Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2020, **11**, 3852

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H-bond donor-directed switching of diastereoselectivity in the Michael addition of α-azido ketones to nitroolefins†

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The development of catalyst-controlled stereodivergent asymmetric catalysis is important for providing facile access to all stereoisomers of chiral products with multiple stereocenters from the same starting materials. Despite progress, new design strategies for diastereodivergent asymmetric catalysis are still highly desirable. Here we report the potency of H-bond donors as the governing factor to tune diastereoselectivity in a highly diastereoselective switchable enantioselective Michael addition of α-azido ketones to nitroolefins. While a newly developed bifunctional tertiary amine, phosphoramide, preferentially afforded *syn*-adducts, an analogous squaramide catalyst selectively gave *anti*-adducts. The resulting multifunctional tertiary azides can be converted to spiro-pyrrolidines with four continuous stereocenters in a one-pot operation. Mechanistic studies cast light on the control of diastereoselectivity by H-bond donors. While the squaramide-catalyzed reaction proceeded with a transition state with both squaramide N–H bonds binding to an enolate intermediate, an unprecedented model was proposed for the phosphoramide-mediated reaction wherein an amide N–H bond and an alkylammonium ion formed *in situ* interact with nitroolefins, with the enolate stabilized by nonclassical C–H···O hydrogen-bonding interactions.

Received 26th January 2020
Accepted 11th March 2020

DOI: 10.1039/d0sc00475h

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Introduction

Chiral molecules with multiple stereocenters in principle exist as enantiomeric pairs of diastereomers.[1] It is important to access all the possible stereoisomers because the absolute and relative configurations often influence their properties such as bioactivity.[2] However, the synthesis of a single diastereomer and enantiomer is inherently favored in most catalytic enantioselective reactions forming multiple stereocenters.[3] Developing catalyst-controlled stereodivergent processes to access all the possible stereoisomers from the same starting materials is challenging.[4] Despite the progress made by varying the reaction conditions[5] or chiral catalysts[6,7] or by dual catalysis,[8] new strategies to realize diastereodivergent asymmetric catalysis (DAC) are still highly sought after.

By contrast, while H-bond donor-containing bifunctional catalysts have found wide application,[9] controlling the diastereoselectivity simply by varying the H-bond donor of such a catalyst is largely unexplored.[10] For bifunctional tertiary amine catalysis, theoretical studies have proposed three types of working models that differ in how H-bond donors of the catalysts interact with the nucleophile and electrophile (Scheme 1A).[11–15] The ion pair-hydrogen bonding model (type A) was initially proposed by Wynberg[11a] and supported by theoretical studies by Cucinotta and Gervasio.[11b] The Brønsted acid-hydrogen bonding model (type B) was revealed by Houk *et al. via* quantum mechanical calculations.[12] The type A model differs from type B in that the H-bond donor of the catalyst is used to activate the electrophile and to stabilize the nucleophilic intermediate, respectively, with the simultaneously formed alkylammonium ion acting as a Brønsted acid to interact with the rest of the nucleophiles or electrophiles, respectively.

When dual H-bond donors such as (thio)urea are involved, the reaction may proceed *via* a transition state of the type A model with both N–H bonds interacting with the electrophile, as suggested by Takemoto *via* experimental studies[13a] and supported by theoretical studies,[13b–d] or *via* model B with both

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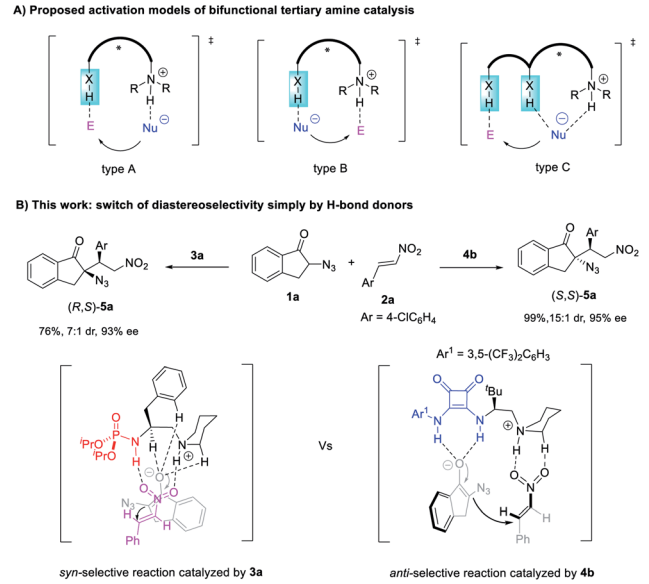
† Electronic supplementary information (ESI) available: Experimental procedure and characterization data. CCDC 1874277–1874279, 1874281 and 1874283. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc00475h



Scheme 1 DAC enabled by H-bond donors.

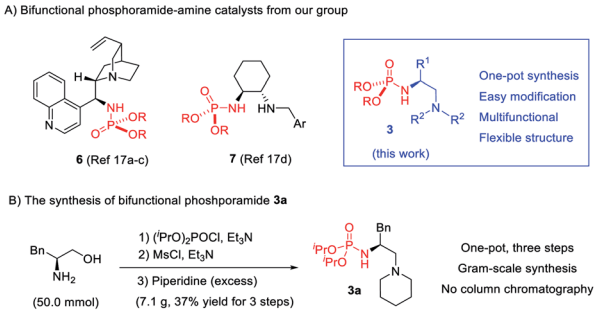
N–H bonds binding to nucleophiles, as revealed by the theoretical calculation by Pápai[14a,b] and Houk.[14c] A more complicated model (type C) was also proposed by Wang *et al.*, with the synergistic action of alkylammonium ions and one N–H bond of (thio)urea on the nucleophile.[15]

Based on these mechanistic insights, we speculate that it is possible to control the diastereoselectivity simply by altering the H-bond donors because they differ greatly from each other in terms of the structure and number of X–H bonds. The interplay of different H-bond donors with alkylammonium ions may create distinct chiral pockets capable of controlling the relative spatial position of both reaction partners to accomplish a diastereodivergent bond-forming process. Here we report the successful reversal of diastereoselectivity in an unprecedented Michael addition of α-azido indanones to nitroolefins catalyzed by bifunctional tertiary amines, simply by varying the H-bond donor of the catalyst from phosphoramide to squaramide (Scheme 1B).

Results and discussion

Catalyst preparation

During our efforts to construct a fully substituted carbon stereocenter by bifunctional tertiary amine catalysis,[16] we initiated a plan to develop phosphoramide-based bifunctional catalysts. This is because phosphoramide is seldom present in chiral ligands or organocatalysts, even though it is a unique single H-bond donor featuring two amide substituents as the shielding group. We have developed two phosphoramide-amine catalysts **6**[17a–c] and **7**[17d] (Scheme 2), which can achieve better enantioselectivity than their analogues with other H-bond donors such as amides, sulfonamides, (thio)urea, and squaramide in two distinct Michael addition reactions, respectively. Inspired by these results, we hope to take advantage of the structural



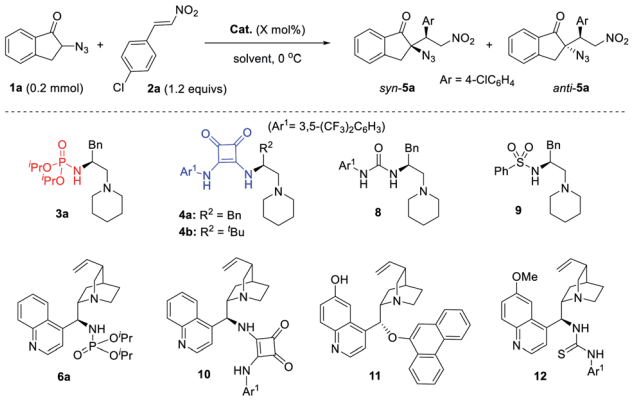
Scheme 2 Bifunctional phosphoramide-amine catalysts.

differences between phosphoramide and another H-bond donor to develop diastereodivergent reactions.

A new phosphoramide-tertiary amine catalyst **3** with a flexible acyclic structure is then developed, the three substituents (R, R^1, and R^2) of which can be modified to improve the stereoselectivity. Given the sufficient structural differences, phosphoramide and the alkylammonium ion formed *in situ* may organize the reaction partners in an orientation substantially different from that effected by another H-bond donor, leading to reversal of diastereoselectivity. Notably, since phosphoramide can serve as an *N*-protecting group, the synthesis of **3** is extremely easy, a simple one-pot three-step operation without column chromatography purification, as exemplified by the access of **3a** in 37% overall yield from (*S*)-phenylalaninol (for details, see the ESI†). The corresponding bifunctional squaramide **4**, urea **8**, and sulfonamide **9** are known catalysts.[18]

Recently, the deprotonative activation of α-azido carbonyl compounds emerged as a fruitful approach for catalytic asymmetric synthesis of α-chiral azides.[19] However, despite achievements, including an elegant diastereodivergent asymmetric aldol reaction of α-azido 7-azaindoline acetamides and *ortho*-substituted benzaldehydes developed by Shibasaki *et al.*,[20] this method has not been applied in the diastereodivergent synthesis of chiral tertiary azides. This lack of application is possibly because, upon treating with a base, α-azido carbonyl compounds may undergo decomposition.[21] In the construction of tetrasubstituted carbon stereocenters, the reactivity is generally lower than that of tertiary ones,[22] so this side reaction may compete with the desired asymmetric reaction. In view of this challenge, along with some successful DAC based on indanone derivatives and nitroolefins,[23] we consider exploiting an unprecedented Michael reaction of α-azido ketones **1** and nitroolefin **2** to test the idea of varying the H-bond donor of bifunctional tertiary amines to alter the diastereoselectivity (Table 1). We speculate that the simultaneous activation of both α-azido indanones and nitroolefins by bifunctional tertiary amines should facilitate the desired Michael addition, while minimizing unwanted side reactions. It should be noted that protocols for the catalytic enantioselective synthesis of chiral tertiary azides are still limited.[24] This new reaction would provide facile access to multifunctional chiral tertiary azides **5** of high synthetic value.

Table 1 Influence of the catalyst structure



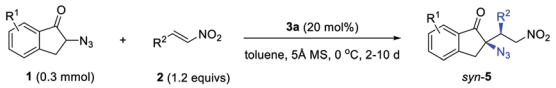
Entry	Cat.	X (mol%)	Solvent	Time (d)	Yield[a] (%)	*syn* : *anti*[b]	ee[c] (%)
1[d]	DABCO	20	DCM	2	45	1 : 1.2	—
2	**3a**	20	Toluene	4	80	5.4 : 1	88
3[e]	**3a**	20	Toluene	7	76	7.0 : 1	93
4	**4a**	20	Toluene	4	80	1 : 11	56
5[f]	**4a**	5	DCE	2	95	1 : 24	70
6[f]	**4b**	5	DCE	2	90	1 : 15	95
7	**8**	20	Toluene	4	52	3.9 : 1	72
8	**9**	20	Toluene	4	51	3.5 : 1	73
9	**6a**	20	Toluene	4	33	1.6 : 1	56
10	**10**	20	Toluene	4	79	1 : 5.2	63
11	**11**	20	Toluene	1	89	1 : 3.0	61
12	**12**	20	Toluene	1	63	1.2 : 1	84

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis. [d] Room temperature. [e] 0.3 mmol, with 90 mg powdered 5 Å MS, [**1a**] = 0.3 M. [f] [**1a**] = 0.1 M. [**1a**] = 0.2 M without noted. DCM: CH_2Cl_2. DCE : CH_2ClCH_2Cl.

Gratifyingly, the switching of diastereoselectivity of the Michael addition of **1a** to **2a** is indeed observed by varying the H-bond donor of the bifunctional amine catalysts. The model addition reaction of **1a** to **2a** was performed at 0 °C, to minimize the decomposition of α-azido indanone **1a** in the presence of a basic catalyst[21] because the racemic version mediated by 1,4-diaza[2.2.2]bicyclooctane (DABCO) gave *anti*-**5a** in 1.2 : 1 dr and around 45% yield, with a substantial amount of side products (entry 1, Table 1). The poor dr also suggested trivial substrate bias[4i,7g] in the diastereoselectivity of this reaction. To our delight, phosphoramide catalyst **3a** gave *syn*-**5a** in 88% ee and 5.4 : 1 dr (entry 2). The addition of MS 5 Å improved the result to 93% ee and 7.0 : 1 dr (entry 3). When replacing the phosphoramide with a squaramide, the resulting catalyst **4a** afforded *anti*-**5a** in 11 : 1 dr (entry 4) and up to 24 : 1 dr with 70% ee by varying the solvent from toluene to DCE (entry 5). This result unambiguously shows the possibility of tuning diastereoselectivity simply by altering the H-bond donor in bifunctional tertiary amine-catalyzed reactions. Further studies revealed that squaramide catalyst **4** was more active, and the catalyst loading could be decreased to 5 mol% (entry 5). The use of 5 mol% *tert*-butyl-substituted squaramide **4b** allowed the reaction to work well in DCE, affording *anti*-**5a** in up to 15 : 1 dr and 95% ee (entry 6). Bifunctional catalysts **8** and **9** bearing urea or sulfonamide as the H-bond donor were also examined and gave *syn*-**5a** as the major product, albeit with inferior results (entries 7 and 8 *vs.* 2). To examine the role of the catalyst skeleton in switching the diastereoselectivity, the cinchona alkaloid-derived phosphoramide **6a** and squaramide **10** were also used. Again, a reversal of diastereoselectivity was observed (entry 9 *vs.* 10), although the dr values were less effective than those obtained by using catalysts **3a** and **4b** (entries 2 and 6). This further supports that phosphoramide and squaramide are mainly responsible for this diastereodivergent reaction but that the catalyst structure also has an impact. Furthermore, catalysts **11** and **12** used by Deng to develop diastereodivergent Michael addition of α-cyanoindanone to 2-chloroacrylonitrile[10] proved to be less effective in the control of diastereoselectivity (entries 11 *vs.* 12). These results justified the necessity of developing new bifunctional tertiary amines for stereodivergent asymmetric catalysis.

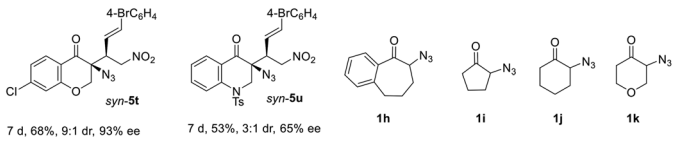
In the following, the scope of bifunctional phosphoramide **3a** mediated *syn*-selective Michael addition reactions was evaluated. All reactions were carried out in toluene at 0 °C, in the presence of 20 mol% **3a** and powdered MS 5 Å, as shown in Table 2. A broad range of nitroolefins **2a–g** with different β-aryl substituents all gave the desired *syn*-**5a–g** in 73–85% yield and with 7 : 1 to 10 : 1 dr values, with 93–96% ee (entries 1–7, Table

Table 2 Scope of *syn*-selective Michael addition



1a: R^1 = H, **1b:** R^1 = 4-Br, **1c:** R^1 = 5-Cl, **1d:** R^1 = 6-Br, **1e:** R^1 = 6-Me

Entry	1	2: R^2	Time (d)	*syn*-5	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**	**2a:** 4-ClC_6H_4	7	*syn*-**5a**	76	7 : 1	93
2	**1a**	**2b:** 3-ClC_6H_4	8	*syn*-**5b**	79	7 : 1	93
3	**1a**	**2c:** 2-FC_6H_4	7	*syn*-**5c**	73	9 : 1	95
4	**1a**	**2d:** Ph	9	*syn*-**5d**	85	9 : 1	96
5	**1a**	**2e:** 4-MeC_6H_4	10	*syn*-**5e**	79	9 : 1	96
6	**1a**	**2f:** 2-naphthyl	7	*syn*-**5f**	81	8 : 1	93
7	**1a**	**2g:** 2-thienyl	7	*syn*-**5g**	85	10 : 1	96
8	**1a**	**2h:** (*E*)-PhCH=CH	8	*syn*-**5h**	76	15 : 1	94
9	**1a**	**2i:** (*E*)-4-BrC_6H_4CH=CH	5	*syn*-**5i**	70	13 : 1	93
10	**1a**	**2j:** (*E*)-3-FC_6H_4CH=CH	6	*syn*-**5j**	68	12 : 1	92
11	**1a**	**2k:** (*E*)-2-FC_6H_4CH=CH	8	*syn*-**5k**	81	12 : 1	94
12	**1a**	**2l:** (*E*)-2-MeC_6H_4CH=CH	9	*syn*-**5l**	80	13 : 1	94
13[d]	**1b**	**2h:** (*E*)-PhCH=CH	4	*syn*-**5m**	88	12 : 1	90
14	**1c**	**2h:** (*E*)-PhCH=CH	2	*syn*-**5n**	79	12 : 1	88
15[d]	**1d**	**2h:** (*E*)-PhCH=CH	4	*syn*-**5o**	72	13 : 1	93
16	**1e**	**2h:** (*E*)-PhCH=CH	8	*syn*-**5p**	69	14 : 1	95
17[e]	**1c**	**2m:** CF_3	3	*syn*-**5q**	75	3 : 1	90
18[e]	**1d**	**2m:** CF_3	2	*syn*-**5r**	76	4 : 1	92
19[e]	**1d**	**2n:** CF_2H	6	*syn*-**5s**	52	2 : 1	87



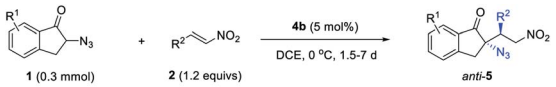
[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis. [d] −20 °C. [e] 5 Å MS was replaced by 20 mol% $K_2HPO_4 \cdot 3H_2O$.

2). β-Alkenyl nitroolefins **2h–l** furnished adducts *syn*-**5h–l** in >12 : 1 dr and 92–94% ee (entries 8–12). Differently substituted α-azido indanones **1b–e** also worked well to give *syn*-**5m–p** with high dr and ee values (entries 13–16). The relative and absolute configurations of *syn*-**5k** were assigned by single-crystal X-ray diffraction analysis (see the ESI†). Notably, β-CF_3 or CF_2H nitroolefins **2m–n**[25] are also viable substrates, affording fluorinated azides *syn*-**5q–s** with high to excellent ee values, albeit in moderate dr (entries 17–19). Their reactivity appeared to be lower than that of β-aryl olefins, but the addition of 20 mol% $K_2HPO_4 \cdot 3H_2O$ facilitated the reaction.[26] In addition, α-azido chromanone **1f** was a viable substrate giving *syn*-**5t** in 9 : 1 dr and 93% ee. α-Azido 2,3-dihydroquinolinone **1g** could also work, but the desired product *syn*-**5u** was obtained in only 3 : 1 dr and 65% ee. However, α-azido benzosuberone **1h** and cyclic ketones **1i–k** failed to react with nitroolefin **2i**.

The scope of the *anti*-selective Michael addition was examined by running the reaction in DCE at 0 °C, under the catalysis of 5 mol% squaramide **4b**. As shown in Table 3, β-aryl nitroolefins **2a–g** worked well with indanone **1a** to give the desired *anti*-**5a–g** in 90–99% yield, 8 : 1 to 25 : 1 dr and 91–97% ee (entries 1–7). Unexpectedly, β-alkenyl nitroolefins were less active under these conditions. For example, it took 10 mol% catalyst **4b** to mediate the reaction of **2h** and **1a**, affording *anti*-**5h** in a diminished 6 : 1 dr with 90% ee (entry 8). Different α-azido indanones **1b–e** reacted smoothly with nitroolefin **2a** to deliver *anti*-**5v–y** in 86–99% yield, 10 : 1 to 30 : 1 dr, and 93–96% ee (entries 9–12). The relative and absolute configurations of product *anti*-**5g** were assigned by X-ray diffraction analysis (see the ESI†). The reversal of diastereoselectivity was also achieved when β-CF_3 or CF_2H nitroethylene **2m–n** was used, affording the desired trifluoromethylated *anti*-**5q–r** or difluoromethylated *anti*-**5s** in 88–93% yield, 7 : 1 to 19 : 1 dr and 94% ee (entries 13–15). These results constitute a rare example of diastereodivergent asymmetric trifluoro- and difluoromethylation reactions.[6f,27] Considering the importance of molecules bearing a CF_3 or CF_2H group at the chiral center for medicinal research,[28,29] this protocol may be potentially useful for drug discovery.

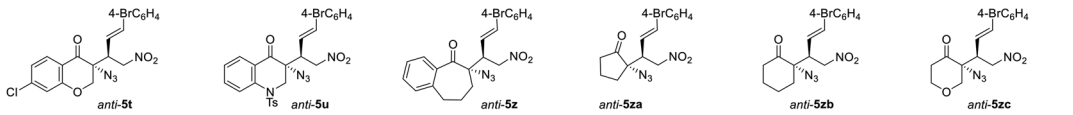
To our delight, owing to the higher activity of the squaramide catalyst, four other types of α-azido ketones readily underwent the desired *anti*-selective addition reaction. α-Azido chromanone **1f** gave product *anti*-**5t** in 18 : 1 dr and 84% ee, and α-azido 2,3-dihydroquinolinone **1g** furnished *anti*-**5u** in 4 : 1 dr and 91% ee. Notably, α-azido benzosuberone **1h** and cyclic

Table 3 Scope of *anti*-selective Michael addition



1a: R^1 = H, **1b:** R^1 = 4-Br, **1c:** R^1 = 5-Cl, **1d:** R^1 = 6-Br, **1e:** R^1 = 6-Me

Entry	1	2: R^2	*T* (d)	*anti*-5	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**	**2a:** 4-ClC_6H_4	2.5	*anti*-**5a**	99	15 : 1	95
2	**1a**	**2b:** 3-ClC_6H_4	2.5	*anti*-**5b**	99	14 : 1	95
3	**1a**	**2c:** 2-FC_6H_4	3	*anti*-**5c**	95	8 : 1	91
4	**1a**	**2d:** Ph	5	*anti*-**5d**	90	20 : 1	96
5	**1a**	**2e:** 4-MeC_6H_4	5	*anti*-**5e**	91	25 : 1	95
6	**1a**	**2f:** 2-naphthyl	5	*anti*-**5f**	99	22 : 1	95
7	**1a**	**2g:** 2-thienyl	5	*anti*-**5g**	97	20 : 1	97
8[d]	**1a**	**2h:** (*E*)-PhCH=CH	5	*anti*-**5h**	78	6 : 1	90
9	**1b**	**2a:** 4-ClC_6H_4	1.5	*anti*-**5v**	89	10 : 1	93
10	**1c**	**2a:** 4-ClC_6H_4	3	*anti*-**5w**	86	17 : 1	95
11	**1d**	**2a:** 4-ClC_6H_4	2	*anti*-**5x**	91	30 : 1	96
12	**1e**	**2a:** 4-ClC_6H_4	4	*anti*-**5y**	99	14 : 1	94
13[e]	**1c**	**2m:** CF_3	3.5	*anti*-**5q**	88	11 : 1	94
14[f]	**1d**	**2m:** CF_3	3.5	*anti*-**5r**	91	19 : 1	94
15[e]	**1d**	**2n:** CF_2H	3	*anti*-**5s**	93	7 : 1	94



7 d, 76%, 18:1 dr, 84% ee[d] | 7 d, 58%, 4:1 dr, 91% ee[g] | 7 d, 70%, 15:1 dr, 95% ee[e] | 2 d, 93%, >50:1 dr, 98% ee[d] | 4 d, 36%, >50:1 dr, 91% ee[d] | 2 d, 58%, >50:1 dr, 96% ee[d]

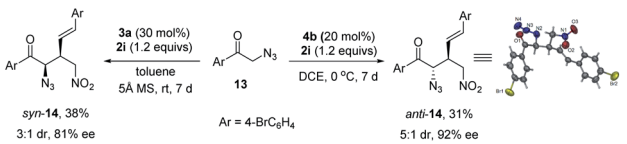
[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by HPLC analysis. [d] 10 mol% **4b**. [e] 20 mol% **4b** and 20 mol% $K_2HPO_4 \cdot 3H_2O$. [f] 10 mol% **4b** and 10 mol% $K_2HPO_4 \cdot 3H_2O$. [g] 20 mol% **4b**.

ketones **1i–k** readily afforded the corresponding tertiary azides *anti*-**5z** and *anti*-**5za–zc** in 15 : 1 to >50 : 1 dr and 91–98% ee.

This stereodivergent protocol could be extended to acyclic α-azido ketones (Scheme 3), as exemplified by the reversal of diastereoselectivity of the reaction of α-azido acetophenone **13** with nitroolefin **2i**. The *syn*-**14** was obtained in 3 : 1 dr and 81% ee by using phosphoramide **3a** as the catalyst, whilst *anti*-**14** was furnished in 5 : 1 dr and 92% ee under the catalysis of squaramide **4b**. Nevertheless, due to the low activity of α-azido acetophenone, the reaction conversion is low in both cases. The relative and absolute configurations of product *anti*-**14** were assigned by X-ray diffraction analysis (see the ESI†).

Product elaboration

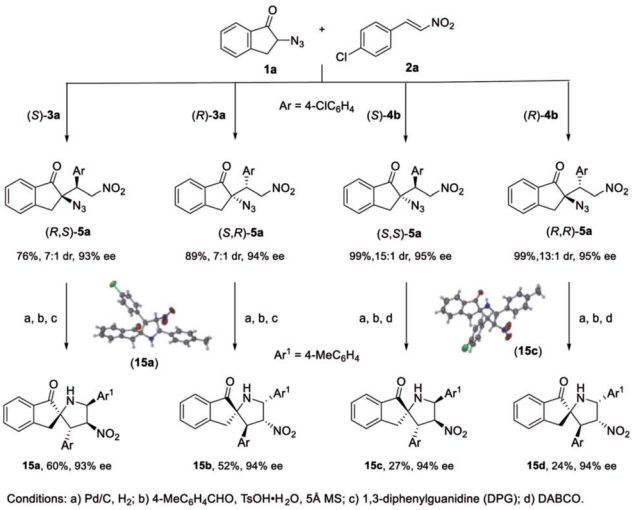
These multifunctional tertiary azides **5** are versatile synthons for aza-spirocycles. For example, by using both enantiomers of catalysts **3a** and **4b**, diastereodivergent asymmetric synthesis of four possible stereoisomers of **5a** was achieved with high yield, dr value, and >90% ee (Scheme 4). They can be converted to the four stereoisomers of spirocycle **15** with acceptable overall yield by a one-pot three-step operation. Structurally diverse spirocycles are privileged scaffolds in natural products, drugs, and bioactive compounds. The thus obtained spiro-pyrrolidines **15** with four continuous stereocenters are of interest for medicinal research, and their synthesis *via* asymmetric [3+2] cycloaddition of nitroolefins and azomethine ylides is unknown.[30] In addition, the skeleton **15** may be used for developing new chiral ligands or organocatalysts.[31]



Scheme 3 DAC reaction of acyclic α-azido ketones.

Mechanistic studies

The reversal of diastereoselectivity simply by varying the H-bond donor of bifunctional tertiary amines is intriguing. Accordingly, mechanistic investigations were conducted. First, to confirm the importance of bifunctional tertiary amine catalysis, the corresponding *N*-methylated catalyst **3b** and phosphoramide **3f** were subjected to the reaction of **1a** and **2a** (Scheme 5). Without free N–H bonds, tertiary amine **3b** exhibited very poor catalytic properties, and monofunctional phosphoramide **3f** was almost inert. This confirmed that both the phosphoramide N–H bond and tertiary amine were crucial for the *syn*-selective Michael addition. In the case of squaramide catalyst **4b**, its two N–H bonds seemed to have different roles in controlling the



Scheme 4 Synthesis of all stereoisomers of **5a** and their conversion to spiro-pyrrolidines **15**.

stereoselectivity, and both were indispensable for the observed reactivity. While the squaramide catalyst **4b** afforded *anti*-**5a** in a high 15 : 1 dr, the shielding of the C3 N–H bond of **4b** by a methyl group led to the reversal of diastereoselectivity because the corresponding **4c** gave *syn*-**5a** in 5.4 : 1 dr, identical to that obtained using phosphoramide **3a**. This finding further supported our idea of controlling the diastereoselectivity by varying the structure of H-bond donors. By contrast, with the methylated C4 N–H bond, catalyst **4d** furnished *anti*-**5a** in a poor 1.4 : 1 dr and 41% ee, much lower than that obtained by squaramide **4b**, suggesting that the C4 N–H bond is important for achieving high *anti* selectivity and enantioselectivity.

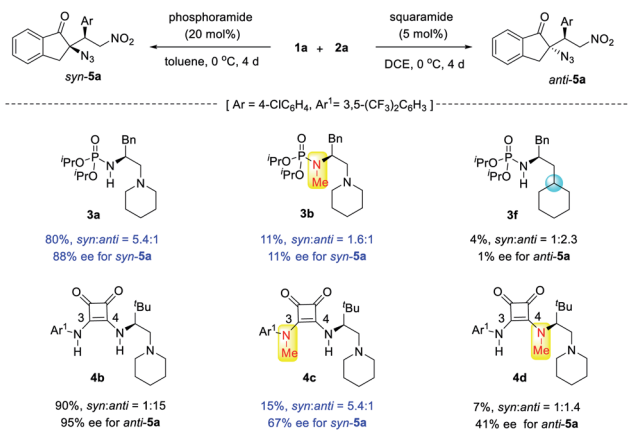
Next, whether nonlinear effects (NLE) were operative in the reaction course was also studied to gain further insight into the behavior of bifunctional tertiary amines.

When the reaction of **1a** and **2a** was conducted with 20 mol% catalyst **3a** prepared with reduced enantiomeric excess, a linear relationship between the catalyst ee value and that of the product *syn*-**5a** was observed (Fig. 1), suggesting a monomeric catalytic species.[32] If the linear relationship was not followed, the association of chiral phosphoramide **3a** might be expected to produce a diastereomeric active species. Unfortunately, the study of the NLE of squaramide **4b**-mediated *anti*-selective reaction failed due to the poor solubility of **4b** in DCE.

To probe the possible mechanism for this DAC, NMR analysis was also carried out (for details, see Section 7 of the ESI†). However, although phosphoramide catalyst **3a** could form H-bonding interactions with α-azido indanone **1a** and nitroolefin **2e**, no useful information about the catalyst-substrate recognition model of the transition state was obtained. In addition, the NMR analysis of squaramide **4b**-mediated reaction failed, due to its extremely poor solubility in CD_2Cl_2 or toluene-d_8. Therefore, theoretical studies were carried out to cast light on the mechanism of the above *syn*- and *anti*-selective Michael reactions, and computed transition state (TS) structures stabilized by different H-bonding interactions are shown below (for details, see the ESI†).

The optimized model for the phosphoramide **3a**-catalyzed reaction of **1a** and **2d**, **TSI2A**, is characterized by the double H-bonding interactions between nitroolefin **2d** with the phosphoramide N–H bond and the in situ-generated alkylammonium ion, as well as three kinds of nonclassical C–H···O hydrogen-bonding interactions[33] between the oxygen anion of enolate derived from **1a** with the N^+–C–H of the quininium ion,[34] the C–H bond of the phenyl ring,[35] and the α-H of the amide nitrogen.[36] The relatively short H···O distances observed for the three kinds of C–H···O contacts were 2.29, 2.31 and 2.25 Å, respectively, obviously shorter than the sum of van der Waals radii of an oxygen atom (1.5 Å) and a carbon-bonded hydrogen (~1.2 Å).[34a] These important H-bonding interactions stabilized the TS and directed the *Re* face nucleophilic addition of enolate to the *Si* face of nitroolefin to give the *syn*-adduct (Fig. 2).

Notably, this model is unprecedented in the literature because the electrophile interacts with both the H-bond donor and alkylammonium ion, whilst the enolate is stabilized by the nonclassical C–H···O hydrogen-bonding interactions. This is distinct from the three models shown in Scheme 1A. The alternative model of double H-bonding interactions with the enolate intermediate (**TSI2B**), type B Brønsted acid-hydrogen bonding model (**TSI2C**), and type A ion pair-hydrogen bonding model (**TSI2D**) are higher in free energy by 2.3, 2.1 and 5.4 kcal mol^{-1}, respectively. This is possibly because the



Scheme 5 Control experiments.

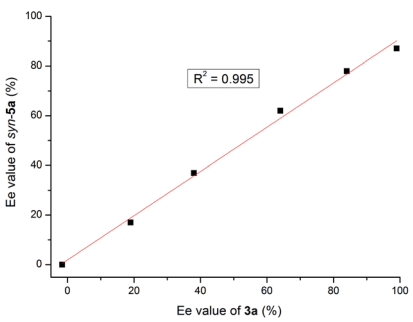


Fig. 1 Result of the nonlinear experiment of **3a** with *syn*-**5a**.

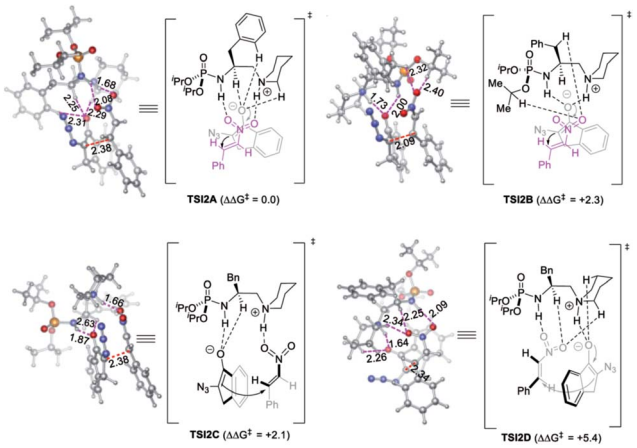


Fig. 2 The optimized structures for TS modes of phosphoramide **3a**-catalyzed α-azido indanone **1a** and nitroolefin **2d**. The relative Gibbs free energies are in kcal mol^{-1}, which were calculated at the IEFPCM-M06-2X-D3/6-311++G(d,p)//IEFPCM-M06-2X/6-31G(d,p) level. The bond distances are given in Å.

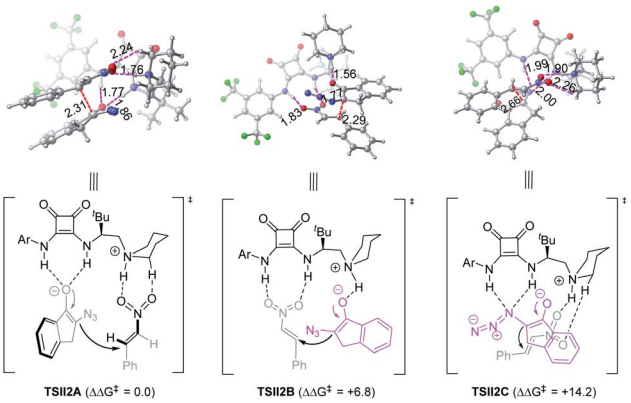


Fig. 3 The optimized structures for TS modes of squaramide **4b**-catalyzed α-azido indanone **1a** and nitroolefin **2d**. The relative Gibbs free energies are in kcal mol^{-1}, which were calculated at the IEFPCM-M06-2X-D3/6-311++G(d,p)//IEFPCM-M06-2X/6-31G(d,p) level. The bond distances are given in Å.

strong steric repulsion of the two isopropoxy groups of the phosphoramide prevents the formation of H-bonding interaction of the enolate with either the phosphoramide or the alkylammonium ion. This model to some extent agreed with the observation that the NMR analysis of the mixture of **3a**, **1a**, and **2e** showed a significantly bigger change in the chemical shift of the phosphoramide N–H bond than that by mixing of **3a** with either **1a** or **2e** (g *vs.* e and f, Fig. S2†). This finding further suggests that it is interesting to employ phosphoramide, the only single H-bond donor bearing two amide shielding groups, to develop new chiral ligands or organocatalysts.

On the other hand, the chiral squaramide **4b**-catalyzed reaction proceeded *via* a typical Brønsted acid-hydrogen bonding model (**TSII2A**, Fig. 3): both N–H bonds of the squaramide interacted with α-azido enolate *via* H-bonding interactions, with a simultaneously generated ammonium moiety bound to nitroolefin, leading to a favorable transition state that enabled the *Si* face nucleophilic attack of α-azido enolate to the *Si* face of nitroolefin to afford the *anti*-product. This working model could also reasonably explain why *N*-methylated squaramide **4c** gave *syn*-adduct **5** as the major diastereomer (Scheme 5), because the lack of a C3 N–H bond made it impossible for squaramide **4c** to form the calculated Brønsted acid-hydrogen bonding model in the transition state, but offered the possibility of forming a transition state resembling that developed by phosphoramide catalyst **3a**. The ion pair-hydrogen bonding model (**TSII2B**) is also obtained, but is higher in free energy by 6.8 kcal mol^{-1}. A transition state with an azido group as an H-bond acceptor[37] was also observed (**TSII2C**) but with a much higher free energy (14.2 kcal mol^{-1}).

Conclusions

In summary, we have demonstrated that H-bond donors can play a key role in controlling diastereoselectivity in a catalytic enantioselective reaction. Accordingly, an unprecedented highly enantioselective diastereodivergent asymmetric Michael addition of α-azido ketones to nitroolefins was developed by using our newly developed bifunctional phosphoramide catalyst **3a** or the analogous squaramide catalyst **4b**. Both cyclic and acyclic α-azido ketones, along with a broad range of nitroolefins, including β-CF_3 or CF_2H nitroolefins, can work under the established conditions. The resulting multifunctional tertiary azides **5** could be used to synthesize aza-spirocycles bearing four continuous stereocenters without a loss of enantioselectivity. Mechanistic studies revealed that the reversal of diastereoselectivity originates from the alternative catalyst-substrate recognition model due to the variation of the H-bond donor of the catalysts from phosphoramide to squaramide. The development of new DAC reactions by using other types of H-bond donors containing bifunctional catalysts is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the financial support from the NSFC (21725203 and 21971067), the Ministry of Education (PCSIRT) and the Fundamental Research Funds for the Central Universities.

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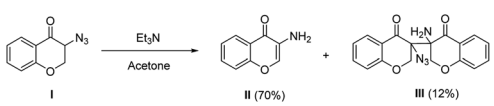

The decomposition of α-azido indanone **1a** at room temperature in the presence of bifunctional tertiary amine catalysts **3a** or **4b** was also detected by TLC analysis, showing that the desired Michael addition competed with the side decomposition of α-azido ketones. This gave a reasonable explanation for why the reaction of less active α-azido tetralone with nitroolefin **2a** ended in a mess under standard conditions, without the formation of the desired Michael adduct

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