Asymmetric Catalysis

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Michael Addition Catalyzed by Chiral Secondary Amine Phosphoramide Using Fluorinated Silyl Enol Ethers: Formation of Quaternary Carbon Stereocenters**

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Abstract: *A chiral secondary amine phosphoramide was developed and identified as a powerful catalyst for the Mukaiyama–Michael addition of fluorinated enol silyl ethers to tetrasubstituted olefins. The resulting products are obtained with high enantioselectivities and contain a quaternary carbon stereocenter bearing either a difluoroalkyl or monofluoroalkyl group.*

Chiral secondary amines play an important role in modern asymmetric organocatalysis.[1] In particular, they have been well established as powerful catalysts in the functionalization of aldehydes and ketones by either enamine catalysis,[1b] iminium catalysis,[1c] or SOMO catalysis.[1d] To explore their potential in activating other types of substrates, several groups have nicely demonstrated that chiral secondary amines could serve as Brønsted bases in deprotonative activation of pronucleophiles (HNu) for asymmetric reactions.[2] However, the activation of trimethylsilyl (TMS)-derived preformed nucleophiles by chiral secondary amines is undeveloped thus far,[3] to the best of our knowledge. In contrast, TMS-derived preformed nucleophiles are useful reagents for reaction design when the corresponding weak HNu are difficult to handle or to activate under catalytic conditions.[4]

Nucleophilic tertiary amine catalysis[5] has found utility in desilylative nucleophile activation. Deng and co-workers, and Denmark and Chung reported the use of cinchona alkaloids to activate TMSCN for cyanosilylation of carbonyl compounds.[6a,b] The groups of Enders, our own, and others utilized chiral bifunctional tertiary amines for the catalysis of the Strecker reaction using TMSCN.[7] Deng and co-workers as well as ourselves have utilized this catalysis pattern to activate enol silyl ethers for the synthesis of chiral alcohols.[8] Based on these results, we reason that chiral secondary amine catalysis should also be viable for desilylative activation directed synthesis, as their generally lower nucleophilicity might be counterbalanced by the reduced steric requirement. The replacement of an alkyl group by a hydrogen atom should facilitate $n \rightarrow \sigma^*$ interactions[5a] between the amine and silicon in terms of avoiding the steric congestion. The resulting hypervalent silicate intermediate may be substantially different from that derived from a tertiary amine in terms of stereochemical constraints and electronic properties. By taking advantage of this difference, it is also possible to develop secondary amine based chiral catalysts to achieve high reactivity and enantioselectivity (for a detailed discussion, see the Supporting Information).

With this hypothesis, we embarked on probing the potential of chiral secondary amines in desilylative nucleophile activation as part of our program in using TMS reagents to construct fully substituted carbon atoms.[7b–d,8b–d,9] Considering inclusion of a hydrogen-bond donor is a fruitful strategy for designing new organocatalysts,[10] and given our interest in bifunctional phosphoramide catalysis,[11] we first tried to develop chiral secondary amine phosphoramide catalysts. The use of a phosphoramide was expected to bring about some beneficial effects: 1) The amide N–H bond may activate the electrophile through hydrogen-bonding interactions, and organize a favorable transition state.[11b] Alternatively, it may act as a Lewis base to enable the bidentate chelation of catalyst to silicon,[12] which is helpful for enantiofacial control, judged by the independent work from the groups of Denmark[12] and Feng.[13] 2) The two amide groups can function as shielding groups from two directions, to enhance face discrimination.[11] Herein we report a novel secondary amine phosphoramide (**C1**), which can be obtained in two steps, thus enabling a highly enantioselective Mukaiyama–Michael (MM) addition[14] using fluorinated enol silyl ethers to tetrasubstituted olefins (Scheme 1).

Fluorinated silyl enol ethers are easily available synthons for constructing chiral centers with an α-fluorinated ketone moiety which has received much attention.[15] The necessity of using them for developing catalytic asymmetric reactions is justified by the finding that deprotonative activation of the corresponding α-fluorinated ketones are unexpectedly difficult.[8bc] While they have found utility in catalytic asymmetric allylic substitution,[16] Mannich,[17] and aldol reactions,[8b–d] none of them led to enantioselective creation of quaternary carbon atoms, a formidable task in organic chemistry.[18] To meet this challenge, along with our efforts in asymmetric

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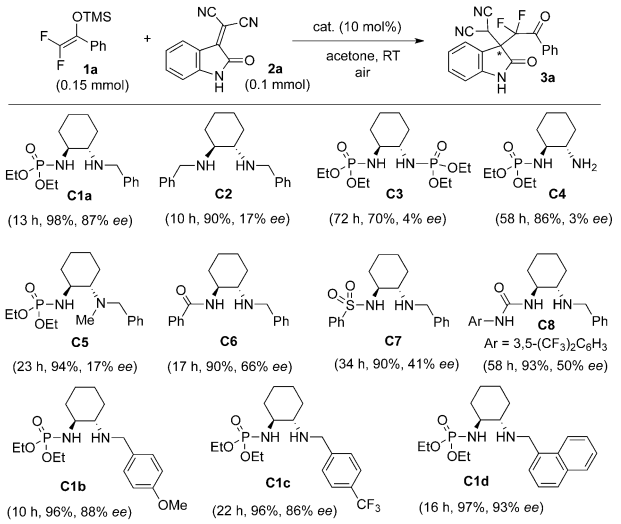


Scheme 1. Catalyst evaluation.

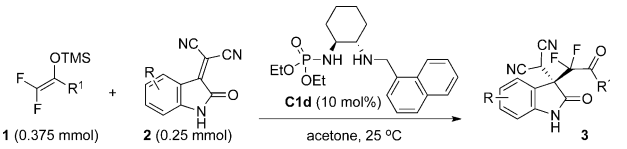
synthesis of quaternary oxindoles,[19] we tried the catalyst **C1** in the MM addition of the difluoroenoxysilane **1a** to the isatylidene malononitrile **2a**,[20a–c] the asymmetric version of which is undeveloped (Scheme 1).[9a] Noticeably, although asymmetric catalytic fluorination or fluoroalkylation is of current interest,[21] efficient syntheses of quaternary chiral carbon atoms with a mono- or difluoroalkyl group are still very limited. Remarkably, the catalyst **C1a** enabled the reaction of **1a** and **2a** to finish within 13 hours when using acetone as the solvent at room temperature, thus giving **3a** in 98% yield and 87% *ee*. It seemed that the secondary amine moiety of **C1a** played a major role in activating **1a**, as the reaction in the presence of the bis(secondary amine) **C2** finished within 10 hours to provide **3a** in 90% yield and 17% *ee*, and that mediated by the bis(phosphoramide) **C3** gave **3a** in only 70% yield and 4% *ee*, even after 72 hours. Moreover, the analogues **C4** and **C5**, bearing a primary amine and tertiary amine moiety, respectively, all proved to be inefficient in terms of both reactivity and enantioselectivity. In contrast, the phosphoramide of **C1a** was an indispensible component, as the secondary-amine-based amide, sulfonamide, and urea **C6**–**C8** all afforded insufficient catalytic activity and selectivity. These results showed that the secondary amine might be more efficient in desilylative nucleophile activation than the corresponding tertiary amine in some cases, and the phosphoramide, a catalyst motif which has received limited attention,[22] had interesting properties worth exploring.

The substituent of the secondary amine moiety of catalyst **C1** obviously influenced the catalytic activity and enantioselectivity (Scheme 1). The replacement of the benzyl group of **C1a** with an electron-rich *p*-methoxybenzyl group resulted in a more active catalyst (**C1b**), thus allowing the reaction to finish within 10 hours to give **3a** in 96% yield and 88% *ee*. In contrast, the corresponding analogue **C1c**, bearing a relatively electron-deficient *p*-trifluoromethylbenzyl group, turned out to be much less reactive, and it took 22 hours for the reaction to go to completion. This observation further supported our hypothesis that the secondary amine moiety acted as a Lewis base to activate the fluorinated enol silyl ether **1a**. Further screenings revealed that the catalyst **C1d** could achieve up to 93% *ee* for adduct **3a**.

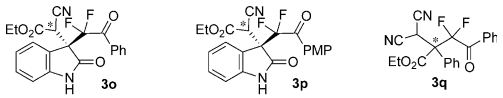
An advantage to be noted is the mild reaction conditions, such as running the reaction at room temperature and open to air. In addition, commercial acetone (water content < 0.3%, *w*/*w*) was used as received, without any treatment, as the presence of less than 3.6 mg of H_2O per 1.0 mL of acetone could accelerate the reaction without erosion of the *ee* value (for the influence of water additive and solvent effects, see Tables S2 and S3 of the Supporting Information). Such reaction conditions were highly desirable but unusual in asymmetric catalysis.

The substrate scope was then studied by using **C1d**, as shown in Table 1. The catalyst loading could be lowered to 1.0 mol%, and the reaction could still go to completion within 2 days, thus giving **3a** in 91% *ee* (entry 2). Whatever the

Table 1: Scope of reaction of **1** and **2**.



	1	2	*t* [h]	3	Yield [%][a]	*ee* [%][b]
1	**1a**: R^1 = Ph	**2a**: R = H	16	**3a**	99	94
2[c]	**1a**: R^1 = Ph	**2a**: R = H	33	**3a**	99	91
3	**1a**: R^1 = Ph	**2b**: R = 5-Me	35	**3b**	99	94
4	**1a**: R^1 = Ph	**2c**: R = 5-MeO	17	**3c**	93	94
5	**1a**: R^1 = Ph	**2d**: R = 5-F	2	**3d**	87	92
6	**1a**: R^1 = Ph	**2e**: R = 5-Cl	18	**3e**	90	90
7	**1a**: R^1 = Ph	**2f**: R = 5-Br	17	**3f**	83	93
8	**1a**: R^1 = Ph	**2g**: R = 6-MeO	19	**3g**	83	93
9	**1a**: R^1 = Ph	**2h**: R = 6-Br	18	**3h**	94	94
10	**1a**: R^1 = Ph	**2i**: R = 7-Cl	36	**3i**	86	95
11	**1a**: R^1 = Ph	**2j**: R = 5,7-Me_2	10	**3j**	96	97
12	**1b**: R^1 = *p*-ClC_6H_4	**2a**: R = H	8	**3k**	99	90
13	**1c**: R^1 = *p*-MeC_6H_4	**2a**: R = H	12	**3l**	95	93
14	**1d**: R^1 = *p*-$MeOC_6H_4$	**2a**: R = H	25	**3m**	99	92
15	**1e**: R^1 = $BnCH_2$	**2a**: R = H	40	**3n**	94	83



95%, 3:1 d.r.
90% *ee*/94% *ee* [d]

1.02 g [e], 99%, 3:1 d.r.
96% *ee*/95% *ee* [d]

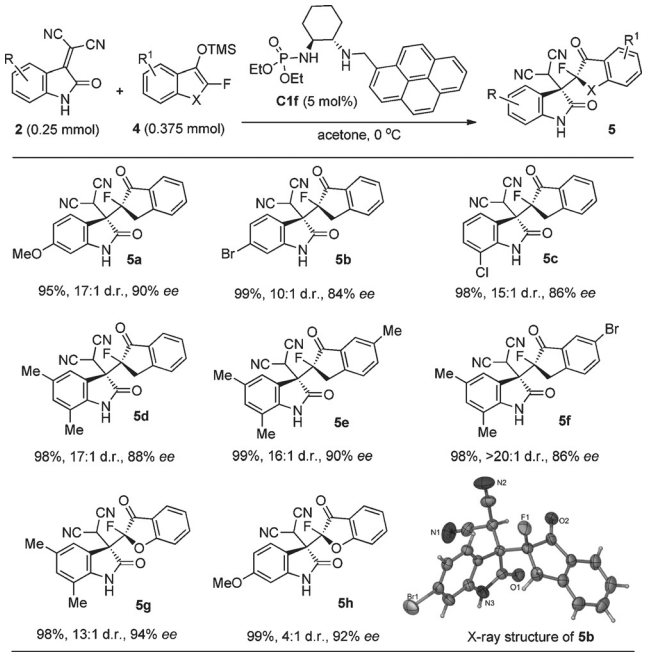
40%, 79% *ee* [f]

[a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Run on 2.0 mmol, using 1.0 mol% **C1d**. [d] At 0°C. [e] Run on 2.5 mmol. [f] Using 30 mol% **C1e** and 3.0 equiv **1a** in PhCl. PMP = *p*-$MeOC_6H_4$.

nature of the substituent on the 5-, 6-, or 7-position of the oxindole framework of **2**, the desired products **3a**–**j** were all obtained in high to excellent yields and with greater than 90% *ee* (up to 97%). In addition, both aryl and aliphatic difluoroenoxysilanes **1b**–**e** worked well to give the products **3k**–**n** in high to excellent *ee* value. Indolylidenecyanoacetate[20d] was workable as well, thus giving **3o**,**p** in excellent yields and *ee* values, when reactions were run on 0°C. We also ran a gram-scale synthesis of **3p** (1.02 g, 99% yield and 96%

ee) to show the practicability of our protocol. Despite moderate d.r. values, the ester group could be removed for product elaboration. We also tried an electron-deficient olefin prepared from α-ketoester and malononitrile, but its reactivity was too low to obtain a good result. For example, the product **3q** was obtained in only 40% yield with 79% *ee* even using 30 mol% of catalyst **C1e** (Ar = 9-anthryl).

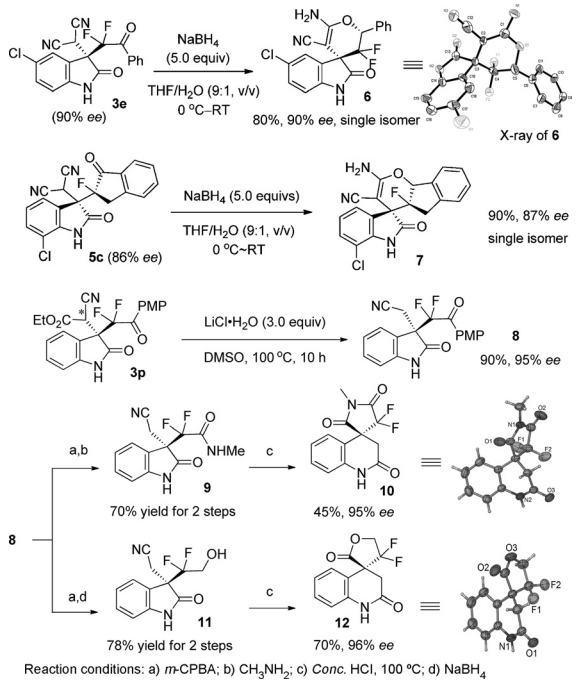
To our delight, the chiral secondary amine phosphoramide **C1** was also potent for the activation of monofluorinated enol silyl ethers (**4**) derived from either an α-fluoroindanone or benzofuranone for the reaction with the isatylidene malononitrile **2** to generate adjacent and fully substituted carbon stereocenters (Scheme 2). Nevertheless, **C1f**, bearing a 1-pyrenylmethyl group on the secondary amine moiety, afforded the best result in this case. The high reactivity of **4** allowed the reaction to run at 0°C to improve stereoselectivity, with 5 mol% **C1f**. Under these reaction conditions, the monofluorinated oxindole derivatives **5** were obtained in excellent yield with high to excellent d.r. and *ee* values, except for **5h** (92% *ee* with moderate 4:1 d.r.). The relative and absolute configuration of **5b** was assigned by X-ray analysis. All the other products **5** were tentatively assigned.



Scheme 2. Scope of the Michael addition of **2** and **4**.[27]

The excellent enantioselectivity achieved by the readily available secondary amine phosphoramide **C1** was very impressive. To the best of our knowledge, this was the first highly enantioselective organocatalytic asymmetric MM reaction to generate all-carbon quaternary carbon stereocenters. It is worth mentioning that previously, only Yamamoto et al. reported a chiral aluminum-catalyzed MM reaction of tetrasubstituted enol silyl ethers to furnish quaternary carbon atoms with excellent *ee* values,[14f] and the use of β,β-disubstituted acceptors for this purpose is unknown.[14] In addition, methods to access quaternary oxindoles bearing a C3 fluoroalkyl group are limited[23] despite the progress in the past few years in catalytic asymmetric synthesis of 3,3-disubstituted oxindole,[24] a type of privileged scaffold in natural products and drugs. As the selective incorporation of a fluoroalkyl group into organic molecules often brings about beneficial effects,[21] these fluorinated oxindoles may be interesting targets for medicinal researches.

Intriguingly, these products could be elaborated into a variety of fluorinated spirocyclic compounds which are highly desirable in chemistry biology and medicinal research.[25] For example, upon treatment of $NaBH_4$, **3e** was converted into spirocyclic oxindole **6** in 80% yield as a single isomer, without loss of enantioselectivity (Scheme 3). Its relative and absolute configuration was determined by X-ray analysis, and allowed the assignment of the absolute configuration of **3e** to be *R*. Similarly, the product **5c** was transformed into the polycyclic compound **7**.



Scheme 3. Reaction conditions: a) *m*-CPBA; b) CH_3NH_2; c) Conc. HCl, 100°C; d) $NaBH_4$. For more details see the Supporting Information.[27] DMSO = dimethylsulfoxide, *m*-CPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran.

Unexpectedly, the difluoromethylated quaternary oxindole **3p** could be converted into C4-fused spirocyclic quinolinones, which added value to our method (Scheme 3). After Krapcho dealkoxycarbonylation, **3p** readily gave product **8** in 90% yield without loss of the *ee* value. Starting from **8**, a sequential Baeyer–Villiger oxidation, aminolysis, and cyclization afforded the spirocyclic quinolinone-pyrroline-2,5-dione **10** in 95% *ee*. Similarly, an oxidation, reduction, and cyclization manipulation gave the quinolinone dihydrofuranone **12** in 96% *ee*. The structure of both **10** and **12** was determined by X-ray analysis.

In summary, we have developed the chiral secondary amine phosphoramide catalyst **C1** for the highly enantioselective Michael addition using fluorinated enol silyl ethers, and highlights synthetic opportunities for chiral secondary amine catalysis in desilylative activation of TMS reagents in developing asymmetric reactions. The resulting fluorinated quaternary oxindoles are interesting targets for medicinal research. The high enantioselectivity achieved by **C1** results from the delicate balance between the secondary benzyl amine and phosphoramide, but the role of phosphoramide is now under investigation.[26] In addition, the use of catalyst **C1** for other TMS-reagent-based asymmetric reactions are now in progress in our laboratory.

Keywords: amines · asymmetric catalysis · chirality · fluorine · organocatalysis

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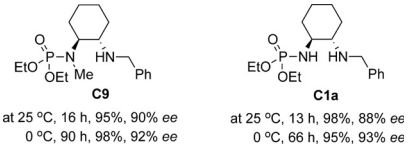
[26] It was not clear now whether the phosphoramide moiety of **C1** served as a hydrogen-bond donor or as a Lewis base, as the N-methylated catalyst **C9** achieved comparable reactivity and *ee* value in the reaction of **1a** and **2a**.



[27] CCDC 1047041 (**5b**), CCDC 1047043 (**6**), CCDC 1047044 (**10**), and CCDC 1047042 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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