiral tetrasubstituted olefinic allylic alcohols with the employment of a P-chiral monophosphorus ligand BI-DIME.

We recently reported⁸ an asymmetric nickel-catalyzed reductive cyclization of alkynones that has led to a series of tertiary allylic alcohols bearing furan/pyran rings in excellent yields and enantioselectivities with AntPhos/BI-DIME⁹ as the chiral ligand. Its broad substrate scope for both alkyl and aryl substrates prompted us to investigate the intermolecular alkylative alkyne–aldehyde couplings with the P-chiral phosphorus ligands developed in our laboratory.¹⁰ Thus, the ternary reactions between 1-phenyl-1-propyne (1a), benzaldehyde (2a), and dimethylzinc were carried out at room temperature in toluene for 16 h under nitrogen in the presence of Ni(COD)_2 (5 mol%) and a P-chiral biaryl monophosphorus ligand (6 mol%). As shown in Table 1, the ligand structure significantly impacts its reactivity and enantioselectivity. When ligand L1 with no substituents on the low aryl ring was employed, the desired coupling product 3a was isolated in 67% yield and 50% ee (entry 1). Nearly no formation of its regio-isomer 3a′ was observed according to 1 H NMR. When BI-DIME with two methoxy substituents on the low aryl ring was used as the ligand, a high yield (95%) and excellent enantioselectivity (90%) were observed (entry 2). However, ligands with aryloxy substituents on the low aryl ring provided little or no formation of 3a (entries 3 and 4). Ligands with alkyl groups at the 2 position of the oxophosphole ring also provided diminished reactivities, as both L5 and L6 were less effective (entries 5 and 6). AntPhos, which was highly effective in reductive cyclization of alkynones, 8 also proved to be less efficient (entry 7). The solvent also played an important role in the reactivity and enantioselectivity, and toluene was found to be the best

State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, 354 Ling Ling Rd, Shanghai 200032, P. R. China. E-mail: tangwenjun@sioc.ac.cn

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Table 1 Enantioselective nickel-catalyzed alkylative couplings of alkynes with aldehydes: optimization of conditions

Me $\hspace{0.1mm} +\hspace{0.1mm}$		$Ni(COD)_{2}$ (5 mol%) Me L^* (6 mol%)	OH Me	OH
Ph	Ph _i	Phi Me ₂ Zn, toluene, rt Me	Ph ⁺ Me [®]	Ph Ph
1a	2a	3a		3a'
R $L1: R_1 = H$	fBu R	٠R fBu OMe MeO		<i>f</i> Bu
L2: R_1 = OMe (BI-DIME) L3: $R_1 =$ OPh L4: $R_1 = O(3.5 \text{-} Me_2C_6H_3)$		$L5: R = Me$ $L6: R = Bn$	L7 (AntPhos)	
Entries ^a	Ligand	Solvent	Yield of $3a^{b}$ (%)	ee^c $(\%)$
$\mathbf{1}$	L1	Toluene	67	50
2	L2	Toluene	95	90
3	L ₃	Toluene	12	74
4	L ₄	Toluene	5	nd
5	L ₅	Toluene	36	76
6	L ₆	Toluene	$<$ 5	nd
7	L7	Toluene	46	42
8	L2	Dioxane	78	79
9	L2	THF	25	70
10		DCM	19	82
11	L2 L2	DME	$\mathbf{0}$	

 a ^a The reactions were carried out in a solvent (0.1 M) at rt under nitrogen for 16 h with 1a (0.20 mmol), 2a (0.40 mmol), $Ni(COD)_{2}$ $(5 \text{ mol}),$ ligand $(6 \text{ mol}),$ and Me₂Zn (0.60 mmol) . The absolute configuration of 2a was determined by comparison of its optical rotation with reported data.^{3f b} Isolated yields, ratio of $3a/3a' > 20/1$ in all cases. ^c Determined by chiral HPLC on a Chiralcel OD-H column.

among the five solvents studied. We believed that the strong solvation of polar solvents with the nickel catalyst inhibited the cycloaddition step of the catalytic cycle.

We then looked into the substrate scope of the reductive alkyne–aldehyde cross-coupling. As can be seen in Table 2, a series of chiral allylic alcohols with tetrasubstituted olefin functionality were prepared in high yields (62–99%), high regioselectivities (3b–ae/3'b–ae > $10/1$), and good to excellent enantioselectivities (78–96% ee). A range of aryl aldehydes was successfully employed regardless of their electronic properties and substitution patterns. No significant electronic effect of the aryl aldehyde was observed on the enantioselectivity of the coupling (3b vs. 3e–h). Besides para- or meta-substituted aryl aldehydes, ortho-substituted aryl aldehydes were also successfully employed for the first time in reductive alkyne–aldehyde cross-couplings to provide excellent ees (3m–p). Both 1- and 2-naphthaldehydes (3q–r) were applicable for this transformation. An array of aliphatic aldehydes (3s–y) was also employed to provide corresponding chiral allylic alcohols in good yields and excellent ees. The enantioselectivities increased with the bulkiness of the aldehyde, as the reaction with pivalaldehyde yielded the alcohol 3y in 95% ee albeit with a moderate yield (62%). 1-Phenyl-1-butyne and 1-phenyl-1-hexyne were also successfully employed to provide the corresponding products

 a Reaction conditions: alkynes (0.20 mmol), aldehydes (0.40 mmol), $Ni(COD)_2$ (5 mol%), L2 (6 mol%), and Me₂Zn (0.60 mmol), toluene (0.10 M), rt under N₂, 16 h, isolated yield. $3b$ -ae/3'b-ae > 19:1 unless otherwise specified. The absolute configurations were determined by comparison of their optical rotations with reported data or by analogy.

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in excellent regioselectivities. This was in contrast to Zhou's system 3f where a significant amount of regio-isomers was formed. Finally, heteroaryls such as thiophene and furan were well tolerated. Both compounds 3ab and 3ac with thiophene moieties were successfully prepared in excellent ees. A moderate ee (79% or 84%) was achieved when 2- or 3-furanaldehyde was employed as the substrate.

To demonstrate the practicality of this transformation, the reaction of 1-phenyl-1-propyne (1a), 2,6-dimethoxybenzaldehyde (2af), and dimethylzinc with the Ni-(R)-BI-DIME catalyst was carried out in toluene on a 1 gram scale. The desired product 3af was obtained in 97% yield and 98% ee, demonstrating a highly efficient and practical example of enantioselective alkylative alkyne–aldehyde cross-coupling with a diortho-substituted aldehyde as the substrate (Scheme 1).

Previous mechanistic studies by Montgomery, $3b,11,13a$ Jamison,^{7a,12,13b,13c} and Houk^{3b,13} as well as by us⁸ on nickel-catalyzed reductive/alkylative alkyne–carbonyl cross-coupling has suggested that the stereoselectivity of this three-component transformation is likely to be determined at the cycloaddition step of alkyne–aldehyde with a $Ni(0)-(R)$ -BI-DIME species. To shed light on the stereochemical translation of this reaction, the two conformers I and II of the cycloaddition intermediates derived from $1a$, $2a$ and the Ni- (R) -BI-DIME complex were subjected to DFT calculations (Fig. 2).¹⁴ The calculated energy of conformer I was ~0.5 kcal mol⁻¹ higher than that of conformer II, which was very likely due to a greater steric influence of the *tert*-butyl group of (R) -BI-DIME over the phenyl group in 1a. The more favorable conformer II led to the chiral alcohol product with the observed stereochemistry. A more sterically crowded $Ni(n)$ structure would provide an even greater energy **Research Article Continuous** Constant to the second on 2018. We were the content of registerion symmetric points of the second of registerion symmetric points and the second of the second of the second only and the secon

Scheme 1 Gram-scale asymmetric alkylative alkyne–aldehyde crosscoupling.

Fig. 2 The DFT calculated conformers I and II of the cycloaddition intermediates derived from 1a, 2a, and the Ni-(R)-BI-DIME complex.

difference between two conformers. Higher enantioselectivities were therefore achieved when more hindered alkyl aldehydes or di-ortho-substituted aryl aldehydes were employed as the reagents.

In summary, we have developed an efficient asymmetric nickel-catalyzed alkylative alkyne–aldehyde cross-coupling with the use of a P-chiral phosphorus ligand BI-DIME. The threecomponent reaction enjoys good to excellent regio- and enantioselectivities, and provides a broad substrate scope with good functional group compatibility. A series of chiral allylic alcohols with tetra-substituted olefin moieties were thus formed in high yields and ees. Our further study focuses on expanding its substrate scope and applications to medicinal chemistry and natural product synthesis.

Acknowledgements

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Notes and references

- 1 Selected reviews: (a) D. J. Ramon and M. Yus, Angew. Chem., Int. Ed., 2005, 44, 1602; (b) B. B. Toure and D. G. Hall, Chem. Rev., 2009, 109, 4439; (c) B. Ganem, Acc. Chem. Res., 2009, 42, 463; (d) A. Domling, W. Wang and K. Wang, Chem. Rev., 2012, 112, 3083; (e) G. Guillena, D. J. Ramon and M. Yus, Tetrahedron: Asymmetry, 2007, 18, 693; (f) C. de Graaff, E. Ruijter and R. V. A. Orru, Chem. Soc. Res., 2012, 41, 3969; (g) J. E. Biggs-Houck, A. Younai and J. T. Shaw, Curr. Opin. Chem. Biol., 2010, 14, 371; (h) N. R. Candeias, F. Montalbano, P. Cal and P. Gois, Chem. Rev., 2010, 110, 6169.
- 2 (a) Comprehensive Organic Synthesis, ed. B. M. Trost, Pergamon Press, Oxford, 1991; (b) A. H. Hoveyda, D. A. Evans and G. C. Fu, Chem. Rev., 1993, 93, 1307; (c) D. Banerjee, K. Junge and M. Beller, Angew. Chem., Int. Ed., 2014, 53, 13049; (d) W. Zi, Y.-M. Wang and D. F. Toste, J. Am. Chem. Soc., 2014, 136, 12864; (e) E. Vedajs and J. A. Mackay, Org. Lett., 2001, 3, 535; (f) M. I. Calaza, E. Hupe and P. Knochel, Org. Lett., 2003, 5, 1059.
- 3 For recent papers on nickel-catalyzed alkylative/reductive alkyne–aldehyde cross-coupling: (a) E. P. Jackson and J. Montgomery, J. Am. Chem. Soc., 2015, 137, 958; (b) M. T. Haynes, P. Liu, R. D. Baxter, A. J. Nett, K. N. Houk and J. Montgomery, J. Am. Chem. Soc., 2014, 136, 17495; (c) S. Z. Tasker, E. A. Standley and T. F. Jamison, Nature, 2014, 509, 299; (d) K. Tanaka and Y. Taiima, Eur. J. Org. Chem., 2012, 3715; (e) J. Montgomery, Acc. Chem. Res., 2000, 33, 467; (f) Y. Yang, S.-F. Zhu, C.-Y. Zhou and Q.-L. Zhou, J. Am. Chem. Soc., 2008, 130, 14052.
- 4 For recent papers on catalytic reductive coupling with other metals: (a) H. A. Reichard, M. Mclaughlin, M. Z. Chen and G. C. Micalizio, Eur. J. Org. Chem., 2010, 391; (b) J. F. Bower,

I. S. Kim, R. L. Patman and M. J. Krische, Angew. Chem., Int. Ed., 2009, 48, 34; (c) E. Skucas, M.-Y. Ngai, V. Komanduri and M. J. Krische, Acc. Chem. Res., 2007, 40, 1394; (d) A. B. Bahadoor, A. Flyer and G. C. Micalizio, J. Am. Chem. Soc., 2005, 127, 3694; (e) I. Ojima, M. Tzamarioudaki and C. Y. Tsai, J. Am. Chem. Soc., 1994, 116, 3643.

- 5 (a) E. Oblinger and J. Montgomery, J. Am. Chem. Soc., 1997, 119, 9065; (b) X. Qi and J. Montgomery, J. Org. Chem., 1999, 64, 9310; (c) M. Lozanov and J. Montgomery, J. Am. Chem. Soc., 2002, 124, 2106; (d) Y. Ni, K. K. Amarasinghe and J. Montgomery, Org. Lett., 2002, 4, 1743.
- 6 For recent papers on non-enantioselective nickelcatalyzed reductive/alkylative coupling: (a) X.-Q. Tang and J. Montgomery, J. Am. Chem. Soc., 1999, 121, 6098; (b) W.-S. Huang, J. Chan and T. F. Jamison, Org. Lett., 2000, 2, 4221; (c) K. Takai, S. Sakamoto and T. Isshiki, Org. Lett., 2003, 5, 653; (d) K. M. Miller, T. Luanphaisarnnont, C. Molinaro and T. F. Jamison, J. Am. Chem. Soc., 2004, 126, 4130; (e) K. M. Miller and T. F. Jamison, J. Am. Chem. Soc., 2004, 126, 15342.
- 7 For recent papers on asymmetric nickel-catalyzed reductive/alkylative coupling: (a) K. M. Miller, W.-S. Huang and T. F. Jamison, J. Am. Chem. Soc., 2003, 125, 3442; (b) K. M. Miller and T. F. Jamison, Org. Lett., 2005, 7, 3077; (c) Y. Sato, N. Saito and M. Mori, *J. Am. Chem. Soc.*, 2000, 122, 2371; (d) Y. Sato, N. Saito and M. Mori, J. Org. Chem., 2002, 67, 9310; (e) Y. Yang, S.-F. Zhu, H.-F. Duan, C.-Y. Zhou, L.-X. Wang and Q.-L. Zhou, J. Am. Chem. Soc., 2007, 129, 2248; (f) M. R. Chaulagain, G. J. Sormunen and J. Montgomery, J. Am. Chem. Soc., 2007, 129, 9568; (g) C. T. Check, K. P. Jang, C. B. Schwamb, A. S. Wong, M. H. Wang and K. A. Scheidt, Angew. Chem., Int. Ed., 2015, 54, 4264. **Organic Chemistry Frontiers**
 F. S. Kim, R. L. Parman and M. J. Krische, Angres: Chem.
 F. S. Residence, M. R. P. Sten, M. P. Sten, M. P. Sten, M. P. Sten, M. C. D. Sten, N. P. Newslett, θ . Newslett, θ . Newslet
	- 8 W. Fu, M. Nie, A. Wang and W. Tang, Angew. Chem., Int. Ed., 2015, 54, 2520.
	- 9 (a) W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, D. Krishnamurthy, N. K. Yee and

C. H. Senanayake, Angew. Chem., Int. Ed., 2010, 49, 5879; (b) W. Tang, S. Keshipeddy, Y. Zhang, X. Wei, J. Savoie, N. D. Patel, N. K. Yee and C. H. Senanayake, Org. Lett., 2011, 13, 1366; (c) S. Rodriguez, B. Qu, N. Haddad, D. C. Reeves, W. Tang, H. Lee, D. Krishnamurthy and C. H. Senanayake, Adv. Synth. Catal., 2011, 353, 533; (d) Q. Zhao, C. Li, C. H. Senanayake and W. Tang, Chem. – Eur. J., 2013, 19, 2261; (e) C. Li, G. Xiao, Q. Zhao, H. Liu, T. Wang and W. Tang, Org. Chem. Front., 2014, 1, 225.

- 10 (a) W. Tang, N. D. Patel, G. Xu, X. Xu, J. Savoie, S. Ma, M.-H. Hao, S. Keshipeddy, A. G. Capacci, X. Wei, Y. Zhang, J. J. Gao, W. Li, S. Rodriguez, B. Z. Lu, N. K. Yee and C. H. Senanayake, Org. Lett., 2012, 14, 2258; (b) K. Li, N. Hu, R. Luo, W. Yuan and W. Tang, J. Org. Chem., 2013, 78, 6350; (c) G. Xu, W. Fu, G. Liu, C. H. Senanayake and W. Tang, J. Am. Chem. Soc., 2014, 136, 570; (d) G. Xu, Q. Zhao and W. Tang, Chin. J. Org. Chem., 2014, 34, 1919; (e) C. Li, T. Chen, B. Li, G. Xiao and W. Tang, Angew. Chem., Int. Ed., 2015, 54, 3792; (f) K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang and W. Tang, Angew. Chem., Int. Ed., 2015, 54, 3033.
- 11 (a) G. M. Mahandru, G. Liu and J. Montgomery, J. Am. Chem. Soc., 2004, 126, 3698; (b) G. M. Mahandru, G. Liu and J. Montgomery, J. Am. Chem. Soc., 2004, 126, 15316; (c) H. A. Malik, G. J. Sormunen and J. Montgomery, J. Am. Chem. Soc., 2010, 132, 6304.
- 12 S. J. Patel and T. F. Jamison, Angew. Chem., Int. Ed., 2003, 42, 1364.
- 13 (a) P. Liu, J. Montgomery and K. N. Houk, J. Am. Chem. Soc., 2011, 133, 6956; (b) P. Liu, P. McCarren, P. H.- Y. Cheong, T. F. Jamison and K. N. Houk, J. Am. Chem. Soc., 2010, 132, 2050; (c) P. McCarren, P. Liu, P. H.-Y. Cheong, T. F. Jamison and K. N. Houk, J. Am. Chem. Soc., 2009, 131, 6654.
- 14 DFT calculations were performed with the Gaussian 03 package and the geometries were optimized with B3LYP and a mixed basis set of 6-31G(d) for all atoms.