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Diastereodivergent Asymmetric Sulfa-Michael Additions of α-Branched Enones using a Single Chiral Organic Catalyst

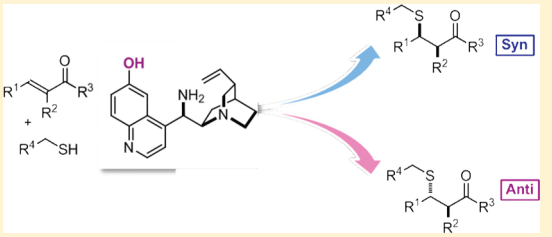
Xu Tian,[†] Carlo Cassani,[†] Yankai Liu,[†] Antonio Moran,[†] Atsushi Urakawa,[†] Patrizia Galzerano,[†] Elena Arceo,[†] and Paolo Melchiorre*[,†,‡]

[†]ICIQ, Institute of Chemical Research of Catalonia, Avenida Països Catalans 16-43007 Tarragona, Spain

[‡]ICREA, Institució Catalana de Recerca i Estudis Avançats, Passeig Lluís Companys 23-08010 Barcelona, Spain

Supporting Information

ABSTRACT: A significant limitation of modern asymmetric catalysis is that, when applied to processes that generate chiral molecules with multiple stereogenic centers in a single step, researchers cannot selectively access the full matrix of all possible stereoisomeric products. Mirror image products can be discretely provided by the enantiomeric pair of a chiral catalyst. But modulating the enforced sense of diastereoselectivity using a single catalyst is a largely unmet challenge. We document here the possibility of switching the catalytic functions of a chiral organic small molecule (a quinuclidine derivative with a pendant primary amine) by applying an external chemical stimulus, in order to induce diastereodivergent pathways. The strategy can fully control the stereochemistry of the asymmetric conjugate addition of alkyl thiols to α-substituted α,β-unsaturated ketones, a class of carbonyls that has never before succumbed to a catalytic approach. The judicious choice of acidic additives and reaction media switches the sense of the catalyst's diastereoselection, thereby affording either the syn or anti product with high enantioselectivity.



INTRODUCTION

The catalytic stereoselective conjugate addition of carbonyl compounds has historically offered a potent synthetic way of producing valuable chiral molecules.[1] Both metal-[1a−c] and organic-[1d,e]based approaches are now so reliable that synthetic chemists can address even the most daunting of challenges connected with the asymmetric catalytic β-functionalization of simple unsaturated carbonyl compounds. In contrast, the activation of sterically hindered carbonyls is a persistent problem. In particular, the catalytic activation of α,β-disubstituted unsaturated ketones remains an elusive target.[2] Conjugate additions to linear α-branched enones generate two adjacent stereocenters through an addition-protonation tandem sequence. All attempts to design a stereocontrolled variant of this process must thus address the challenge of diastereo- as well as enantioselectivity (Figure 1). This requires the ability of a chiral catalyst to (i) effectively activate the highly hindered keto-moiety, while (ii) selectively shielding one of the two faces of the electrophilic unsaturated π-system to forge the β-stereocenter with high fidelity. Finally, (iii) strict control over the transient enolate/enamine geometry is necessary to ensure a catalyst-directed protonation event.

From a wider perspective, the complex stereoselectivity issues inherent to this type of chemical transformation provide the opportunity to face one of the most significant limitations of asymmetric catalysis: when applied to processes that generate chiral molecules with multiple stereogenic centers in a single step, chemists cannot selectively access the full matrix of stereoisomers using a single chiral catalyst.

Mirror image products (complementary enantioselectivity) can be individually provided by the enantiomeric pair of a chiral catalyst.[3] However, researchers are largely still not able to modulate the sense of diastereoselectivity (control over the relative stereochemistry) using a single chiral catalyst. A diastereochemical switch generally requires the use of distinct chiral catalysts[4,5] or ligands,[6] the addition of different Lewis acids[7] or tailored substrate modifications.[8] Less explored is the approach of changing the reaction conditions to tune the functions of a single catalyst.[9]

Herein, we demonstrate the ability of a chiral organic small molecule, the cinchona-based primary amine **5**, to catalyze the highly stereoselective sulfa-Michael addition (SMA) of different alkyl thiols to a range of linear α-branched enones. We have found that the catalytic function of the primary amine **5** can be modulated to induce diastereodivergent pathways by applying an external chemical stimulus. By judiciously choosing different acidic additives and reaction media, we can switch the enforced sense of diastereo-induction, thus allowing access to all possible stereoisomeric products of the SMA reaction.

This article reports our efforts toward optimizing the syn- and anti-SMA reaction conditions, and offers a rationalization for the switchable selectivity of catalyst **5**.

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RESULTS AND DISCUSSION

Standard Reaction Optimization. Our laboratory and others, independently, have recently established cinchona derivatives of type **5** (chiral primary amines easily derived from natural sources) as general and effective covalent binding activators of sterically congested carbonyl compounds.[10] In particular, we have demonstrated the versatility of these organic molecules in the context of the stereoselective iminium-catalyzed SMA of alkyl thiols to both α,β-unsaturated enones[11a] and α-branched α,β-unsaturated aldehydes.[11b] The unique ability of 6′-hydroxy-9-amino-9-deoxyepiquinidine **5**[12]

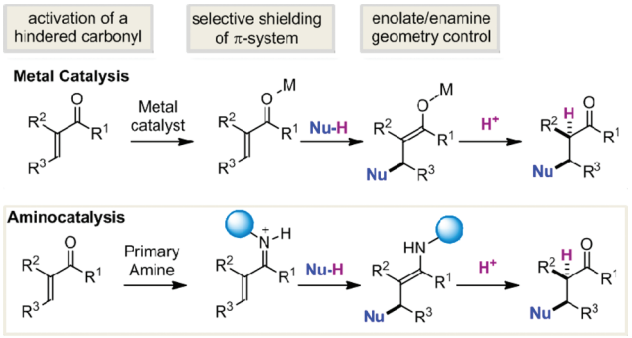
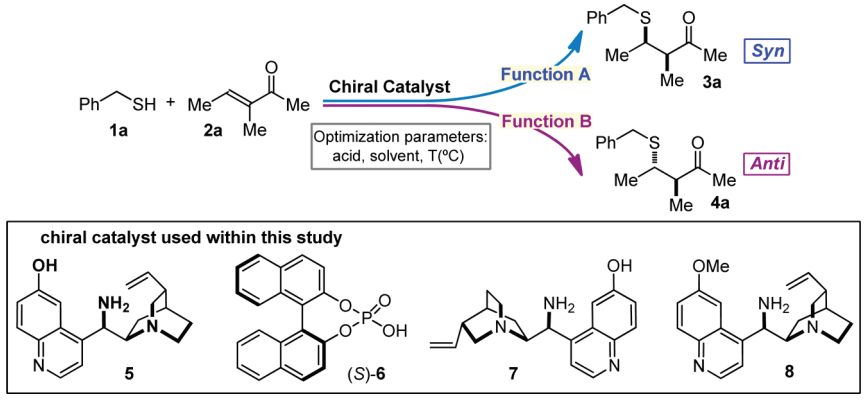


Figure 1. Challenges arising from the catalytic activation of α-branched enones.

to engage in iminium ion formation with encumbered carbonyls prompted us to explore its behavior with respect to the stereoselective SMA[13] of α-branched α,β-unsaturated ketones. Considering the synthetic usefulness of simple alkyl S-centered nucleophiles,[14] we focused on the conjugate addition of benzyl mercaptan **1a** to the α-branched enone **2a** as the model reaction. This transformation generates two adjacent stereocenters through a conjugate addition-protonation tandem sequence, leading to the *syn*-**3a** and *anti*-**4a** products. Gratifyingly, catalyst **5** showed high efficiency in activating the sterically hindered substrate **2a**. Extensive optimization studies are reported in Tables S1−5 within the Supporting Information, with selected results summarized in Table 1.

The absence of any substantial diastereoselectivity in the presence of a strong base or an achiral iminium-forming catalyst (entries 1−2) excluded the possibility of a selective pathway induced by substrate control.[15] In the absence of an acidic additive, catalyst **5** afforded the selective formation of the syn product **3a** with a moderate level of enantiomeric excess (ee) (entry 3). Under these conditions, the catalytic profile of amine **5** is dictated by the tertiary bridgehead amine, which likely channels the SMA reaction through a general base-catalyzed mechanistic pathway.[16,17] We then sought to favor the iminium activation of the enone **2a** by addition of an acid cocatalyst that, by protonating the quinuclidine moiety, would suppress the chemical handle necessary for base catalysis,[18] while providing the strongly acidic conditions required for iminium ion formation.[19] Combinations

Table 1. Selected Optimization Studies[a]



entry	catalyst (mol %)	acid (mol %)	pK_a	solvent	°C	conv (%)	dr *syn*-**3a**:*anti*-**4a**	*ee* (%) **3a**/**4a**
1	DBU(20)			toluene	25	67	1:1.6	
2	$BnNH_2$ (30)	TFA (30)		toluene	25	60	1.8:1	
3	**5** (20)			$CHCl_3$	25	29	5:1	65/49
4	**5** (20)	CH_3CO_2H (20)	4.76	$CHCl_3$	25	35	6.5:1	77/17
5	**5** (20)	$PhCO_2H$ (40)	4.20	$CHCl_3$	25	40	8.5:1	82/17
6	**5** (20)	$PhCO_2H$ (40)	4.20	toluene	25	11	8:1	81/78
7	**5** (20)	2-F-$C_6H_4CO_2H$ (20)	3.27	$CHCl_3$	25	35	7:1	79/55
8	**5** (20)	2-F-$C_6H_4CO_2H$ (40)	3.27	$CHCl_3$	25	42	6:1	88/59
9	**5** (20)	2-NO_2-$C_6H_4CO_2H$ (40)	2.17	$CHCl_3$	25	15	1.3:1	72/86
10	**5** (20)	TFA (40)	0.3	$CHCl_3$	25	13	1:1.5	<5/92
11	**5** (20)	(*S*)-**6** (30)	<2.0	$CHCl_3$	40	28	1:1.3	35/93
12	**5** (10)	(*S*)-**6** (10)	<2.0	acetone	40	62	1:6.2	<5/98

[a] Both diastereomeric ratios (dr) and conversion were determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric excess (*ee*) values were determined by GC analysis on commercially available chiral stationary phases. Reactions carried out using 2 equiv of **1a** and $[\mathbf{2a}]_0$= 0.25M. Reaction time: 16 h. pK_a values determined in H_2O. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; $BnNH_2$ = benzylamine; TFA = trifuoroacetic acid; DPP = diphenyl hydrogen phosphate.

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Table 2. Catalyst Structure−Reactivity/Stereoselectivity Studies of the SMA Reaction[a]

entry	catalyst (mol %)	acid (mol %)	solvent	°C	conv (%)	dr *syn*-**3a**:*anti*-**4a**	*ee* (%) **3a**/**4a**
1	**5** (20)	2-F-$C_6H_4CO_2H$ (40)	$CHCl_3$	25	42	6:1	88/59
2	**8** (20)	2-F-$C_6H_4CO_2H$ (40)	$CHCl_3$	25	26	7:1	77/n.d.
3	**5** (10)	(*S*)-**6** (10)	acetone	40	62	1:6.2	<5/98
4	**8** (10)	(*S*)-**6** (10)	acetone	40	25	1:1.7	n.d./97
5	**5** (20)	2-F-$C_6H_4CO_2H$ (40)	acetone	25	35	2.1:1	30/83
6	**5** (20)	(*S*)-**6** (30)	$CHCl_3$	40	28	1:1.3	35/93
7	**5** (10)	TFA (10)	acetone	40	18	1:1.7	n.d./98
8	**5** (20)		acetone	40	14	4.5:1	<5/<5
9		(*S*)-**6** (40)	acetone	40	18	4.2:1	<5/<5
10	**5** (10)	(*R*)-**6** (10)	acetone	40	39[b]	1:5.2	n.d./96
11	**5** (10)	DPP (10)	acetone	40	52[b]	1:6.1	<5/98
12	**7** (10)	(*S*)-**6** (10)	acetone	40	51[b]	1:4.1	n.d./92[c]
13	**7** (10)	(*R*)-**6** (10)	acetone	40	43[b]	1:3.9	n.d./94[c]
14	**7** (10)	DPP (10)	acetone	40	66[b]	1:2.5	n.d./94[c]

[a] Both diastereomeric ratios (dr) and conversion were determined by ^{1}H NMR analysis of the crude mixture. Enantiomeric excess (ee) values were determined by HPLC or GC analysis on commercially available chiral stationary phases. Reaction time: 16 h. Reactions in chloroform carried out using 2 equiv of **1a** and $[\mathbf{2a}]_0$ = 0.25M. Reactions in acetone carried out using 2 equiv of **1a** and $[\mathbf{2a}]_0$ = 0.5M; n.d.= not determined. [b] Yield of the isolated product after 60 h reaction time. [c] Reaction leading to the opposite enantiomer of anti-**4a**.

of benzoic acid derivatives with amine **5** effectively promoted the SMA reaction, imparting a good level of syn diastereoselection and moderate enantioinduction (entries 5−7). Evaluation of the reaction media indicated chloroform as the best solvent. Notably, a 1:2 ratio of amine **5** to *ortho*-fluorobenzoic acid offered an effective catalytic system for achieving syn diastereoselectivity while inferring high enantiomeric excess (*ee* = 88%, entry 8).

We were pleased to observe that strong acids (pK_a in water <2.5, entries 9−11) could greatly alter the stereochemical outcome of the reaction. The loss of diastereocontrol was accompanied by a remarkable increase in the enantiomeric excess of the *anti*-**4a** adduct (>92% ee), while the *syn*-**3a** product distribution was essentially racemic. We thus undertook an extensive optimization (detailed within Tables S6−11 in the Supporting Information) to identify a catalytic system capable of a high level of anti diastereoinduction. By combining amine **5** with the commercially available chiral phosphoric acid (*S*)-**6**[20] in a 1:1 ratio (10 mol %), switching the solvent to acetone,[21] and heating to 40 °C, we obtained the anti diastereoisomer **4a**, essentially as a single enantiomer (entry 12, table 1).[22]

Further Experimental Observations. The initial results indicated that the pK_a of the acidic additive and the reaction media can be used to switch the sense of the catalyst's diastereoselection, thereby affording either the enantioenriched syn or anti product on demand. To gain more insight into the factors responsible for the uncommon diastereoswitching behavior of amine **5**, we further studied the SMA reaction of **1a** and enone **2a** (see Tables S6−11 and Figures S2−3 within the Supporting Information, with selected results detailed in Table 2).

First, we evaluated the influence of the hydroxyl group at the 6′ position of the catalyst scaffold.[23] The primary amine **8**, directly derived from natural quinidine, in combination with benzoic acid promoted the syn SMA reaction of **1a** and **2a** in chloroform leading to product *syn*-**3a** with slightly lower stereoselectivity than when using catalyst **5** (compare entries 1 and 2, Table 2; further results for the **8**-catalyzed syn-selective SMA reaction are reported in Supporting Information Table S5). In marked contrast, when mixed with the chiral phosphoric acid (*S*)-**6** in acetone, amine **8** promoted the SMA reaction yielding the anti-diastereoisomer **4a** with very high enantioselectivity but with essentially no control over the relative stereochemistry (compare entries 3 and 4, Table 2). This result underlines how the hydrogen-bonding donor[24] moiety at the 6′ position of the cinchona scaffold was essential to channel the reaction toward an anti-diastereoselective pathway.

The anti-diastereoselective pathway, however, is also strictly dependent on the choice of solvent and the nature of the strong acid used. The amine **5**/*ortho*-fluorobenzoic acid combination, which proved effective for promoting the syn-diastereoselective reaction in chloroform, led to poor stereocontrol when used in acetone (entry 5), while the amine **5**/(*S*)-**6** catalyst salt did not afford relative stereocontrol in chloroform (entry 6). Moreover, when a strong acid other than the phosphoric acid derivative was used in combination with amine **5** (e.g., TFA, entry 7), a complete loss of diastereoselectivity was observed, although the *anti*-**4a** isomer was generated with very high enantiomeric purity. These results suggest that the constructive cooperation of three crucial parameters is necessary for inducing the anti-diastereoselectivity. These are (i) the hydroxyl group at the 6′ position of the catalyst **5**, (ii) the nature of the reaction medium, and (iii) the strong hydrogen-bonding ability of the phosphate anion. Each of these factors, individually, is necessary but not alone sufficient for switching the catalyst's diastereochemical preference.

Within this context, it is intriguing to consider how combining the amine **5** and the acid **6** results in a unique mechanistic pathway. The discrete catalysts, when operating individually under general base and Brønsted acid[25] catalysis, respectively, still promoted the SMA addition in acetone but induced a syn-selective racemic pattern (entries 8 and 9).

Finally, to gain insight into the specific role played by the two chiral entities of the **5**/**6** catalyst salt,[26] we used the mismatched combinations to promote the anti SMA reaction (compare entries 3 and 10). The combination of amine **5** with (*R*)-**6** gave lower reactivity and slightly decreased stereoselectivity (96% ee against 98% ee). This suggests that the chiral primary amine was mainly dictating the enantioselectivity of the process, while the

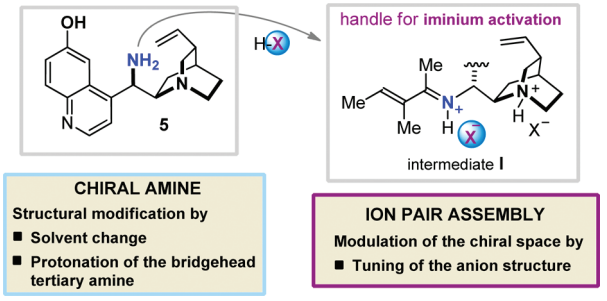


Figure 2. Switching the diastereoselectivity of chiral amine **5**: providing distinct chiral environments for the SMA reaction by exploiting the catalyst's conformational flexibility and the tunable nature of the ion pair intermediate **I**. H−X: acidic additive.

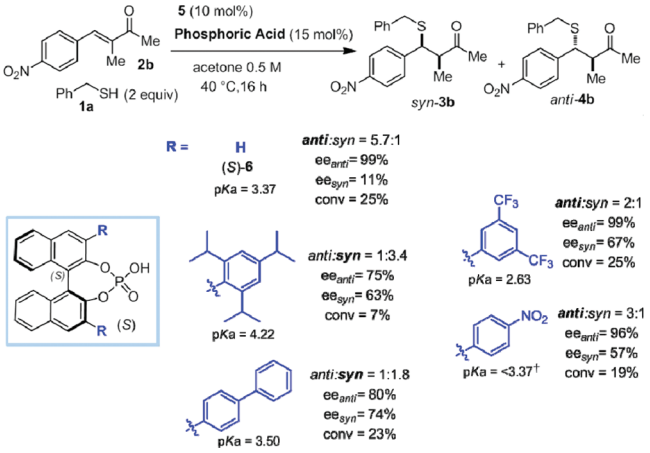


Figure 3. Correlation between the catalyst's functional switch and the hydrogen-bonding ability of the phosphate anion. When bulkier phosphates than (*S*)-**6** are used, a syn-selective pathway is dominant, presumably due to a weaker binding ability of the anion. Interestingly, the inductive effect of electron withdrawing groups (*p*-NO_2 and CF_3 moieties) at the 3- and 3′-substituents of phosphoric acids preserved the anti-diastereoselectivity. The p*K*a values are referred to DMSO, as given in ref 34. †p*K*a value is not available: inductive effects should presumably render this compound more acidic than **6**.

chiral phosphoric acid cocatalyst was needed to induce an anti diastereoselective pathway. The small influence of the phosphoric acid chiral backbone on the enantioselectivity prompted us to investigate the effect of diphenyl hydrogen phosphate (DPP), an achiral acid (entry 11). Indeed, DPP led to comparable results, in terms of efficiency and stereoselectivity, to those obtained with the chiral acid **6**. This further supported the notion that, while the hydrogen-bonding ability of the phosphate counteranion strongly influenced the structural assembly of the iminium intermediate (vide infra), its chirality was not essential for the stereochemical outcome of the asymmetric transformation.

Interestingly, the opposite configuration of the SMA product could be accessed by simply selecting the appropriate enantiomer of the catalyst. Thus, combining the pseudoenantiomeric catalyst **7**,[27] derived from quinine, with (*R*)-**6**, (*S*)-**6** or DPP afforded *anti*-**4a** with opposite absolute configuration while maintaining a high level of selectivity (entries 12−14).

Mechanistic Considerations. We propose that the same general mechanism (covalent-based organocatalysis through iminium activation of α-branched enones) is operative in the two stereodivergent chemical pathways.[17,18] The conceptual framework for rationalizing the diastereodivergent behavior of amine **5** is as follows: the addition of acidic additives and the change of the reaction medium induce a three-dimensional structural modification of the catalyst's structure (Figure 2). Altering the chiral catalyst conformation may in turn reflect on different catalyst-substrate specific interactions and distinct transition state structures that could channel the transformation through diastereodivergent pathways.

Changing the reaction conditions, including solvent and temperature,[28] or using light,[29] has already been used in asymmetric catalysis to modulate the chiral space in which an enantioselective catalytic reaction takes place, thus leading to enantiodivergent reaction outcomes. This strategy has provided individual access to either product enantiomers from a single enantiomer of the chiral synthetic catalyst. The results reported above suggest that the synthetic potential of chiral molecules whose catalytic function changes in response to an external stimulus can be further expanded to attack longstanding problems in chemical synthesis: modulating the enforced sense of diastereoselectivity on demand using a single chiral catalyst.

The following two factors explain the induced modification of the chiral space where the sulfa-Michael reaction takes place (Figure 2):

(i). Flexibility of the Cinchona Scaffold. Cinchona alkaloid derivatives[30] of type **5** are characterized by a high degree of conformational flexibility in solution,[31] and three-dimensional structural switches can be induced by different chemical stimuli, such as a solvent change[31a] or protonation of the N-quinuclidine moiety.[32] Since the catalytic function of the cinchona scaffold is intimately related to its spatial architecture, a conformational change may induce a different catalytic behavior. It has already been shown how modulation of the solvent polarity directly reflects on the ability of a cinchona catalyst to induce a preferred handedness in the product formed during an asymmetric transformation.[33] Along this line, we have carried out vibrational circular dichroism (VCD), circular dichroism (CD) and nuclear magnetic resonance (NMR) spectroscopic analyses of the **5**/*ortho*-fluorobenzoic acid and **5**/diphenyl hydrogen phosphate combinations (see Figures S7−S28 in the Supporting Information). These studies provided insight into the conformational behavior of each catalytic system in chloroform and acetone. Interestingly, we have found that, whereas the two catalytic salts did not show clear chiroptical distinctions, a change of the solvent greatly altered their ground-state conformations.

(ii). Modular Nature of the Ion-Pair Molecular Assembly. Amine **5**, which bears a pendant primary amino moiety, can effectively condense with hindered carbonyls[12,22a] in the presence of an acidic additive to form a covalently bound reactive catalytic species, the iminium ion intermediate (intermediate **I** in Figure 2). The distinctive feature of such an ion pair assembly as a chiral molecular catalyst is that its stereocontrolling ability can be fine-tuned by structurally modifying both the cation and the anion.[26]

We investigated further to evaluate the influence of the counteranions on the catalyst's function. Previous observations indicated that substituting the carboxylate with a phosphate anion induces the functional change in the ion-pair molecular assembly **I**. The results detailed in Figure 3 (see also Table S6 within the Supporting Information) show how the syn to anti switch of the catalyst's diastereoselection seems to strongly depend on the hydrogen-bonding ability of the acid-anion. Indeed, phosphates are strong H-bond acceptors. (*S*)-**6** or

DPP can induce a catalyst conformational change, promoting an anti-selective reaction manifold. But when bulkier phosphates (which bind more weakly to the catalyst) are used, a syn-selective pathway for the SMA reaction is dominant. This is presumably because of the reduced binding ability of the anion, which cannot induce the catalyst conformational change.

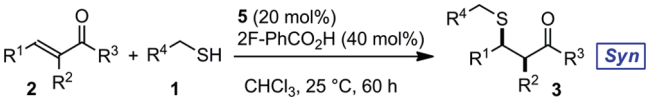
Together with the conformational flexibility of amine **5**, the use of structurally different counteranions provides distinct chiral environments in which the enantioselective SMA reaction can take place. This creates opportunities for designing a programmable organocatalyst with multiple stereochemical preferences.

We are aware that important information on the active catalytic species can be obtained by characterizing the covalent reactive intermediate, the iminium ion assembly **I** generated by condensation of the cinchona-based primary amine with the carbonyl compound. This would provide a more reliable picture of the mechanism. In general, however, the nature of the ion pairs in iminium-catalyzed reactions is poorly understood. Its characterization is a challenging and sought-after target for many practitioners of organocatalysis.[35,36] Our attempts to detect the covalent active intermediate **I** by CD and NMR spectroscopic studies have not produced important results to date.[37] Further extensive efforts are needed, combining spectroscopic and theoretical approaches to detect, analyze, and characterize the reactive intermediates involved in the catalysis. Investigations along these lines are underway in our laboratories.

Reaction Scope of the *syn*-SMA. Having identified the chemical stimuli (the acidic additive and the reaction medium) that allow us to tune the diastereoselectivity of catalyst **5**, we explored the substrate scope of the SMA reaction.

Table 3 summarizes the results obtained in the syn-selective sulfa-Michael addition/protonation sequence of α-branched enones

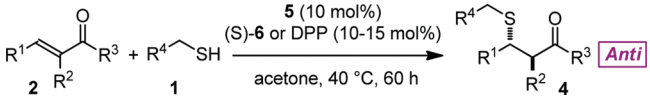
Table 3. Syn-Selective SMA of α-Branched Enones: Nucleophile and Electrophile Scope[a]



entry	R^1	R^2	R^3	R^4	3	yield (%)[b]	syn/anti	*ee* (%)
1	Me	Me	Me	Ph	**a**	68	5.1:1	86
2	4-NO_2-C_6H_4	Me	Me	Ph	**b**	79	5.1:1	88
3	4-NO_2-C_6H_4	Me	Me	Ph	**b**	50	3.5:1	77[c]
4	Ph	Me	Me	Ph	**c**	54	3.5:1	85
5	4-Br-C_6H_4	Me	Me	Ph	**d**	60	3.8:1	89
6	4-NO_2-C_6H_4	Et	Me	Ph	**e**	68	9.3:1	87
7	4-NO_2-C_6H_4	Me	Et	Ph	**f**	40	5.0:1	81
8	Et	Ph	Me	Ph	**g**	60	2.8:1	73
9	Me	Me	Me	4-MeO-C_6H_4	**h**	56	4.9:1	90
10	Me	Me	Me	4-Cl-C_6H_4	**i**	65	5.0:1	89
11	Me	Me	Me	CH=CH_2	**j**	60	7.8:1	87
12	Me	Me	Me	CO_2Et	**k**	68	5.5:1	61

[a] Reactions carried out using 3 equiv of **1** and $[\mathbf{2}]_0$= 0.5M. Results represent the average of two runs per substrate. For all the enones **2** used, *E*/*Z* ratio >95:5. *ee* value refers to the major *syn*-**3** compound. [b] Yield of the isolated product **3**. [c] Reaction performed at 15 °C over 5 days with catalyst **7**, leading to the opposite enantiomer: *syn*-(3*S*,4*R*)-**3b**.

Table 4. Anti-Selective SMA of α-Branched Enones: Nucleophile and Electrophile Scope[a]



entry	R^1	R^2	R^3	R^4	4	yield (%)	anti/syn	*ee* (%)
1	Me	Me	Me	Ph	**a**	80 (68)	6.2:1 (6.1:1)	98 (98)
2	Me	Me	Me	Ph	**a**	43 (66)	3.9:1 (3.0:1)	94 (94)[b]
3	4-NO_2-C_6H_4	Me	Me	Ph	**b**	77 (56)	5.7:1 (4.7:1)	99 (96)
4	4-NO_2-C_6H_4	Me	Me	Ph	**b**	48	2.8:1	97[b]
5	CH_2Bn	Me	Me	Ph	**c**	69	8.2:1	97
6	Ph	Me	Me	Ph	**d**	41 (44)	5.2:1 (5.1:1)	99 (95)
7	4-NO_2-C_6H_4	Et	Me	Ph	**e**	35	1.8:1	98
8	4-MeO-C_6H_4	Me	Me	Ph	**f**	42	4.2:1	99
9	4-Br-C_6H_4	Me	Me	Ph	**g**	59 (38)	6.5:1 (6.3:1)	99 (96)
10	4-Cl-C_6H_4	Me	Me	Ph	**h**	58 (59)	5.3:1 (5.3:1)	99 (98)
11	2-thiophenyl	Me	Me	Ph	**i**	44	4.2:1	98
12	CO_2Et	Me	Me	Ph	**j**	56	5.2:1	96
13	Me	Me	Me	4-MeOC_6H_4	**k**	42 (68)	7.1:1 (7.0:1)	98 (98)
14	Me	Me	Me	4-Cl-C_6H_4	**l**	58 (71)	7.2:1 (4.2:1)	94 (97)
15	Me	Me	Me	CH=CH_2	**m**	73	4.8:1	98
16	Me	Me	Me	CO_2Et	**n**	50 (65)	2.4:1 (2.0:1)	92 (83)

[a] Results in parentheses refer to the reactions catalyzed by the amine **5**/diphenyl phosphoric acid (DPP) combination. Reactions carried out using 2 equiv of **1** and $[\mathbf{2}]_0$ = 0.5 M. Results represent the average of two runs per substrate. For all the enones **2** used, *E*/*Z* ratio >95:5. When the β-substituent of enones **2** is an aromatic group, 15 mol % of the phosphoric acid (*S*)-**6** has been used. Other substrates perform better in the presence of 10 mol % of (*S*)-**6**. Ee value refers to the major *anti*-**4** compound. Yield of isolated product **4**. [b] Reaction performed with catalyst **7**, leading to the opposite enantiomer of *anti*-**4**.

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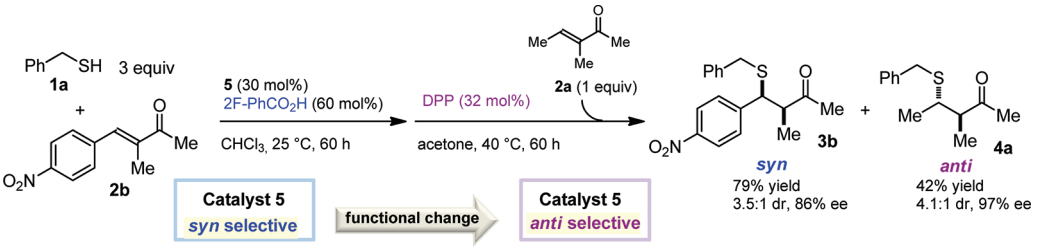

Figure 4. Switching diastereoselection in a single reaction flask and during the course of the reaction. The catalyst's syn preference is inactivated when the achiral phosphoric acid (DPP) is added to the reaction medium.[38]

using a combination of amine **5** (20 mol %) and *ortho*-fluorobenzoic acid (40 mol %) using chloroform as the reaction medium. The method shows a good-to-high level of diastereoselectivity and enantiocontrol over a wide substrate range. Both aliphatic and aromatic substituents at the β position are well-tolerated (entries 1−5).

The presence of a more sterically demanding group at the branched R^2 α-position or at the R^3 position does not influence the reactivity profile of the catalyst system: the corresponding syn-adducts **3e**−**g** are obtained in good chemical yield with a high level of stereocontrol (entries 6−8). Remarkably, a broad range of alkyl mercaptanes, containing either aromatic or vinyl moieties, can also be used in the syn-selective SMA reaction (entries 9−11). Moreover, a thioglycolate derivative is a suitable nucleophile (entry 12).

Reaction Scope of the anti-SMA. The anti-selective SMA protocol, induced by using the phosphoric acid (*S*)-**6** (10 mol %, 1:1 with the amine **5**) in acetone solvent, offers a wide substrate scope for both the electrophilic and nucleophilic components, affording the desired adducts **4** with synthetically useful diastereomeric ratios and excellent enantioselectivities (*ee* values ranging from 92% to 99%). The results reported in Table 4 demonstrate that a variety of substituents at the β position can be accommodated. Aromatics with diverse electronic properties (entries 1−11), as well as an ester group (entry 12), are tolerated. Moreover, using different alkyl thiols affords access to optically active chiral sulfur compounds bearing removable *S*-protecting groups (entries 13−16).[14] Importantly, using the achiral acid DPP in the anti-selective SMA reaction provided comparable results in terms of efficiency and stereoselectivity. These results are shown in parentheses in Table 4.

Switching Diastereoselection during the Course of the Reaction. We then wondered if it would be possible to switch the diastereoselectivity of catalyst **5** on demand during the course of the reaction and in the same reaction flask. Initially, we used a combination of **5** and *ortho*-fluorobenzoic acid to select the syn-directing pathway for the reaction between thiol **1a** and enone **2b** in chloroform, leading to the adduct *syn*-**3b** (Figure 4). Our challenge was then to switch the catalytic behavior of **5** after the syn-reaction reached completion. We reasoned that a stronger acid, namely the achiral phosphoric acid DPP, would reset the previous function, encoding the diastereo-switching information within the catalyst. The use of 1:1 molar ratio of phosphoric acid ($pK_a \approx 1.9$ in H_2O) to amine **5** likely leads to a quantitative association with the quinuclidine tertiary amine moiety, the most basic site of the catalyst, thus displacing *ortho*-fluorobenzoic acid ($pK_a = 3.27$ in H_2O) from the acid−base equilibrium with **5**.[38] Indeed, after we added DPP as the designer acid, acetone (2:1 ratio to the original chloroform), and a different enone substrate

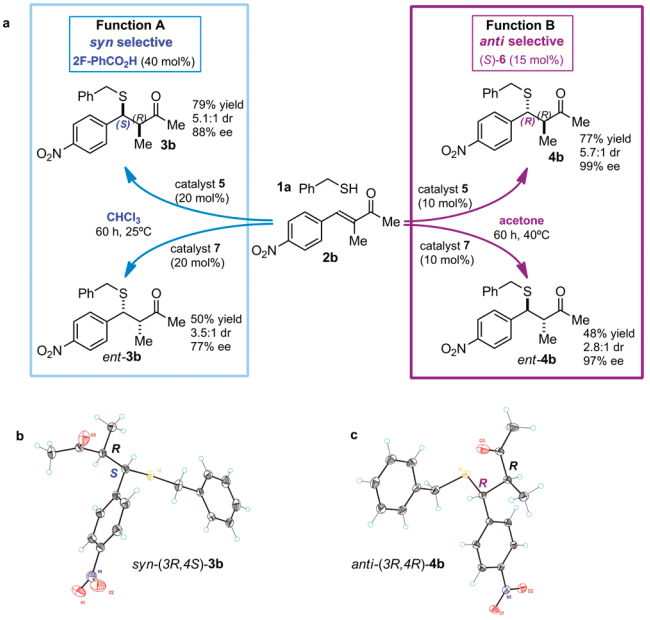

Figure 5. (a) Accessing the full matrix of the stereoisomers of the SMA reaction. (b) X-ray structure of *syn*-**3b**. (c) X-ray structure of *anti*-**4b**. ORTEP drawing at 50% probability.[39]

2a in the same flask, an anti-selective addition of thiol **1a** to **2a** proceeded to afford *anti*-**4a** with a high level of stereocontrol, testifying to the change in catalyst function. In this experiment, both syn and anti products were synthesized in the same reaction flask and using a single catalyst, and then individually isolated by chromatographic purification.

Achieving the Full Matrix of Possible Stereoisomeric Products of the SMA. Finally, the ability to selectively channel the reaction manifolds toward complementary diastereochemical outcomes using a single chiral catalyst[27] was exploited to access the full matrix of possible stereoisomeric products of the SMA reaction (Figure 5a). When carried out in chloroform, the *ortho*-fluorobenzoic acid/catalyst **5** combination induced a syn selective outcome of the SMA of **1a** to enone **2b** (bearing an aryl β-substituent). In acetone, the phosphoric acid (*S*)-**6** switched the catalyst's induction toward anti-selectivity. The same designer acid-induced diastereo-switching behavior was observed with the quasi-enantiomeric catalyst **7**,[27] derived from quinine, thus allowing access to the full matrix of possible stereoisomeric products of the SMA reaction.

The relative and absolute configurations of the syn and anti products **3b** and **4b** were unambiguously determined by anomalous dispersion X-ray diffraction analysis (Figure 5b and 5c).[39]

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The opposite absolute configuration at the β carbon−sulfur stereogenic center is further evidence of how the catalyst functional switch drastically influences the stereochemical outcome of the reaction. As the conjugate addition step (in contrast to the protonation step) must be under the stereocontrol of the catalyst, this evidence highlights the uncommon potential of the chiral amine **5** to catalyze two enantio-, as well as diastereodivergent, SMA reactions when properly influenced by external stimuli (appropriate acid and solvent).[40]

CONCLUSION

We have documented the possibility of using a single chiral catalyst to fully control the stereochemical outcome of the asymmetric conjugate addition of alkyl thiols to α,β-disubstituted unsaturated ketones, an elusive class of Michael acceptors. The judicious choice of a designer acidic additive and the reaction medium switches the sense of the catalyst's diastereoselection, establishing a direct connection between the enantioselective catalyst and the operator (the chemist). We are currently undertaking further mechanistic investigations to fully understand the origin of the diastereoswitching behavior. We believe that programming the catalytic function of a catalyst using an external chemical stimulus may provide new synthetic opportunities and conceptual perspectives for successfully attacking major challenges connected with the preparation of chiral molecules that cannot be addressed by traditional approaches. We are currently seeking to develop chiral catalysts that allow for reversible function-switching.

ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures, optimization studies, compound characterization, VCD, CD, and NMR conformational analyses, HPLC traces, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
pmelchiorre@iciq.es

Author Contributions
X.T. and C.C. contributed equally to this work.

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(17) Amine **5** is characterized by a dichotomous catalytic behavior. This organic molecule can execute its catalytic functions using both covalent and noncovalent-based organocatalysis. The result obtained when using amine **5** as a general base activator (entry 3, Table 1) suggested that a chiral molecule, which can use completely distinct modes of substrate activation (in this case, covalent and noncovalent catalysis), could provide an appropriate strategy for inducing mechanistically unrelated and (dia)stereodivergent reaction pathways. It is a remarkable coincidence that the free base catalyst **5** (a general base catalyst) gives rise to similar selectivity with respect to the **5**/*ortho*-fluorobenzoic acid system (operating under iminium activation, compare entries 3 and 8 in Table 1).

(18) General base catalysis is inhibited when an acidic additive is present. A natural cinchona alkaloid, such as quinidine, is an active yet nonselective catalyst for the SMA reaction (operating via general base catalysis). However, the addition of benzoic acid resulted in a completely inactive system. See Figure S2 within the Supporting Information for more details.

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(37) During the CD spectroscopic studies on the two catalytic salts (detailed in the Supporting Information) we tried to detect the iminium ion formation after addition of a large excess of an aliphatic α-branched enone. This attempt, however, did not produce any appreciable change in the CD spectra. Moreover, it was not possible to detect the covalent intermediate by NMR spectroscopy.

(38) A control experiment (Supporting Information Figure S6) revealed that catalyst **5** (20 mol%), when mixed with 40 mol% of *ortho*-fluorobenzoic acid and 20 mol% of **6** in acetone, is programmed for an anti-directing function. Indeed, the reaction between **1a** and **2a** afforded the anti adduct **4a** with 4.6:1 dr and 97% ee_{anti}. As reported in Supporting Information Figure S5, the chiral acid (*S*)-**6** can also be used to switch the diastereoselectivity of catalyst **5** during the course of the reaction, in a similar experiment to that detailed in Figure 4.

(39) Crystallographic data for compounds **3b** and **4b** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 804889 and CCDC 804888, respectively.

(40) The fact that the products are not diastereomeric at the α but at the β carbon (the site of the initial nucleophilic attack) is rather intriguing. This inspired us to carefully consider an alternative explanation for the observed stereochemical outcome, specifically that the switch of the catalyst functions is connected with completely unrelated mechanisms of catalysis. In ref 17, we have already commented on the potential of amine **5** to use completely distinct modes of catalysis for activating the reagents of the SMA reaction and, more importantly, on the possibility of controlling its catalytic functions by applying an external stimulus: indeed, an acidic additive could be used to modulate the catalyst behavior by switching the catalytic potential from base catalysis (activation of the thiol) to iminium activation of the enone. However, as commented in ref 18, a general base catalysis mechanism under acidic conditions (in the presence of the 2-F-benzoic acid) is not very plausible. At the present stage of investigation, we consider that the more plausible mechanistic picture is the one described within the main text, where the same general mechanism (iminium activation) is operative in the two stereodivergent chemical pathways.