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Acyl Phosphonates: Good Hydrogen Bond Acceptors and Ester/Amide Equivalents in Asymmetric Organocatalysis

Hao Jiang, Márcio W. Paixão, David Monge, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Received November 25, 2009; E-mail: kaj@chem.au.dk

Abstract: This study demonstrates that unsaturated acyl phosphonates are excellent hydrogen-bond acceptors in enantioselective organocatalysis. By employing chiral thioureas or squaramides as catalysts, the acyl phosphonates are effectively coordinated and activated by hydrogen bonding, thereby providing successful relay of the chirality from the catalyst to the substrate. A variety of highly stereoselective conjugate additions to α,β-unsaturated acyl phosphonates were performed, using different carbon-based nucleophiles such as oxazolones, indoles, and 1,3-dicarbonyl compounds. The reaction concept has been developed to be a double nucleophilic reaction, and it is shown that the acyl phosphonates serve as masked ester or amide equivalents, which upon quenching with the second nucleophile generate the parent structures in situ. Accordingly, formal C−C bond formation reactions of ester and amide substrates are achieved, affording a broad spectrum of optically active conjugate adducts in good yields and excellent enantioselectivities. Based on the experimental results, the mechanisms for the different reactions are discussed, including the approach of the oxazolones, indoles, and 1,3-dicarbonyl compounds to the acyl phosphonate coordinated to the catalyst and the role of the catalyst for the reaction course of the nucleophiles.

Introduction

Enantioselective nucleophilic addition to electron-poor alkenes is a fundamental transformation in asymmetric synthesis. Nowadays, rapid advances in asymmetric catalysis have generated a broad scope of effective methods for β-functionalization of various Michael acceptors such as enals, enones, nitro alkenes, and vinyl sulfones.[1] Interestingly, activation and chiral induction of simple conjugated esters or amides remains a challenging task, with fewer successful reports. Especially simple alkenyl esters have proven to be difficult substrates for effective chirality relay in asymmetric catalysis. An in-direct, but equally efficient, strategy to encounter this problem is the use of activated ester surrogates as masked equivalents of the desired products. A nucleophile is first added in a stereoselective manner to the unsaturated ester surrogates, and upon completion of reaction, a second nucleophile is employed for a subsequent acyl substitution reaction, furnishing the overall formal ester functionalization reaction by a double nucleophilic addition sequence. Attractive ester and amide surrogates are expected to possess certain qualities: (i) enhanced activation of the substrate toward nucleophilic attack; (ii) improved coordination to the chiral catalyst; (iii) easy and mild replacement upon demand and preferably in a one-pot fashion (Scheme 1). Despite the extensive research in activated ester equivalents, only few truly meet all three criteria. Examples of successful cases includes the use of unsaturated activated imides, 2-acyl imidazoles, styrylisoxazoles, or *N*-acylpyrroles, which have been employed in the described stereoselective double nucleophilic reactions using organometallic catalysis or organocatalysis.[2]

Acyl phosphonates were introduced as activated ester surrogates in asymmetric catalysis by Evans et al.[3] Because of the

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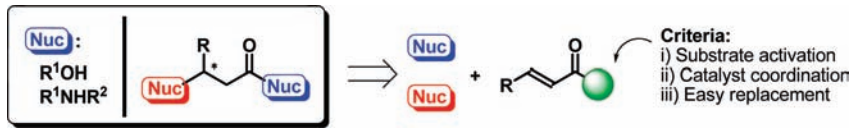
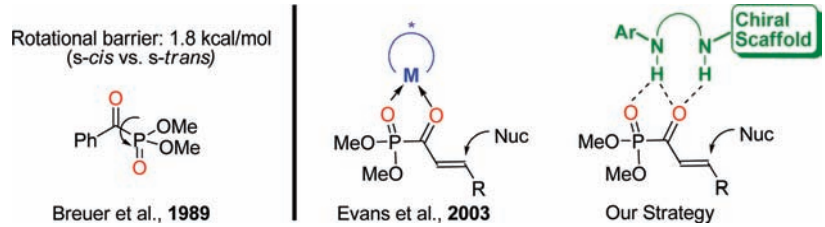
(2) For selected examples, see. (a) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 2035. (b) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029. (c) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064. (d) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (e) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. (f) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810. (g) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (h) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (i) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (j) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263, and references therein. (k) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240. (l) Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983. (m) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276. (n) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (o) Sibi, M. P.; Ma, Z.-H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (p) Coquiere, D.; Feringa, B. L.; Roelfes, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 9308. (q) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (r) Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. P. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9342. (s) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (t) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. See also ref 11d.

Scheme 1. Formal β-Funtionalizations of Esters and Amides Using Activated Ester Surrogates



Scheme 2. Acyl Phosphonates and Methods of Activation



observed lability of the C−P bond, they serve as effective acyl donors, enabling simple transformation to the parent ester or amide motif. The adjacent C═O and P═O groups are generally positioned with a dihedral angle of 180° as result of dipole effects; however, reorientation in the presence of favorable interactions is possible, as demonstrated by Breuer et al., who calculated the energy difference between s-trans and s-cis conformation of the C−P bond of dimethyl benzoylphosphonate to be only 1.8 kcal.[3i] In their study, Evans et al. have demonstrated that chelation of chiral metal complexes to α,β-unsaturated acyl phosphonates is possible, enabling their application in enantioselective conjugate additions and hetero Diels−Alder reactions.[3a−c] Foreshadowed by this work, an alternative activation strategy was pursued.

In the following, we will demonstrate that by application of a strong hydrogen(H)-bond donor, such as a chiral thiourea, the acyl phosphonate motif can be effectively coordinated and activated, enabling formal β-functionalizations of esters and amides using enantioselective H-bonding catalysis (Scheme 2).[4]

Herein, we report our investigations in the use of acyl phosphonates as H-bond acceptors in enantioselective organocatalysis.[5] Important carbon-based nucleophiles such as oxazolones, indoles, and cyclic 1,3-dicarbonyl compounds were successfully introduced with good yields and excellent enantio- and diastereoselectivities using small molecule chiral H-donors as catalysts. This new approach permits an easy and straightforward route to a range of highly potent optically active β-substituted esters and amides that may serve as chiral building blocks in asymmetric synthesis.

Results and Discussion

Oxazolone Additions. The chemistry of oxazol-5-(4*H*)-ones (referred to as oxazolones in the remaining text) dates more than a century previous, when Plöchl et al. in 1883 described the first synthesis via a condensation reaction of benzaldehyde and hippuric acid in presence of acetic anhydride.[6] For a period of time, the structure of penicillin was incorrectly thought to be an oxazolone, leading to increased interest in this class of compound in the 1940s.[7] The chemistry of oxazolones was later extensively explored, revealing multiple reactivity patterns, including nucleo- and electrophilic pathways. Serving as a general and flexible structural skeleton, oxazolones are an excellent template for diversity-oriented syntheses of important and relevant products, such as amino acids and versatile heterocyclic structures.[8]

Nucleophilic addition of oxazolones takes place to either the C-2 or C-4 carbon atoms, affording in both cases a quaternary stereogenic center. As outlined in Scheme 3, regioselective addition of oxazolones to electrophiles such as acyl phosphonates may afford two possible addition adducts **A** or **B**. From C-2 addition, a rare class of optically active quaternary

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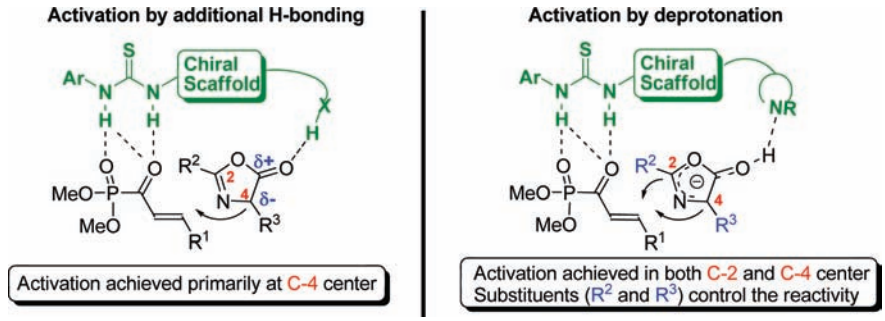
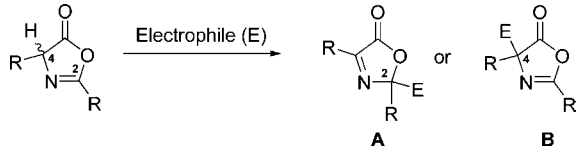


Figure 1. The influence of catalyst and substituents on regioselectivity.

N,O-acetals,[8h,9] with two continuous stereocenters, is obtained. Alternatively, if the reaction occurs at the C-4 carbon atom, forming the addition adduct **B**, a range of masked α,α-disubstituted amino acids[10] is accessible. Because of the synthetic relevance of both classes of compounds, control of reaction pathways is highly desired. Initial observations led us to believe that the issue of regioselectivity can be addressed by proper selection of substituents and catalyst.

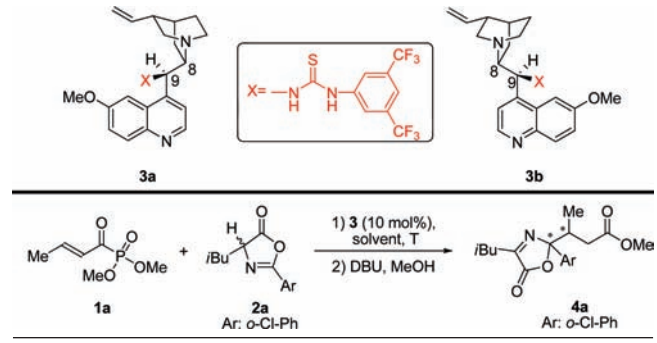
Scheme 3. Regioselectivity of Nucleophilic Oxazolone Additions to Electrophiles



We envisioned that a bifunctional thiourea catalyst with a basic site might deprotonate the oxazolone prior to addition, revealing an oxazole enolate species, where both the C-2 and the C-4 position are activated (Figure 1, right). In such a case, the electronic nature of the side chains on the oxazolones ring (R^2 and R^3) should have decisive influence on the reaction course. Alternatively, omission of the basic site or exchange for an additional hydrogen-donor group on the catalyst (Figure 1, left) would lead to nucleophilic attack primarily at the C-4 center.

For the reaction of acyl phosphonates with oxazolones, we started our screening with the cinchona alkaloid-based thiourea catalysts **3a**,**b**[11] (Table 1) because they are easily available in multigram quantities. 2-(2-Chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **2a** with an electron-deficient aromatic ring attached to C-2 and an alkyl chain at C-4 was identified as a good candidate to promote the selective C-2 conjugate addition. The reaction of (*E*)-dimethyl but-2-enoylphosphonate **1a** with **2a** in the presence of catalyst **3a** or **3b** in toluene as solvent at −20 °C afforded exclusively the desired C-2 addition product **4a** upon quenching with DBU and a second nucleophile (MeOH). The methyl ester product **4a** is formed as a single diastereomer in 72% and 82% ee, respectively (entries 1, 2). The use of halogenated solvents such as CH_2Cl_2 and $CF_3C_6H_5$ led to slight erosion of yield and enantioselectivity (entries 3, 4). A lowering of the temperature to −40 °C or variation in the stoichiometry of the reaction partners had limited effect on the outcome of the reaction (entries 5, 6). However, further dilution of the reaction mixture ([**1a**] = 0.2 M) led to an increase in enantioselectivity, furnishing the product **4a** in 67% yield and 90% ee (entry 8).

Table 1. Screening Results of C-2 Selective Addition of 2-(2-Chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **2a** to (*E*)-Dimethyl But-2-enoylphosphonate **1a**[a]



entry	catalyst	[**1a**] (M)	solvent	*T* (°C)	yield (%)[b]	ee (%)[c]
1	**3a**	1.0	toluene	−20	37	−72
2	**3b**	1.0	toluene	−20	62	82
3	**3b**	1.0	CH_2Cl_2	−20	34	74
4	**3b**	1.0	$CF_3C_6H_5$	−20	41	72
5	**3b**	1.0[d]	toluene	−20	53	82
6	**3b**	1.0	toluene	−40	62	83
7	**3b**	0.33	toluene	−20	50	89
8	**3b**	0.2	toluene	−20	67	90

[a] Unless otherwise stated, 0.1 mmol of **1a**, 0.3 mmol of **2a** and 0.01 mmol of **3** were reacted at the given temperature for 24−48 h. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] **1a** (0.3 mmol) and **2a** (0.1 mmol) were employed. [**2a**] = 1 M.

Having in hand an efficient protocol for C-2 selective addition of 2-(2-chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **2a** to (*E*)-dimethyl but-2-enoylphosphonate **1a**, we explored the scope of the reaction of various oxazolones and alcohols/amines in the double nucleophilic reaction with aliphatic acyl phosphonates, and the results are presented in Table 2. Various aliphatic side chains at the C-4 position of the oxazolone were evaluated (**2a**−**c**) all forming the desired C-2 alkylated products **4a**−**c** as single diastereomers. Increased the steric bulk had minor effects on the enantioselectivity (compare Table 2, entries 1, 2, 4) and by using the quasienantiomer of the catalyst (**3a**), the opposite

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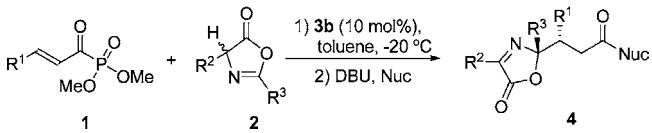
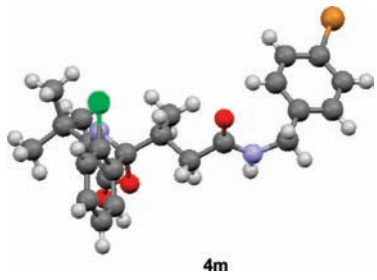
Table 2. Scope of the C-2 Selective Addition of Oxazolones to Acyl Phosphonates[a,g]



1 2 4

entry	R^1	R^2/R^3	nucleophile	yield (%)[b]	ee (%)[c]
1	Me (**1a**)	*i*Bu/*o*-Cl-Ph (**2a**)	MeOH	67 (**4a**)	90
2	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	MeOH	63 (**4b**)	93
3	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	MeOH	57 (*ent*-**4b**)[e]	−90
4	Me (**1a**)	*t*Bu/*o*-Cl-Ph (**2c**)	MeOH	74 (**4c**)	91
5[d]	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	EtOH	55 (**4d**)	92
6	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	BnOH	50 (**4e**)	88
7	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	$BnNH_2$	79 (**4f**)	90
8	Me (**1a**)	*i*Pr/*o*-Cl-Ph (**2b**)	Morpholine	30 (**4g**)	86
9	Me (**1a**)	*i*Bu/*o*-F-Ph (**2d**)	MeOH	74 (**4h**)	90
10	Me (**1a**)	*i*Pr/*o*-Br-Ph (**2e**)	MeOH	73 (**4i**)	92
11	Me (**1a**)	*i*Pr/*o*-Me-Ph (**2f**)	MeOH	56 (**4j**)	82
12[d]	Pr (**1b**)	*i*Pr/*o*-Br-Ph (**2e**)	MeOH	71 (**4k**)	95
13[d]	Hex (**1c**)	*i*Pr/*o*-Br-Ph (**2e**)	MeOH	62 (**4l**)	94
14	Me (**1a**)	*t*Bu/*o*-Cl-Ph (**2c**)	*p*-Br-$BnNH_2$	50 (**4m**)	99[f]

[a] Unless otherwise stated, 0.1 of mmol **1a**, 0.3 of mmol **2a** and 0.01 mmol of **3b** were reacted at −20 °C for 24−48 h. [**1**] = 0.2 M. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] **1a** (0.3 mmol) and **2a** (0.1 mmol) were employed. [**2**] = 0.2 M. [e] Catalyst **3a** was used. [f] Performed on 0.2 mmol scale. Yield and ee determined after single recrystallization ($CHCl_3$/*n*-hexane). [g] Other substitution patterns are also allowed on the phenyl ring; however, chiral separation for determination of ee was not possible for these compounds.



4m

Figure 2. X-ray structure of compound **4m**.

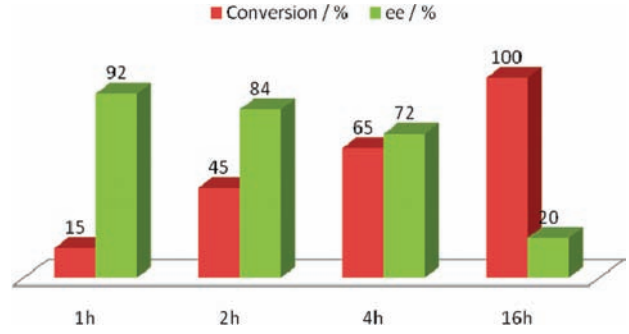
enantiomer of the product was formed (entry 3). Alternatively, when the reaction intermediate was quenched with EtOH or BnOH, the corresponding ethyl and benzyl ester adducts **4d**,**e** were obtained, while the use of $BnNH_2$ and morpholine as the nucleophilic partners rendered the requested amide products **4f**,**g** (entries 5−8). The aryl group attached to C-2 position can also be altered, as different electron-withdrawing (entries 9, 10) and donating substituents (entry 11) can be applied, giving the products **4h**−**j** in 56−74% yield and 82−92% ee. Finally, other aliphatic acyl phosphonates **1b**,**c** were reacted with oxazolone **2e** under the same reaction conditions, furnishing the desired optically active esters **4k**,**l** in 62−71% yield and 94−95% ee (entries 12, 13). The absolute configuration of the product **4m** is unequivocally established to be (*R*,*R*) by X-ray analysis (Figure 2)[12] and the remaining configurations are assumed by analogy.

The obtained optically active products **4** might undergo a number of transformations leading to various useful functional groups,[8h] thus highlighting the synthetic relevance of the stereoselective addition reaction. We will only present two transformations (Scheme 4).

Treatment of the C-2 addition product **4i** with $NaBH_4$ led to the formation of a single product identified as compound **5** (Scheme 4, left). Apparently, despite the presence of several reduction-prone sites, the activated lactone motif is selectively targeted, furnishing the surprisingly stable γ-lactol product **5** in 75% yield after purification on silica gel. Literature reports show that addition of organometallic reagents such as Grignard reagents also occurs selectively to the lactone motif of the oxazolone in the presence of esters and imines.[13]

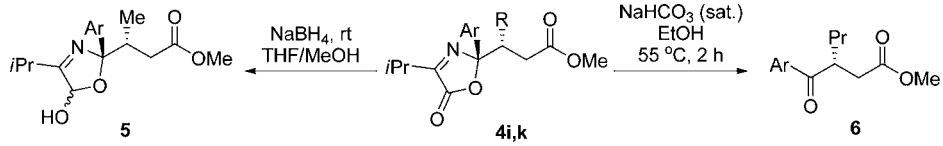
Ring-opening of the oxazolone moiety also proved to be possible, as exemplified for the formation of Stetter product **6** (from **4k**).[14] Initial investigations revealed that acidic or Lewis acidic conditions promoted the desired product in either low yield or as a racemate. Treating the C-2 addition adduct with weak base under gentle heating proved to be the most suitable condition in respect to selectivity of reaction and preservation of optical integrity.[15] As presented in Chart 1, even under these fairly mild conditions, rapid racemization of product **6** is observed, leaving nearly racemic products after 14 h of reaction. Quenching of the reaction mixture after 2 h afforded the desired product **6** in 40% yield (45% conversion) and 84% ee, while unreacted starting material is easily recovered (48%) with the same optical purity as applied (Scheme 4, right). It should be noted that this class of products (as **6**) has usually been accessible by chiral carbene catalysis or the use of a stoichiometric amount of optically active reagents.[15]

Chart 1. Racemization in Oxazolone Opening of **4k**



As proposed in Figure 1, the regioselectivity of the addition of oxazolones to acyl phosphonates is believed to be controlled by both catalyst and substituents on the nucleophile. Consequently, careful selection of catalyst may lead to regioreversal addition from C-2 to C-4 carbon center. On the basis of the considerations in Figure 1, we initiated our investigation by using thiourea **3c** derived from enantiopure (1*S*,2*R*)-1-aminoindan-2-ol as H-bonding catalyst.[16] To our delight, exchange of the basic site of the cinchona-derived catalyst **3a**,**b** with an

Scheme 4. Transformations of the C-2 Addition Adducts **4i**,**k**



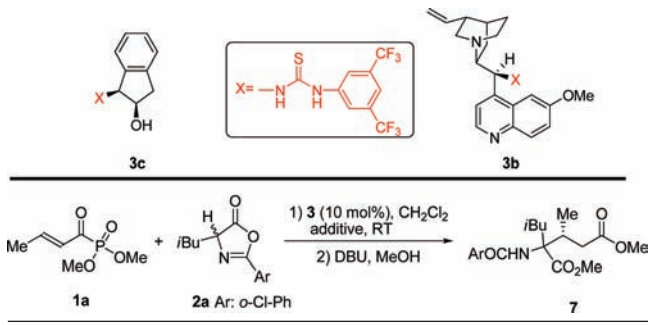
5
75% yield, 5:1 dr

4i,k
Ar: *o*-Br-Ph

6
40% yield, 84% ee
(48% recovered **4k**)

additional hydroxy-directing group switches the regioselectivity completely from C-2 to C-4 addition (Table 3). The reaction between (*E*)-dimethyl but-2-enoylphosphonate **1a** and 2-(2-chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **2a** afforded upon quenching with DBU and MeOH the open quaternary amino acid derivative **7** as the single product in 53% yield, albeit with a low enantiomeric excess of 13% ee (entry 1). The change of the regioselectivity suggests that the nature of the chiral functional group of the catalyst is essential for the outcome of the reaction. Several other chiral thioureas were evaluated as catalysts of the regioreversal C-4 addition reaction; however, only low to moderate regio- and enantioselectivities were observed. The best results were obtained using catalyst **3a** in combination with organic acids as additives, thereby protonating the basic quinuclidine and quinoline motifs.[17] By only employing 10 mol % of TFA as cocatalyst, a 2:1 mixture of product **4a** and **7** is formed (entry 2). Increasing the amount to 50 mol % gave exclusively and directly the desired C-4 addition amino acid product **7**, albeit in racemic form (entry 3). A catalyst/acid ratio of 1:2 proved to be the optimum condition, forming **7** in excellent regioselectivity and moderate enantioselectivity (entry 4). Substituting TFA with other acids such as L-proline had no influence on the stereochemical outcome of the reaction (entry 7), while temperature alterations lowered the enantioselectivity considerably (entries 5, 6). The results demonstrate that the nature of the chiral functional group in the catalyst is essential for the regioselectivity of the addition reaction. Furthermore, under standard conditions when the aromatic C-2 substituent of the oxazolone is replaced with an alkylic chain, such as *t*Bu, a mixture of C-2 and C-4 addition products is formed with moderate enantio- and diastereoselectivity, stating the importance of substitution pattern in control of regioselectivity.

Table 3. C-4 Addition of 2-(2-Chlorophenyl)-4-isobutyloxazol-5(4*H*)-one **2a** to Acyl Phosphonate **1a**



entry	catalyst	additive (mol %)	*T* (°C)	**4a**:**7**[b]	ee (%)[c]
1	**3c**	-	rt	5:95 (53%)[d]	13
2	**3a**	TFA (10)	4	2:1	nd
3	**3a**	TFA (50)	4	5:95	0
4	**3a**	TFA (20)	4	5:95 (60%)	55
5	**3a**	TFA (20)	−20	5:95	30
6	**3a**	TFA (20)	40	5:95	0
7	**3b**	L-proline (20)	4	5:95	−50

[a] Unless otherwise stated, 0.1 mmol of **1a**, 0.3 mmol of **2a**, 0.01 mmol of **3** and the appropriate additive were reacted at the given temperature until completion of the reaction as monitored by TLC (usually 4−48 h). [b] Determined by NMR of the crude reaction mixture. No distereoselectivity of product **7** was achieved. In parentheses is the given yield of isolated product. [c] Determined by chiral stationary phase HPLC. [d] A single diastereomer of **7** was isolated.

Friedel−Crafts Alkylation. Encouraged by the results obtained in the oxazolone addition to acyl phosphonates and in continuance of our exploration of acyl phosphonates as a powerful ester/amide surrogate in asymmetric H-bonding catalysis, we continued the evaluation of other carbon-based nucleophiles suitable for the catalytic system. The Friedel−Crafts alkylation also represents one of the cornerstones in organic chemistry. The robustness of the reaction and the diversity, with which elemental starting materials can be converted, has driven unrelenting developments in this field of research for more than a century. During the past decade, a number of asymmetric catalytic variants of the Friedel−Crafts alkylation have been reported[18] and enantioselective addition of aromatic compounds to electron-poor alkenes has been realized for electrophiles such as nitroalkenes, enals, enones, and unsaturated α-keto esters. In 2003, Evans et al. reported a formal Friedel−Crafts alkylation of esters and amides using acyl phosphonates and a chiral scandium complex as electrophile and catalyst, respectively.[3c]

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(12) CCDC 752315 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/ retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336-033.

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(17) For study on the basicity and nucleophilicity of the two nitrogen centers in cinchona alkaloids, see. (a) Maida, M.; Horn, M.; Zipse, H.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 7157. (b) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6176.

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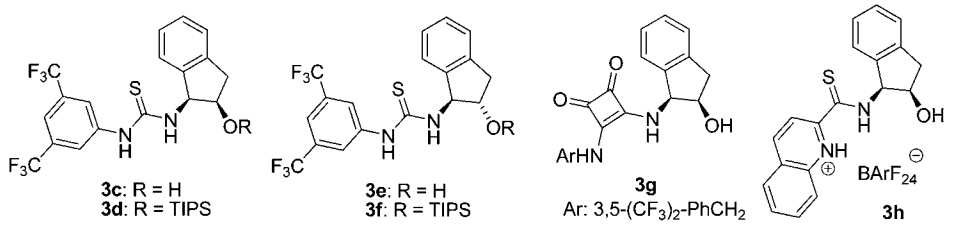
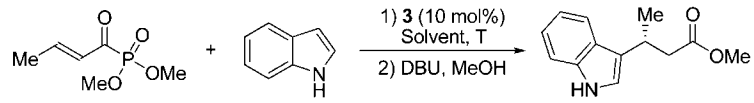
Table 4. Screening of the Friedel−Crafts Alkylation of (*E*)-Dimethyl But-2-enoylphosphonate **1a** with Indole **8a**





1a **8a** **9a**

entry	catalyst	solvent	*T* (°C)	[**8a**] (M)	yield (%)[b]	ee (%)[c]
1	**3c**	CH_2Cl_2	rt	0.5	87	74
2	**3d**	CH_2Cl_2	rt	0.5	40	0
3	**3e**	CH_2Cl_2	rt	0.5	37	0
4	**3f**	CH_2Cl_2	rt	0.5	34	0
5	**3g**	CH_2Cl_2	rt	0.5	82	60
6	**3h**	CH_2Cl_2	−30	0.5	93	20
7	**3c**	toluene	rt	0.5	85	64
8	**3c**	MeCN	rt	0.5	17	49
9	**3c**	$ClCH_2CH_2Cl$	rt	0.5	74	74
10	**3c**	THF	rt	0.5	10	39
11	**3c**	CH_2Cl_2	−20	0.5	81	79
12	**3c**	CH_2Cl_2	−30	0.5	73	79
13	**3c**	CH_2Cl_2	−40	0.5	61	79
14	**3c**	CH_2Cl_2	−20	0.1	65	81
15[d]	**3c**	**CH_2Cl_2**	**−20**	**0.05**	**60**	**86**

[a] Unless otherwise stated, all reactions were performed with 0.1 mmol of **1a** and **8a** and 0.01 mmol of catalyst **3** at the given temperature. Reactions performed at rt were quenched after 4 h. For other temperatures, quenching occurred after 40 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Performed with 0.2 mmol of **1a** and 0.1 mmol of **8a**.

As will be apparent in the following, comparably good results can be achieved using metal-free conditions and by application of chiral thiourea catalysts.

Complementary to the work of Evans et al. focusing on the use of N-alkylated indoles as nucleophiles, we turned our attention toward the corresponding NH-free counterparts. The initial screening results are as outlined in Table 4. Various amino indanol derived catalysts **3c**−**h** were evaluated for the reaction between (*E*)-dimethyl but-2-enoylphosphonate **1a** and indole **8a** in CH_2Cl_2. It appears that a free hydroxy group and the syn-relation between the hydroxy and thiourea moiety proved to be decisive for the reactivity and the enantioselectivity of the reaction. Application of thiourea **3c** as catalyst afforded the β-arylated ester product **9a** in 87% yield and 74% ee (Table 4, entry 1). Instead, changing the configuration of the two functional groups of the catalyst to trans (**3e**) diminished both the yield and selectivity (entry 3). Similar poor results were observed using O-silylated catalysts **3d**,**f** (entries 2, 4). It is previously reported that the squarate motif provides better coordination than thioureas because of increased H-bond distance and H-donor capacity.[19] By employing a squaramide **3g** as chiral inducer, product **9a** was formed with slightly lower enantioselectivity (entry 5). The protonated catalyst **3h**[20] also afforded the product in excellent yield; however, the enantioselectivity (20% ee) was disappointing (entry 6). Having confirmed **3c** as the optimum catalyst for the reaction, a simple solvent screening was carried out. Excellent reactivity was obtained in apolar solvents such as toluene; however, a small decrease in enantioselectivity was observed compared with CH_2Cl_2 (entry 7). Other polar aprotic solvents such as MeCN or THF had a destructive effect on the rate of the reaction forming **9a** in <20% yield and <50% ee after 4 h of reaction (entries 8, 10). It was only in other chlorinated solvents such as DCE that results similar to those obtained with CH_2Cl_2 were reached (entry 9). Decreasing the temperature of the reaction to −20 °C had a positive effect on the enantioselectivity (entry 11), while lowering the temperature further gave no improvements (entries 12, 13). Lastly, dilution of the reaction mixture and the use of 2 equiv of **1a** provided the final enhancement in terms of selectivity, affording **9a** in 60% yield and 86% ee (entry 15).

To demonstrate the scope of the organocatalytic Friedel−Crafts alkylation, a plethora of indoles **8** and alcohol/amine nucleophiles were evaluated for the reaction with the acyl phosphonates **1a**,**b** (Table 5). Using EtOH instead of MeOH for the in situ acyl substitution led to an increase in the enantioselectivity, forming the β-functionalized ethyl ester product **9b** in 68% yield and 90% ee (entries 1, 2). To validate that a broad range of ester and amide products can be accessed, a representative selection of alcohols and amines were employed, forming the arylated adducts **9a**−**e** in 80−90% ee (entries 1−5).

Interestingly, the optical purity of the obtained ester or amide products seems to be dependent on the applied nucleophilic species. It has been observed that a partial racemization can take place in the optically β-arylated acyl phosphonate during the second nucleophilic attack. The degree of racemization is presumably influenced by the nucleophilicity and basicity of

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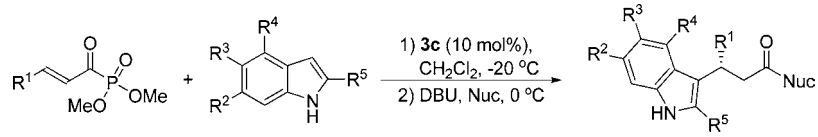
Table 5. Scope of the Organocatalytic Friedel−Crafts Alkylation Reaction



1 **8** **9**

entry	R^1 (**1**)	$R^2/R^3/R^4/R^5$ (**8**)	nucleophile	yield (%)[b]	ee (%)[c]
1	Me (**1a**)	H/H/H/H (**8a**)	MeOH	60 (**9a**)	86
2	Me (**1a**)	H/H/H/H (**8a**)	EtOH	68 (**9b**)	90
3	Me (**1a**)	H/H/H/H (**8a**)	BnOH	57 (**9c**)	83
4	Me (**1a**)	H/H/H/H (**8a**)	$BnNH_2$	63 (**9d**)	80
5	Me (**1a**)	H/H/H/H (**8a**)	morpholine	63 (**9e**)	87
6	Me (**1a**)	OMe/H/H/H (**8b**)	EtOH	93 (**9f**)	90
7	Me (**1a**)	H/OMe/H/H (**8c**)	EtOH	74 (**9g**)	82
8	Me (**1a**)	H/H/OMe/H (**8d**)	EtOH	84 (**9h**)	83
9	Me (**1a**)	H/OMe/H/Me (**8e**)	EtOH	87 (**9i**)	85
10	Me (**1a**)	H/Cl/H/H (**8f**)	EtOH	86 (**9j**)	90
11	Me (**1a**)	H/I/H/H (**8g**)	EtOH	70 (**9k**)	85
12[d]	Pr (**1b**)	H/H/H/H (**8a**)	EtOH	92 (**9l**)	72

[a] Unless otherwise stated, all reactions were performed with 0.2 mmol of **1**, 0.1 mmol of **8** and 0.01 mmol of **3c** in 2 mL of CH_2Cl_2 at −20 °C. The reactions were quenched the appropriate alcohol/amine upon completion of reaction, usually after 40−60 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Performed at 0 °C.

the chosen nucleophile, and reaction time. We have noted that prolonged reaction time for the second nucleophilic attack can lead to a further racemization as, for example, observed for the ethyl ester adduct **9b** (90% ee) which was recovered with only 68% ee when stirred with DBU and BnOH for 24 h.

Additionally, we demonstrate that the described Friedel−Crafts alkylation is unbiased toward substitution on the indole nucleophiles. Having an electron-donating substituent at various positions on the indole ring was tolerated, furnishing the desired addition products **9f**−**i** in 74−93% yield and 82−90% ee (Table 5, entries 6−9). Moreover, electron-poor indoles such as **8f** and **8g** could also be included as reaction partners. Under the optimized conditions, the β-arylated ethyl esters **9j**,**k** were afforded in 90% and 85% ee, respectively. Variation of the side chain of the acyl phosphonate is also possible as shown for substrate **1b**, leading to isolation of **9l** in 92% yield and 72% ee.

1,3-Dicarbonyl Addition. Nowadays, developments in C−C bond-forming reactions with an aim for rapid and stereoselective generation of all carbon quaternary stereocenters has evolved as a major area of interest.[21] In this respect, addition of activated carbon nucleophiles such as 1,3-dicarbonyl compounds to electron-poor alkenes represents an obvious and straightforward reaction strategy. However, while the asymmetric catalytic conjugate addition of simple malonates and nonsubstituted β-ketoesters is well described in the literature, reactions between α-substituted 1,3-dicarbonyls and β-substituted Michael acceptors leading to the formation of two stereogenic centers (of which one is quaternary all carbon) are more difficult. The primary challenge lies with the efficient control of both the enantio- and diastereoselectivity of the reaction. The use of enals, enones, and nitroalkenes as electrophiles in such reactions has been realized using metal or organocatalysts with varying success.[22] To the best of our knowledge, the addition of prochiral α-substituted 1,3-dicarbonyl compounds to esters or surrogates has not been performed with good enantioselectivity. We envisioned that by reacting acyl phosphonates with cyclic 1,3-dicarbonyl compounds in combination with H-bonding catalysis, ester or amide products carrying an all-carbon stereocenter can be formed. Initial catalyst screening indicated that thiourea catalysts such as **3a**,**b** were inefficient as a rate enhancer, providing only low conversion after prolonged reaction times when reacting methyl 2-oxocyclopentanecarboxylate **10a** with electrophile **1a**. Inspired by recent work of Rawal et al.,[19] we turned our attention toward the use of chiral cinchona alkaloid derived squaramides as the H-bonding motif. Gratifyingly, the squaramide catalyst **3i** that originated from cinchonine catalyzed the reaction to full conversion within 40 h, forming the desired Michael adduct *ent*-**11a** in 73% yield, 10:1 dr, and 91% ee as presented in Scheme 5. Synthesizing catalyst **3j** using quinine as the chiral scaffold allowed access to the opposite enantiomer of the product (**11a**) in similar yield and diastereoselectivity, and slightly higher enantioselectivity (95% ee). Quenching the reaction with EtOH or $BnNH_2$ as nucleophiles afforded the ethyl ester **11b** or benzyl amide **11c** in 94% and 92% ee, respectively. Increased steric bulk of the ester group had a diminishing effect with respect to yield (65%) and enantioselectivity (88% ee) of the product **11d**, while the diastereoselectivity remained unaf-

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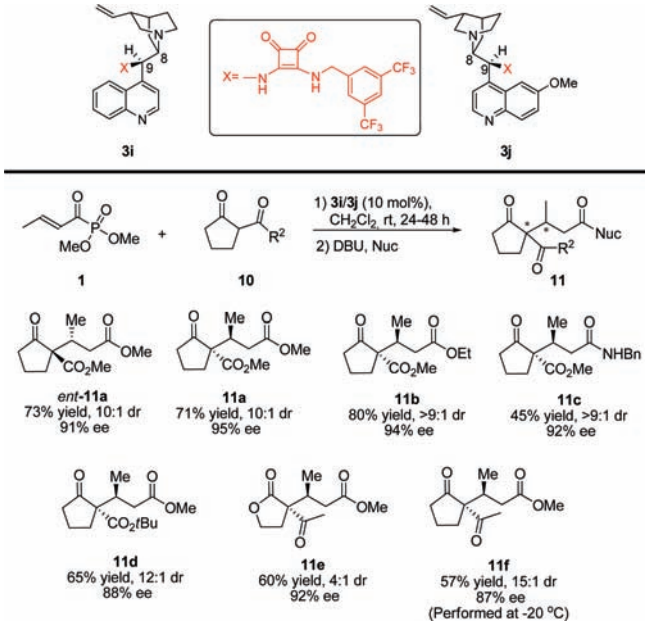
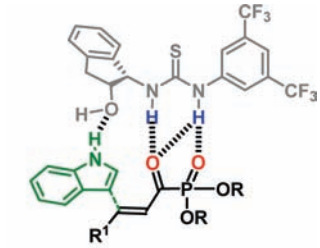
fected. Substrate scope could be further broadened to include a cyclic lactone and 1,3-diketone, giving rise to the formation of compounds **11e**,**f** in 60% yield, 4:1 dr, 92% ee, and 57% yield, >15:1 dr, 87% ee, respectively.

Scheme 5. Addition of Cyclic 1,3-Dicarbonyl Compounds to (*E*)-Dimethyl But-2-enoylphosphonate **1a**



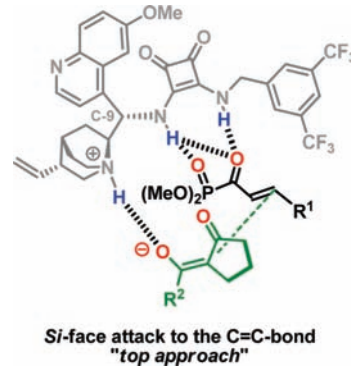
Mechanistic Aspects. The stereochemical course of the different reactions show some interesting outcomes. In the Friedel−Crafts alkylation, the absolute configuration of product **9a** is determined to be 3*R*, by chemical correlation to previous reports (see Supporting Information). Remaining configurations of the Friedel−Crafts products **9** are assumed by analogy. In contrast to the work by Evans et al., using N-alkylated indoles as nucleophiles, the present indole nucleophiles require the free indole-NH functionality, as the N-methylated analogue gave a much slower reaction and a racemic product. Thus, catalyst **3c** is believed to direct the approach of the indole to the acyl phosphonate with weak hydrogen bonding to the indolic proton,[16] while the electrophile is activated and positioned for the nucleophilic attack from the Re-face by the thiourea motif as outlined in Scheme 6.

Scheme 6. Mechanistic Considerations for the Approach of Indole to the Acyl Phosphonate Coordinated to the Thiourea Catalyst **3c**



The stereoselectivity of the 1,3-dicarbonyl addition to acyl phosphonates is believed to origin from bifunctional coordination of the nucleophilic and electrophilic reaction partners to the quinine-derived catalyst **3j**. It is proposed that the acyl phosphonate is hydrogen bonded to the squaramide motif, placing the alkene side chain out to the steric less-demanding area away from the C-9 center of the catalyst, while the 1,3-dicarbonyl compound is deprotonated and directed for the nucleophilic attack by the tertiary nitrogen atom of the catalyst (Scheme 7). The R^2-group of the nucleophile is oriented away from the reaction site and the subsequent conjugate addition approaches to the Si-face of the C=C bond, accounting for both the enantio- and diastereoselectivity of the reaction.

Scheme 7. Mechanistic Considerations for the Approach of 1,3-Dicarbonyl Compounds to the Acyl Phosphonate Coordinated to the Thiourea Catalyst **3j**



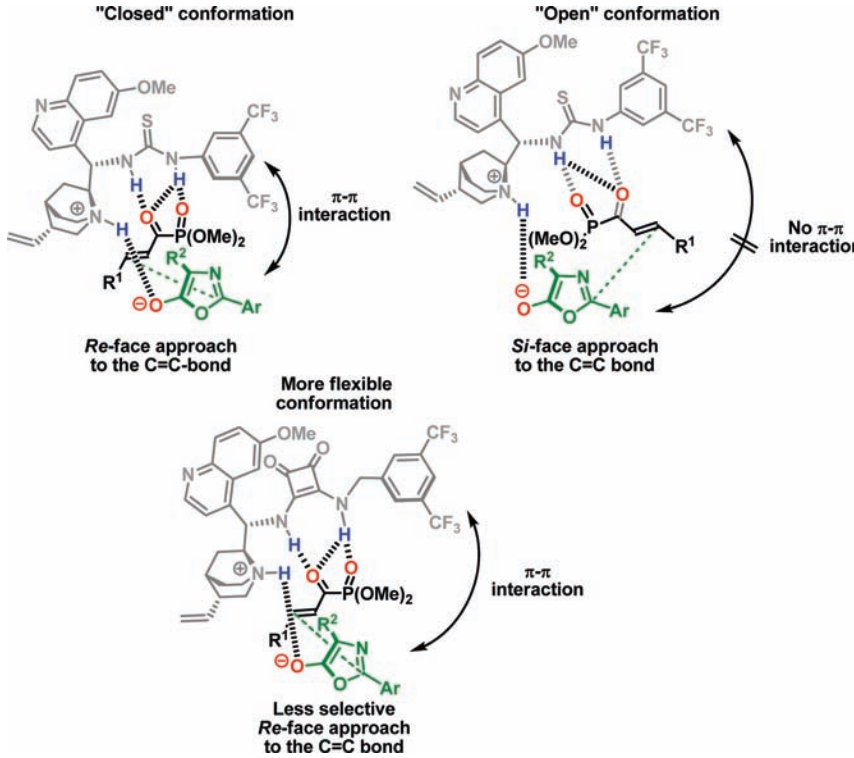
An interesting aspect appeared when comparing the stereochemical outcome of the oxazolone and 1,3-dicarbonyl addition products **4** and **11**. It appears that by using another quinine-derived catalyst **3b**, the C-2 addition of the oxazolone to acyl phosphonate takes place to the Re-face of the C=C-bond, in contrast to the Si-face approach of the 1,3-dicarbonyl addition.[23,24] The squaramide catalyst **3j** used for the 1,3-dicarbonyl addition (Si-face selective) can also be applied for the oxazolone C-2 addition resulting in selective Re-face attack (70% ee), thereby ruling out the influence of the H-bonding motif of the catalyst (squarate vs thiourea). A plausible explanation may be a form of "induced fit" property of the cinchona catalyst in the transition state, where the oxazolone and 1,3-dicarbonyl compounds trigger different conformations of the substrate−catalyst complex. As presented in Scheme 8, top left, the oxazolone might react as its enolate, having character of an electron-rich aromatic compound, which might form $\pi-\pi$ interactions with the electron-poor aryl group adjacent to the thiourea motif. It is tentatively proposed that this interaction brings the quinuclidine group (also coordinated to the oxazole enolate) closer to the aryl thiourea moiety, forming a "closed" conformation of the catalyst which projects the olefin side chain of the acyl phosphonate away from the 3,5-bistrifluoromethyl aryl group because of steric hindrance, resulting in Re-face attack of the nucleophile and a stereochemical outcome of the reaction in accordance with the experimental results.

The alternative is an "open" form catalyst conformation as postulated in the mechanism of the 1,3-dicarbonyl addition; in this case the olefin of the acyl phosphonate is placed in the opposite direction compared to the "closed" conformation, thus favoring a Si-face attack, Scheme 8, top right. However, in this

(23) Absolute configuration determined by chemical correlation to ref 22b.

(24) Similar observations could be made by inspection and comparison of previous literature reports, where the cinchona-alkaloid-based H-bonding catalysts were employed. However, such an "inversion" of addition pattern has not been discussed previously (compare refs 8b,11c, 19).

Scheme 8. Different Mechanistic Considerations for the Approach of Oxazole Enolate to the Acyl Phosphonate Coordinated to the Catalysts **3b**,**j**



case, the "open" catalyst conformation neglects the positive $\pi-\pi$ interactions and is therefore disfavored (in contrast to the 1,3-dicarbonyl addition, where no $\pi-\pi$ interactions are present).

Another possible indication of two conformations of the catalyst−substrate complex is observed when using a catalyst with an additional methylene between the H-bonding motif and the electron-deficient aryl group (**3j**). The increased flexibility and extended distances lead to a more flexible "closed" conformation of the substrate−catalyst complex, and this loss of rigidity results in inferior control and slightly reduced enantio- and diastereoselectivity (70% ee and 5:1 dr). Another possibility is a change in operational pathway of the catalyst, such as self-association of the cinchona alkaloid catalyst, as noncovalent dimers have been observed.[25]

Conclusion

We have demonstrated that unsaturated acyl phosphonates are excellent hydrogen-bond acceptors in enantioselective organocatalysis. A variety of highly stereoselective conjugate additions to α,β-unsaturated acyl phosphonates were performed, using different carbon-based nucleophiles such as oxazolones, indoles, and cyclic 1,3-dicarbonyl compounds. Moreover, it is shown that the acyl phosphonates may serve as masked ester or amide equivalents which upon quenching generated the parent structures in situ. The presented approach allows for an efficient route to formal β-functionalizations of simple esters and amides, affording a broad spectrum of optically active conjugate adducts in good yields and excellent enantioselectivities. Hence, the use of acyl phosphonates in combination with hydrogen-bonding catalysis may serve as a general template for formal ester/amide functionalization. The mechanism for activation of both the acyl phosphonate and indole, oxazolone, and 1,3-dicarbonyl compounds, as well as the stereoselective approach of the latter to the olefin in the conjugated addition reaction, by the chiral catalyst is also presented.

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Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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