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Enantioselective Addition of Activated Terminal Alkynes to 1-Acylpyridinium Salts Catalyzed by Cu−Bis(oxazoline) Complexes

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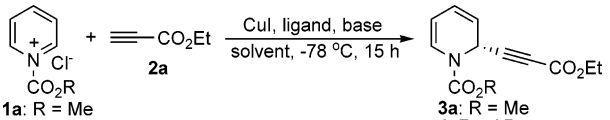
Piperidine units are frequently found in many natural products and designed bioactive molecules.[1] Their stereoselective synthesis remains a great challenge.[1−8] Among existing approaches for assembling these N-heterocycles,[1−8] asymmetric attack of nucleophiles onto activated pyridines is very attractive because it offers a direct access to dihydropyridines that can be converted into substituted piperidines by different transformations. Great progress has been achieved in this area due to seminal contributions from the laboratories of Comins,[3] Marazano,[4] Mangeney,[5] Charette,[6] Yamada,[7] and Shibasaki.[8] However, most studies are focused on using chiral pyridine substrates,[3−7] and only one example of a catalytic asymmetric reaction (addition of TMSCN to *N*-acylpyridinium) was reported.[8] Inspired by recent progress on the direct, enantioselective addition of 1-alkynes to imines[9] and CuI-catalyzed three-component coupling of pyridine, acid chlorides, and alkynes,[10] we decided to develop a catalytic asymmetric addition of terminal alkynes to 1-acylpyridinium salts.

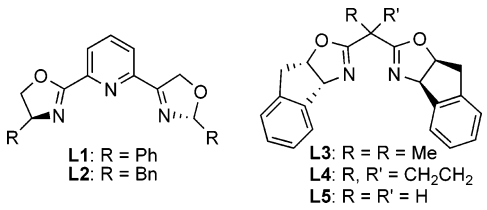
As summarized in Table 1, we selected the reaction of ethyl propiolate **2a** with 1-acylpyridinium salts **1** for model studies, mainly because their addition products are valuable intermediates for the elaboration of indolizidines. Initially, tridentate bis(oxazolinyl)pyridine **L1**, the best ligand in Li's direct addition of terminal alkynes,[9a] was tested. We were pleased to find that, under the induction of this ligand, CuI-catalyzed addition of **2a** to **1a** (generated in situ from pyridine and methyl chloroformate) afforded the desired addition product **3a** in 78% yield and 50% ee (entry 1). Benzyl-substituted ligand **L2** gave similar results (entry 2). The enantioselectivity increased to 74% when using bidentate bis(oxazoline) **L3** as a ligand. Further improvements were observed when the two less bulky bis(oxazoline) ligands **L4** and **L5** were used (entries 4 and 5). Switching the base from *i*-Pr_2NEt to *i*-Pr_2NPr-*n* provided the best enantioselectivity (entry 6), while *i*-Pr_2-NBu-*n* gave **3a** in only 65% ee (entry 7). The solvent has an influence on the asymmetric induction, as well, chloroform gave a slightly lower ee value, and the enantioselectivity dropped to 55% when the reaction was performed in MeCN (compare entries 5 with 8 and 9). In addition, it was found that the N-substituents in **1** influence the reaction dramatically, and *iso*-butyl-substituted **1b** showed similar reactivity as **1a** (entry 10), while benzyl substituted **1c** was inert under the current reaction conditions (entry 11). It is noteworthy that excess amounts of methyl chloroformate, base, and ethyl propiolate are required to obtain satisfying results. When equimolar amounts of these reagents were used, **3a** was isolated in poor yields (entry 12), presumably due to incomplete formation of **1**. Attempts to reduce the loading of the catalyst and ligand to 5 mol % also resulted in low yield and enantioselectivity (entry 13). Further optimization is needed to overcome these drawbacks.

Table 1. CuI-Catalyzed Addition of Ethyl Propiolate **2a** to 1-Acylpyridinium Salts **1** in the Presence of Different Ligands and Bases[a]



entry	R	ligand	base[b]	solvent	yield (%)[c]	ee (%)[d]
1	Me	**L1**	**B1**	CH_2Cl_2	78	50
2	Me	**L2**	**B1**	CH_2Cl_2	71	51
3	Me	**L3**	**B1**	CH_2Cl_2	67	74
4	Me	**L4**	**B1**	CH_2Cl_2	63	87
5	Me	**L5**	**B1**	CH_2Cl_2	75	88
6	Me	**L5**	**B2**	CH_2Cl_2	72	94
7	Me	**L5**	**B3**	CH_2Cl_2	74	65
8	Me	**L5**	**B1**	$CHCl_3$	77[e]	83
9	Me	**L5**	**B1**	MeCN	71	55
10	*i*-Bu	**L5**	**B1**	CH_2Cl_2	72	86
11	Bn	**L5**	**B1**	CH_2Cl_2	*f*	
12	Me	**L5**	**B2**	CH_2Cl_2	15[g]	
13	Me	**L5**	**B2**	CH_2Cl_2	47[h]	69

[a] Reaction conditions: CuI (0.05 mmol), ligand (0.05 mmol), pyridine (0.5 mmol), $ClCO_2R$ (2.5 mmol), **2a** (2.5 mmol), base (2.5 mmol), solvent (1 mL). [b] **B1**: *i*-Pr_2NEt, **B2**: *i*-Pr_2NPr-*n*, **B3**: *i*-Pr_2NBu-*n*. [c] Isolated yields. [d] Determined by HPLC on chiral stationary phase. [e] Reaction was carried out at −60 °C. [f] No addition product was determined. [g] 0.5 mmol of **2a**, $ClCO_2Me$, and base were used. [h] 5 mol % CuI and ligand were used.



The optimized reaction conditions were then examined by varying the 1-alkynes, and the results are summarized in Table 2. Methyl propiolate led to almost identical yield and selectivity as ethyl propiolate (entry 1). However, when benzyl propiolate was employed, only 86% ee was observed (entry 2), indicating that increasing the size of the propiolate remarkably decreases the enantioselectivity. This trend was also seen when ynones were applied under these reaction conditions. The highest ee value was recorded using 1-pentyn-3-one (entry 4). With increasing chain length of the ynones, the enantioselectivity gradually dropped (compare entries 4−7). Benzoxy-substituted ynone also worked well, affording dihydropyridine **3h** in 73% yield and 77% ee (entry 7). Its additional functional group allows further conversion to more complex molecules. It is noteworthy that in these cases no 1,4-addition products of 1-acylpyridinium salt **1a** were detected.

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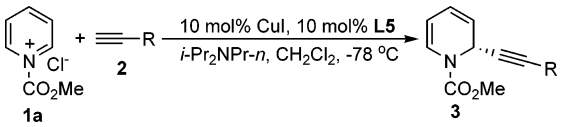
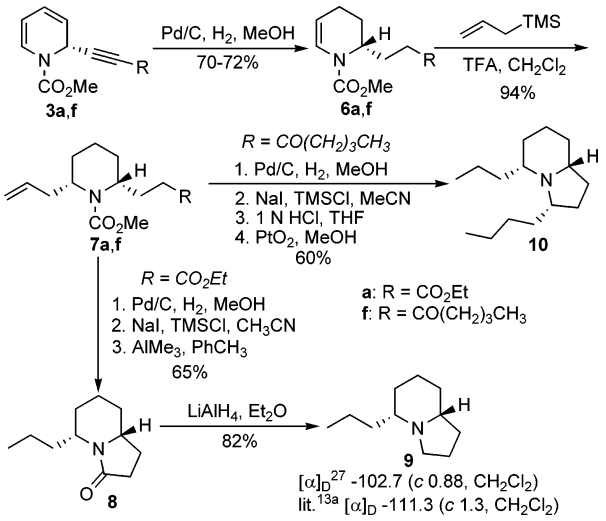
Table 2. CuI/**L5**-Catalyzed Addition of 1-Alkynes **2** to 1-Acylpyridinium Salt **1a**[a]



entry	R	product	time (h)	yield (%)[b]	ee (%)[c]
1	CO_2CH_3	**3b**	15	74	95
2	CO_2Bn	**3c**	15	81	86
3	$COCH_3$	**3d**	15	69	93
4	$COCH_2CH_3$	**3e**	15	65	99
5	$CO(CH_2)_3CH_3$	**3f**	15	70	91
6	$CO(CH_2)_4CH_3$	**3g**	15	68	90
7	$CO(CH_2)_3OBn$	**3h**	15	70	77
8	Ph	**3i**	12	75	1
9	$(CH_2)_3CH_3$	**3j**	17	63	11
10	CH_2OAc	**3k**	15	77	3

[a] Reaction conditions: CuI (0.05 mmol), **L5** (0.05 mmol), **2** (2.5 mmol), pyridine (0.5 mmol), $ClCO_2Me$ (2.5 mmol), *i*-Pr_2NPr-*n* (2.5 mmol), CH_2Cl_2 (1 mL). [b] Isolated yields. [c] Determined by HPLC on chiral stationary phase.

Scheme 1. Synthesis of Indolizidines 167B and 223AB



We then explored the possibility of using inactivated 1-alkynes. To our surprise, the reaction with these 1-alkynes proceeded smoothly providing the corresponding dihydropyridines **3i**−**3k**. However, only little asymmetric induction was observed. These results demonstrate that the carbonyl group adjacent to the alkyne moiety is essential for the enantioselectivity of the addition. Possibly the electron-withdrawing property of the carbonyl group enhances the conformational stability of the transition state or results in π-stacking with another group in the substrate or the Cu complex leading to a high degree of asymmetric induction.

The present addition products are obviously useful building blocks for the elaboration of a wide range of polysubstituted piperidines and indolizidines.[11] As an example, partial hydrogenation of dihydropyridines **3a** and **3f** was achieved (Pd/C, H_2, MeOH) to afford tetrahydropyridines **6** (Scheme 1). Treatment of **6** with allyl trimethylsilane in the presence of TFA[12] produced **7a** and **7f** as the only stereoisomer, respectively. Hydrogenation of **7a** followed by deprotection with TMSI and $AlMe_3$-mediated cyclization afforded lactam **8**, which was reduced with LAH to furnish indolizidine 167B **9**.[13] The value of the optical rotation of synthetic **9** ($[\alpha]_D^{27}$ −102.7 (*c* 0.88, CH_2Cl_2)) was in close proximity to that reported for (5*R*,9*R*)-indolizidine 167B ($[\alpha]_D$ −111.3 (*c* 1.3, CH_2Cl_2)).[13a] Thus, we established that the absolute configuration of our addition products is *R*. In the same manner, indolizidine 223AB **10**[14] was elaborated from **7f** in 60% overall yield in four simple steps. To date, our method represents the shortest synthesis of these two alkaloids.

In conclusion, we have developed the first catalytic asymmetric addition of 1-alkynes to 1-acylpyridinium salts. It was found that the carbonyl group in the 3 position of the 1-alkynes is important for the enantioselectivity of the reaction. These findings may shed light on other additions using 1-alkynes as substrates. The reaction provides highly functionalized dihydropyridines with excellent enantioselectivity, which are valuable building blocks for assembling complex N-heterocycles. Further exploration of the scope and limits of the synthetic application is in progress.

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Supporting Information Available: Experimental and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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