RESEARCH ARTICLE

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

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

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 tetra-substituted 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 reactions[1] 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 alcohols[2] 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-

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 reported[8] 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-DIME[9] 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
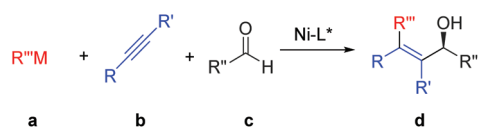

Fig. 1 Nickel-catalyzed alkylative alkyne–aldehyde cross-coupling.

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
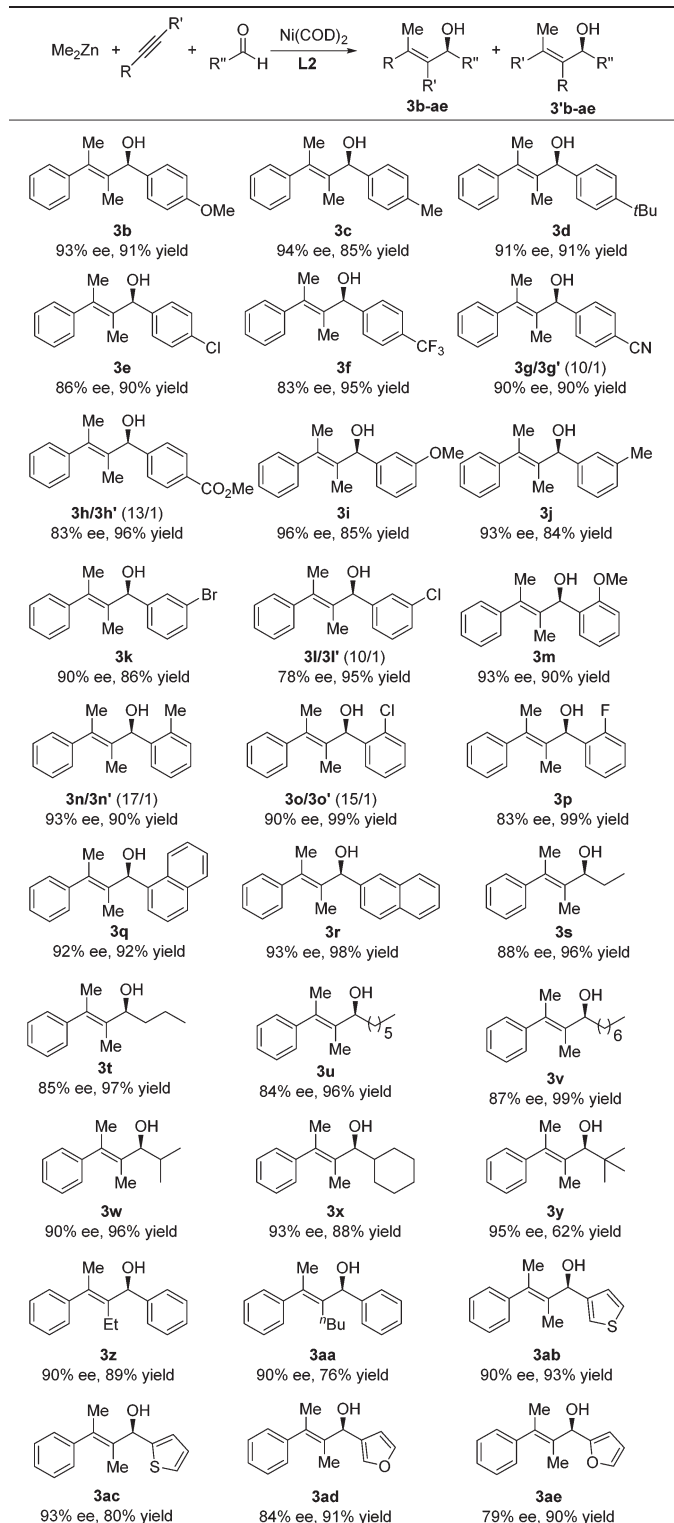
Table 1 Enantioselective nickel-catalyzed alkylative couplings of alkynes with aldehydes: optimization of conditions
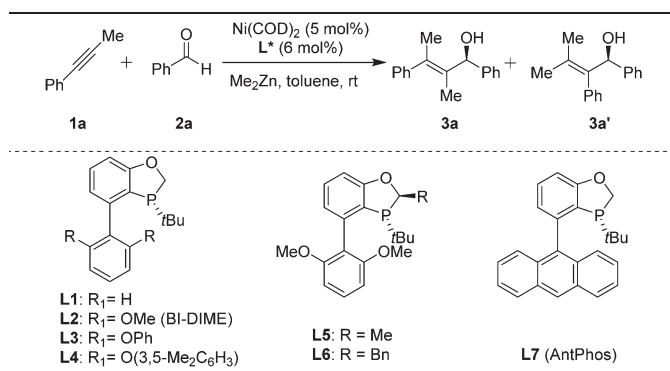
Entries[a]	Ligand	Solvent	Yield of 3a[b] (%)	ee[c] (%)
1	**L1**	Toluene	67	50
2	**L2**	Toluene	95	90
3	**L3**	Toluene	12	74
4	**L4**	Toluene	<5	nd
5	**L5**	Toluene	36	76
6	**L6**	Toluene	<5	nd
7	**L7**	Toluene	46	42
8	**L2**	Dioxane	78	79
9	**L2**	THF	25	70
10	**L2**	DCM	19	82
11	**L2**	DME	0	—

[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 mol%), ligand (6 mol%), and Me$_2$Zn (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.

Table 2 Substrate scope[a]

[a] Reaction conditions: alkynes (0.20 mmol), aldehydes (0.40 mmol), Ni(COD)$_2$ (5 mol%), **L2** (6 mol%), and Me$_2$Zn (0.60 mmol), toluene (0.10 M), rt under N$_2$, 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.

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

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 di-*ortho*-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 us[8] 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(II) structure would provide an even greater energy
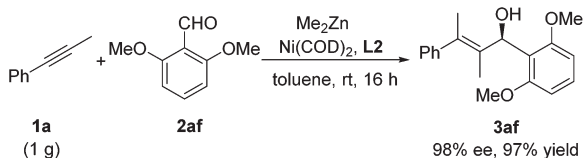
difference between two conformers. Higher enantioselectivities were therefore achieved when more hindered alkyl aldehydes or di-*ortho*-substituted aryl aldehydes were employed as the reagents.

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 three-component 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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Scheme 1 Gram-scale asymmetric alkylative alkyne–aldehyde cross-coupling.

1a (1 g) + 2af → 3af (98% ee, 97% yield)

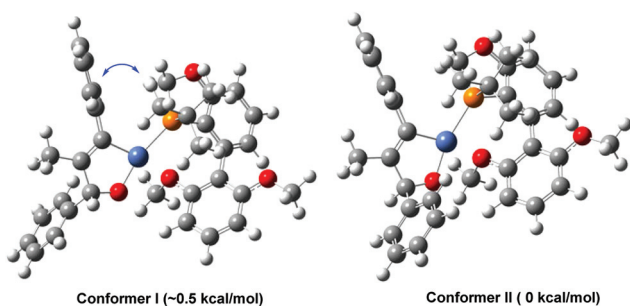Conformer I (~0.5 kcal/mol)   Conformer II (0 kcal/mol)

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

1324 | *Org. Chem. Front.*, 2015, **2**, 1322–1325

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Org. Chem. Front., 2015, **2**, 1322–1325 | **1325**