Asymmetric Catalysis

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The Long-Arm Effect: Influence of Axially Chiral Phosphoramidite Ligands on the Diastereo- and Enantioselectivity of the Tandem 1,4-Addition/Fluorination**

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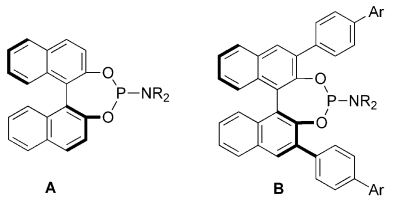
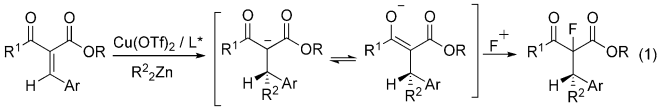
Dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday

Chiral monodentate phosphoramidites provide an important class of ligands, and enjoy high prestige in the field of asymmetric catalysis.[1] In this context, binol-derived phosphoramidites have emerged as a highly versatile and readily accessible subset of chiral ligands. Most of these ligands with subtle structural variations at the amine moiety have been proven to be highly effective in a wide range of asymmetric reactions.[2] In sharp contrast to the great success of the simple phosphoramidites **A**, limited progress has been made to attach the bulky groups directly at the 3,3′-positions of the binaphthol backbone.[3] In our efforts to develop superior catalysts for new and challenging asymmetric reactions, we considered a long-arm approach, and envisioned that introduction of the bulky substituents at the 3- and 3′-position of the binaphthol unit could positively influence the stereoselectivity of asymmetric transformations by narrowing the space around the P-ligated metal center as well as relaying the axial chirality to the reaction site. This strategy led to the discovery of the new catalysts **B**, which gives access to enantiomeric fluorinated products of a catalyzed tandem sequence.



Conjugate addition of organometallic reagents to alkylidene β-ketoesters results in the formation of a carbon–carbon bond with concurrent generation of two contiguous stereogenic centers.[4] However, the stereocenter flanked by both carbonyl groups may suffer potential loss of its stereochemical integrity as a result of rapid epimerization. Consequently, little progress has been made in the use of alkylidene β-ketoesters as Michael acceptors. Only recently, two impressive studies by Hird and Hoveyda,[5a] and Shizuka and Snapper[5b] have led to the development of catalytic enantioselective additions of dialkylzinc and allylsilane reagents to cyclic alkylidene β-ketoesters as mixtures of ketone/enol tautomers, but it was not known whether these strategies were applicable to acyclic alkylidene β-ketoesters. Herein, we developed a novel catalytic asymmetric tandem 1,4-addition/fluorination process by using fluorinating reagents as the terminal electrophile. This approach not only helps solve the longstanding problem of epimerization of the adduct, but also introduces a fluorine-containing chiral center [Eq. (1)].



Owing to the unique properties of fluorinated compounds, stereoselective construction of organofluorine molecules under mild reaction conditions has been highly desirable in organic and medicinal chemistry.[6] We demonstrate that, in the presence of the new chiral ligands **B**, the present tandem transformation provides a facile route to chiral fluorinated products with adjacent carbon- and fluorine-substituted tertiary and quaternary stereocenters, respectively, in high yield (up to 91%) and excellent diastereo- and enantioselectivity (up to 99:1 d.r., 98% *ee*).[7]

In a first series of experiments, six known binol-derived monodentate phosphoramidite ligands **1a–f** (Figure 1) were screened in the copper-catalyzed tandem reaction of the acyclic alkylidene β-ketoester **2a** with *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorinating reagent in dichloromethane at 0°C. The results are listed in Table 1. It was found that all such ligands gave uniformly high diastereoselectivity (entries 1–6). A moderate yield with modest enantioselectivity could be obtained in the presence of ligand **1b** (entry 2). An ethyl group in the amino moiety was found to be optimal among other the alkyl groups (entries 1 and 3–

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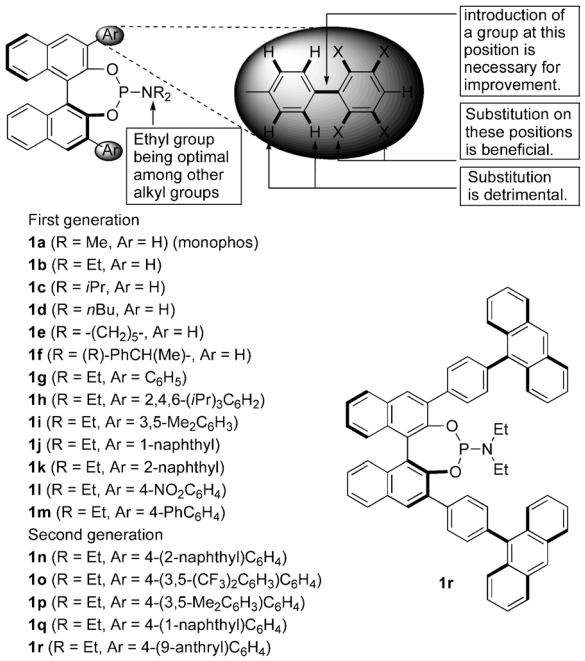
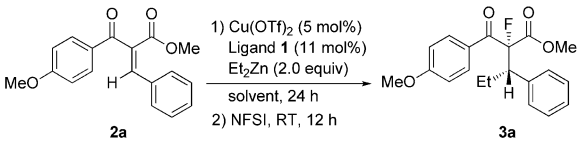


Figure 1. Design of ligands used for screening.

6). After a systematic study of various substituents (Figure 1; entries 7–13), we were pleased to find that ligand **1m**, which incorporates a 4-biphenyl substituent at the 3- and 3′-positions of the binaphthyl backbone, affords the tandem product **3a** in 60% yield with good enantioselecitivity (76% *ee*). Further optimization of the enantioselectivity was achieved with ligand **1m** by screening different solvents and lowering the reaction temperature (entries 14–22). Thus, the tandem reaction of the alkylidene β-ketoester **2a** could be efficiently performed in toluene at −40°C providing the fluorinated product **3a** in 81% yield with a 98:2 d.r. and 84% *ee*. These results clearly validate the strategy and suggested that additional improvement on the enantioselectivity might be feasible by fine-tuning the substituents at the 3- and 3′-positions of the binaphthyl bakcbone. The initial success with the 4-biphenyl-substituted ligand **1m** prompted us to design and synthesize a second generation of the phosphoramidite ligands containing substituted biphenyl groups. Gratifyingly, examination on the second generation ligands in the same test reaction revealed that the enantioselectivity can be significantly improved from 84% *ee* (**1m**; entries 21 and 22) to 90% *ee* (**1q**) and 94% *ee* (**1r**; entries 26–27). The evolution of the ligand **1r** seems to have followed a well-defined modular modification on the biphenyl skeleton as summarized in Figure 1. No less remarkable is the diastereoselectivity of the process, which amounts to greater than 99:1 d.r. for the catalyst **1r**. These results highlight the power of combining rational design and systematic screening in catalyst development.

With an effective chiral catalyst in hand, we next investigated the scope of the catalytic tandem reaction by employing a range of acyclic alkylidene β-ketoesters and dialkylzinc reagents, and the results are summarized in Table 2. The substrate scope appeared to be exceedingly broad, with aryl

Table 1: Screening of ligands and condition optimization for the tandem reaction.

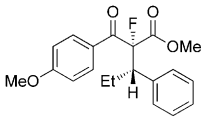
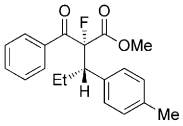
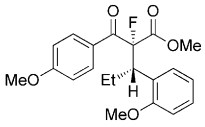
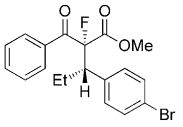
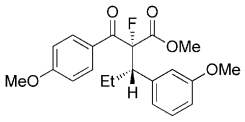
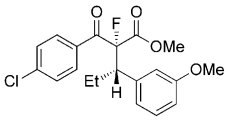
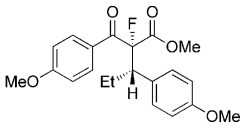
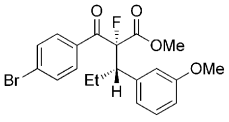
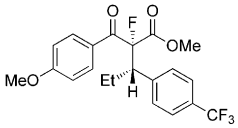
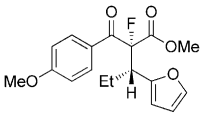
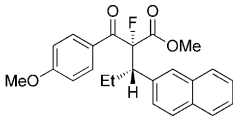
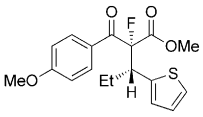
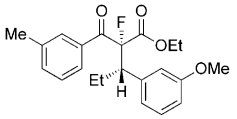
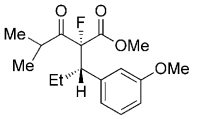
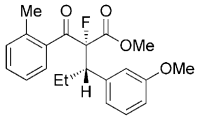
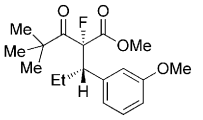
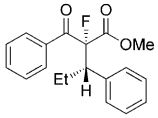
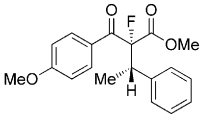
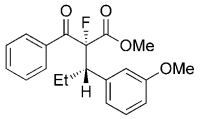
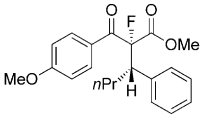
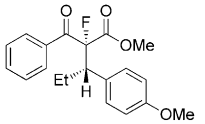
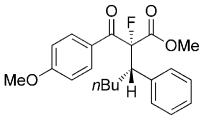


Entry	Ligand	Solvent	*T* [°C]	Yield [%][a]	d.r.[b]	*ee* [%][c]
With first generation ligands:						
1	**1a**	CH_2Cl_2	0	50	93:7	30
2	**1b**	CH_2Cl_2	0	42	96:4	45
3	**1c**	CH_2Cl_2	0	37	96:4	20
4	**1d**	CH_2Cl_2	0	39	96:4	22
5	**1e**	CH_2Cl_2	0	40	96:4	29
6	**1f**	CH_2Cl_2	0	35	92:8	31
7	**1g**	CH_2Cl_2	0	58	95:5	70
8	**1h**	CH_2Cl_2	0	22	95:5	5
9	**1i**	CH_2Cl_2	0	30	95:5	55
10	**1j**	CH_2Cl_2	0	44	97:3	57
11	**1k**	CH_2Cl_2	0	40	97:3	74
12	**1l**	CH_2Cl_2	0	15	98:2	76
13	**1m**	CH_2Cl_2	0	60	98:2	76
14	**1m**	Et_2O	0	42	93:7	67
15	**1m**	THF	0	55	92:8	74
16	**1m**	benzene	0	52	95:5	75
17	**1m**	xylene	0	60	97:3	74
18	**1m**	toluene	0	68	98:2	76
19[d]	**1m**	toluene	0	60	97:3	76
20	**1m**	toluene	−20	65	98:2	79
21[e]	**1m**	toluene	−40	81	98:2	84
22[e]	**1m**	toluene	−50	63	97:3	84
With second generation ligands:						
23[e]	**1n**	toluene	−40	70	99:1	78
24[e]	**1o**	toluene	−40	69	98:2	82
25[e]	**1p**	toluene	−40	84	99:1	84
26[e]	**1q**	toluene	−40	72	98:2	90
27[e]	**1r**	toluene	−40	81	99:1	94

[a] Yield of isolated product. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase and is given only for the major diastereoisomer. [d] 2 mol% $Cu(OTf)_2$ was used. [e] Reaction time was 48 h.

substituents on both the ketone and the alkylidene moieties spanning a diverse range of sterically and electronically different groups. The tandem reactions all proceeded uneventfully to give the fluorinated products **3a**–**o** in good yields (78–91%) and high enantioselectivities (86–98% *ee*) with nearly perfect diastereoselectivities (entries 1–15). Alkylidene β-ketoesters bearing heteroaromatic rings also furnished the corresponding fluorinated products (entries 16 and 17). It is worth noting that alkyl-substituted substrates also provided the tandem products **3r** and **3s** in good yields and enantioselectivities with high diastereoselectivities (entries 18 and 19). The effect of other dialkylzinc reagents (Me_2Zn, nPr_2Zn, nBu_2Zn) was next probed (entries 20–22). The *ee* values obtained with the Me, Et, *n*Pr, and *n*Bu zinc reagents follow a rather interesting trend in their reaction with the same substrate and seem to correlate well the size of the alkyl groups, that is, 85% *ee* (Me), 94% *ee* (Et), 97% *ee* (*n*Pr), and 96% *ee* (*n*Bu). A possible rationalization could be

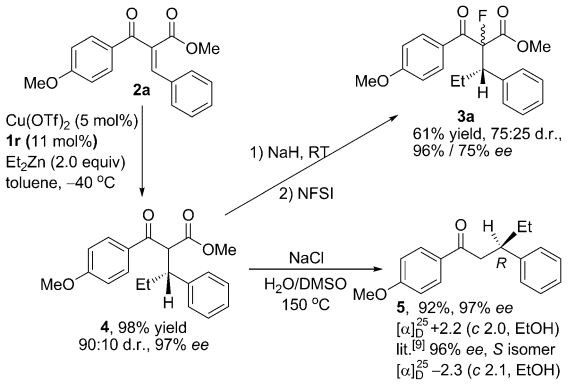
Table 2: The scope of the copper-catalyzed asymmetric tandem reaction of the alkylidene β-ketoesters **2**.

Entry	Product		Yield [%][a]	d.r.[b]	*ee* [%][c]	Entry	Product		Yield [%][a]	d.r.[b]	*ee* [%][c]
1		**3a**	81	>99:1	94	12		**3l**	89	>99:1	95
2		**3b**	84	>99:1	92	13		**3m**	80	>99:1	88
3		**3c**	91	99:1	96	14		**3n**	84	97:3	95
4		**3d**	82	>99:1	92	15		**3o**	80	>99:1	93
5		**3e**	87	>99:1	87	16		**3p**	72	95:5	82
6		**3f**	78	>99:1	98	17		**3q**	86	>99:1	84
7		**3g**	79	>99:1	94	18		**3r**	77	96:4	84
8		**3h**	82	>99:1	97	19		**3s**	76	>99:1	86
9		**3i**	81	>99:1	90	20		**3t**	90	>99:1	85
10		**3j**	89	>99:1	94	21		**3u**	81	>99:1	97
11		**3k**	91	>99:1	86	22		**3v**	79	>99:1	96

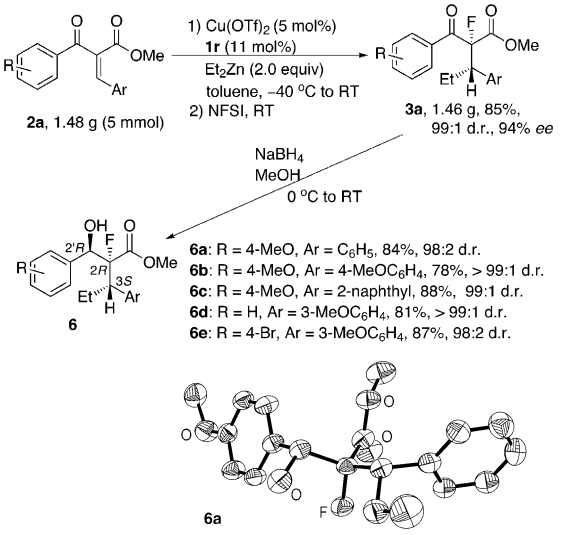
[a] Yield of isolated product. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase and the absolute configuration of other adducts were assigned on the basis of analogy with study of **3a** (Scheme 2).

the tendency for the larger nucleophiles to react more stereoselectively with the enone substrate.

Notably, when the addition intermediate **4**, isolated by flash filtration through a thin layer of silica gel in almost quantitative yield with 90:10 d.r. and 97% *ee*, was employed as a substrate under the current tandem reaction conditions or in the presence of diethyl zinc, no reaction was observed. Subjection of the intermediate **4** to sodium hydride and *N*-fluorobenzenesulfonimide afforded the fluorinated product **3a** in 61% yield with moderate diastereoselectivity (75:25 d.r.; Scheme 1). These results show that the one-pot tandem trap is crucial for the transformation stereoselectivity.[8] In addition, decarboxylation of the addition intermediate **4** gave the acyclic ketones **5** in high yield and without detectable loss of enantioselectivity. The absolute configuration of the ketone was determined by preparing known compound **5**.[9]



Scheme 1. Stepwise synthesis of fluorinated product **3a** (96% and 75% *ee* are for the major and minor diastereoisomer, respectively) and decarboxylation of the addition intermediate **4**.



Scheme 2. Scaled-up tandem reaction and transformation of the fluorinated product.For the X-ray crystal structure the thermal ellipsoids are shown at 50% probability.

As expected, almost the same result was obtained when the model tandem reaction was scaled up to the gram scale (Scheme 2). More significantly, the presence of the β-ketoester moiety within the fluorinated products allows access to optically enriched alcohols with three contiguous stereogenic centers. For example, a reduction process using $NaBH_4$ gives rise to the corresponding α-fluoro-β-hydroxyesters **6** in good yield and excellent diastereoselectivity without racemization. Furthermore, the single stereoisomer of **6a** proved to be crystalline, thus allowing the determination of the absolute configuration of three adjacent stereogenic centers by means of X-ray crystallographic analysis.[10] In combination with the above-mentioned transformation (Scheme 1), the absolute configuration of the major stereoisomer **6a** was determined to be 2*R*,3*S*,2′*R*. Thus, the absolute configuration of the tandem fluorinated product **3a** is assigned as 2*R*,3*S*.

In summary, we have developed a promising new generation of chiral monodentate phosphoramidite ligands for the copper-catalyzed tandem 1,4-addition/fluorination sequence. The tandem transformation can be performed effectively with a range of acyclic alkylidene β-ketoesters and various dialkylzinc reagents to afford the tandem fluorinated products with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters. In particular, this new class of modular phosphorus compounds enlarges the structural diversity of the binol-derived monodentate phosphoramidite ligands. Additional uses of these ligands in other unexplored asymmetric transformations are ongoing in our laboratories and will be reported in due course.

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Keywords: asymmetric catalysis · enantioselectivity · fluorine · ligand design · tandem reactions

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