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COMMUNICATION

Catalyst-Enabled Site-divergent Stereoselective Michael Reactions: Overriding Intrinsic Reactivity of Enynyl Carbonyl Acceptors

Daisuke Uraguchi,[a] Ryo Shibazaki,[a] Naoya Tanaka,[a] Kohei Yamada,[a] Ken Yoshioka,[a] and Takashi Ooi[a],[b]*

Abstract: A site-divergent stereoselective Michael reaction system is developed based on the identification of two distinct catalysts. Cinchonidine-derived thiourea catalyzes the 1,4-addition of prochiral azlactone enolates to enynyl *N*-acyl pyrazoles in a highly diastereo- and enantioselective manner to give stereochemically defined alkynes, while *P*-spiro chiral triaminoiminophosphorane catalytically controls the stereoselective 1,6-addition and the consecutive γ-protonation of the vinylogous enolate intermediate to afford *Z*,*E*-configured conjugated dienes. This 1,6-adduct serves as a valuable precursor for the synthesis of a 2-amino-2-deoxy sugar.

Selective modification of specific sites or functional groups of an organic compound that has multiple sites of reactivity (site-selective reaction) is a powerful tool for rapidly increasing molecular complexity, thereby allowing the design of a straightforward synthetic route to access complex targets.[1] This advantage stems from the fact that the site-selective reaction leaves other reactive functional groups intact and the product could be directly subjected to subsequent transformations. However, site-selectivity primarily depends on the intrinsic reactivity preference of the substrates, leading to the formation of a mixture of isomers, especially when the molecule of interest has several similar functional groups. This common trend causes an inherent difficulty in not only enhancing the substrate-controlled selectivity but also overriding it by a catalyst with recognition elements, capable of differentiating the subtle steric and electronic differences between potential reactive sites.

When this regiochemical consideration is coupled with a stereochemical issue in a general synthetic context, simultaneous dictation of both the selectivities poses a more profound challenge, particularly in catalytically directing the bond-forming reactions that involve multiple stereoselectivity factors.[2-5] One of the synthetically relevant carbon-carbon bond formations that are associated with this innate selectivity problem is the Michael addition of prochiral enolates to extended conjugate systems, such as dienyl carbonyl compounds. Various different strategies have been introduced to control the reaction site together with relative and absolute stereochemistry.[6,7] However,

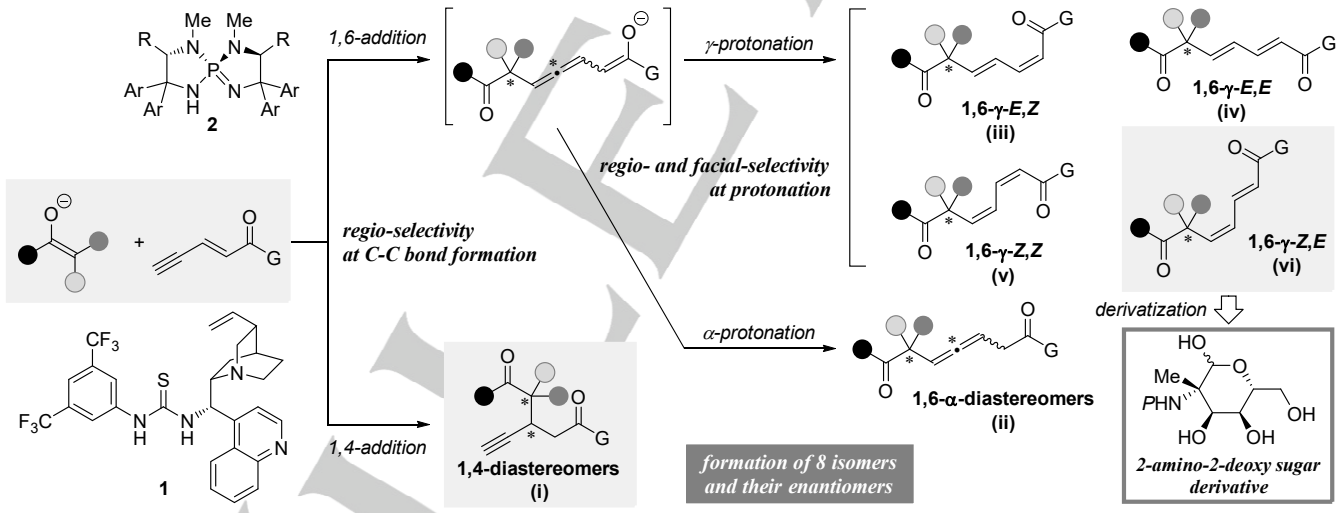

Figure 1. *Site-divergence and Multiple Selectivity Control in Michael Addition of Prochiral Enolates to Enynyl Carbonyl Compounds.*

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catalyst-dependent switching of the reaction site with preservation of the rigorous stereocontrol has to date proved elusive, despite offering an expedient means to access structurally distinct yet stereochemically homogeneous conjugate adducts from a single set of substrate combination. This situation reflects that regiochemical control still heavily relies on the exploitation of the intrinsic reactivity preference of the employed substrates, especially in attaining selectivity at a remote terminal site of the conjugated acceptor; hence, full synthetic potential of this class of vinylogous Michael technologies remains to be realized. Here, we report a complete site-divergence in the Michael addition of

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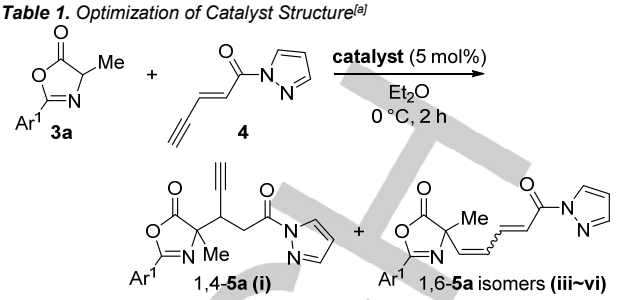
azlactone enolates to enynyl *N*-acyl pyrazoles enabled by the identification of two requisite catalysts, cinchonidine-derived thiourea **1** and *P*-spiro chiral triaminoiminophosphorane **2**, to afford 1,4- and 1,6-adducts, respectively, with discrete structural and stereochemical integrity. Furthermore, synthetic utility of the unprecedented 1,6-addition system for enynyl carbonyl acceptors is clearly demonstrated by the concise derivatization of the configurationally defined, conjugated diene product to a novel 2-amino-2-deoxysugar, 2-amino-2-deoxy-2-Me-D-altrofuranose derivative, bearing a chiral tetrasubstituted carbon.[8]

The Michael addition of prochiral enolates to enynyl carbonyl compounds potentially produces eight isomers and their enantiomers (total sixteen isomers) (Figure 1). The selective 1,4-addition with discrimination of prochiral faces of both an enolate and the enynyl acceptor gives stereochemically defined, functionalized alkynes **(i)**.[9-11] On the other hand, 1,6-addition involves the generation of a *s-cis*/*trans*-vinylogous enolate; thus, regio- and facial-selectivity in the protonation of this intermediate should be controlled in concert with regio- and stereoselectivity of the initial carbon-carbon bond formation to obtain enantioenriched allenes **(ii)** or conjugated dienes **(iii)**–**(vi)**. The diversity of regio- and stereochemical outcomes amplifies the complexity of the possible product distribution, rendering the catalyst-directed multiple selectivity control extremely challenging. In fact, no catalytic protocol is available for the selective production of the stereochemically pure Michael adduct out of the sixteen isomers, despite the significant potential for the stereoselective construction of valuable organic frameworks. Therefore, we decided to focus on this Michael reaction system.

At the outset, we examined the intrinsic reactivity of enynyl *N*-acyl pyrazole **4**[12] as a Michael acceptor toward an enolate of alanine-derived azlactone **3a**[13] using several common achiral bases as catalysts (Table 1, entries 1–4). While the treatment of **4** with **3a** under the influence of KO*t*Bu (1 equiv) in Et_2O at 0 °C preferably gave a diastereomeric mixture of the 1,4-adduct, 1,4-**5a** [type **(i_a)** and **(i_b)**], the use of a catalytic quantity of relatively strong organic bases resulted in the formation of complex mixtures containing all the expected adducts except for the allene isomer, 1,6-α-diastereomers **(ii)**. It is noteworthy that representative chiral bases such as (−)-cinchonine and (+)-cinchonidine were also totally ineffective in attaining an appreciable level of regioselectivity (entries 5 and 6). These results clearly indicated the difficulty in guiding the enolate nucleophile to a specific reactive site of **4**. In marked contrast, however, when (+)-cinchonidine-derived thiourea **1** was employed as a bifunctional catalyst at ambient temperature, 1,4-**5a** was obtained exclusively in high yield with nearly complete diastereo- and enantioselectivity (entry 7).[14] Switching the solvent to toluene allowed the reaction to proceed smoothly with 10 mol% of **1** without affecting the selectivity profile (Scheme 1).

This intriguing finding prompted us to investigate the substrate generality of the **1**-catalyzed 1,4- and stereoselective Michael addition with respect to the structural feature of azlactone **3**. The representative results are summarized in Scheme 1. In general, 10 mol% of **1** was sufficient for the bond formation to occur with high efficiency and virtually complete regio-, diastereo-, and enantioselectivities. While higher catalyst loading in Et_2O was necessary to attain useful reactivity in the reactions with **3** bearing a longer or branched alkyl group as the C-4 substituent, phenylglycine-derived azlactone **3i**, whose nucleophilicity is known to be low due to the high stability of its enolate ion, was found to react smoothly with rigorous selectivity control. The relative and absolute stereochemistry of the Michael adduct was

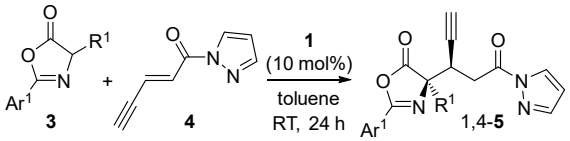
Table 1. *Optimization of Catalyst Structure*[a]



entry	catalyst	yield	isomeric ratio[c]						ee
		[%][b]	(i_a)	(i_b)	(ii)	(iii)	(iv)	(v)	(vi)	[%][d]
1	KO*t*Bu[e]	45	51	36	–	–	–	6	8	–
2	TMG[f]	40	12	30	–	1	29	2	25	–
3	DBU	84	2	8	–	1	46	6	37	–
4	TBD[g]	60	9	35	–	–	39	9	9	–
5	(−)-cinchonine[f,h]	47	8	6	–	2	19	25	40	nd[i]
6	(+)-cinchonidine[f,h]	23	18	34	–	1	12	14	21	nd[i]
7	**1**[f,h]	85	2	**98**	–	–	–	–	–	96[j]
8	**2a** (R = *i*Pr, Ar = Ph)	93	10	–	–	–	4	3	**83**	93
9	**2b** ((*S*)-*s*Bu, Ph)	96	6	–	–	–	2	2	**90**	96
10	**2c** (Me, Ph)	99	2	–	–	–	3	4	**91**	78
11	**2d** (*i*Bu, Ph)	94	4	–	–	–	2	5	**88**	82
12	**2e** (Bn, Ph)	90	9	–	–	–	9	3	**79**	95
13	**2f** ((*S*)-*s*Bu, 4-FC_6H_4)	98	6	–	–	–	2	1	**91**	96
14	**2g** ((*S*)-*s*Bu, 4-MeC_6H_4)	99	7	–	–	–	3	2	**88**	94
15	**2h** ((*S*)-*s*Bu, 3-FC_6H_4)	96	5	–	–	–	2	1	**92**	97
16	**2i** ((*S*)-*s*Bu, 3-MeC_6H_4)	99	1	–	–	–	5	1	**93**	96

Ar^1 = 2,6-$(MeO)_2C_6H_3$

*[a] Conditions: 0.10 mmol of **3a**, 0.11 mmol of **4**, 5 mol% of catalyst in Et_2O (1.0 mL) at 0 °C. [b] Isolated yields of the isomeric mixture of **5a**. [c] Determined by ^1H NMR analysis of crude aliquot. See Fig. 1 for the general structures of isomers **(i)–(vi)**. [d] Enantiomeric excesses of 1,6-γ-Z,E-**5a**. [e] 100 mol% of catalyst. [f] 30 mol% of catalyst. [g] 50 mol% of catalyst. [h] At RT for 24 h. [i] nd = not determined. [j] Enantiomeric excess of 1,4-**5a** (i_b).*



R^1 =			
Me (**5a**):	84%, 99% ee	$PhCH_2$ (**5e**):	92%, 99% ee
$Me(CH_2)_5$ (**5b**):*	89%, 99% ee	4-$MeOC_6H_4CH_2$ (**5f**):	85%, 99% ee
$MeS(CH_2)_2$ (**5c**):	73%, 99% ee	4-$ClC_6H_4CH_2$ (**5g**):	80%, 99% ee
Me_2CHCH_2 (**5d**):*	93%, 99% ee	*N*-Ts-3-IndolylCH$_2$ (**5h**):	84%, 99% ee
		Ph (**5i**):	88%, 96% ee

Scheme 1. *1,4-Selective Michael Addition to Enynyl N-Acyl Pyrazole **4**. * With 30 mol% of **1** in Et_2O.*

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unambiguously determined by single crystal X-ray diffraction analysis of 1,4-**5a** (see SI).[15]

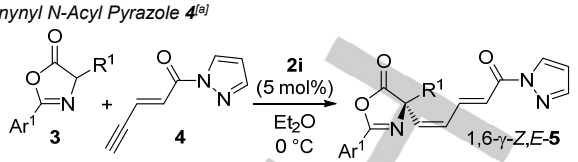
Having identified the catalyst capable of promoting 1,4-selective reaction with rigorous control of stereoselectivity, we turned our attention to search for a catalyst effective for overturning the regiochemical preference to 1,6-selectivity while conserving a comparable level of stereocontrol, thereby establishing a site-divergent stereoselective Michael reaction protocol. Toward this end, we applied *P*-spiro chiral triaminoiminophosphorane **2**[7,16] as a catalyst, considering the unique ability of its conjugate acid **2**·H to recognize both a nucleophile and an electrophile through hydrogen-bonding interactions for providing them unusual mutual orientation in the transition state of the subsequent bond formation.[7b,7c,17] Interestingly, the reaction of **3a** with **4** in the presence of L-valine-derived **2a**[18] in Et_2O at 0 °C selectively afforded 1,6-γ-*Z*,*E*-**5a** **(vi)** in high yield with excellent enantioselectivity (Table 1, entry 8); this revealed that **2**·H indeed diverted the site-selectivity by guiding the enolate of **3a** to the terminal carbon of **4** and also facilitated the γ-protonation of the intermediary vinylogous enolate with precise control of the diene geometry.[19] This initial observation encouraged us to evaluate the effect of catalyst structure on the regio- and stereochemical outcomes (entries 9–12). While satisfactory levels of isomeric ratios and enantiomeric excesses were generally observed with **2** bearing different alkyl substituents of amino acid origin (R), L-isoleucine-derived iminophosphorane **2b** exhibited the highest performance in regio- and enantiocontrol (entry 9). The steric and electronic properties of the aromatic appendage of **2** (Ar) slightly affected the selectivity profile and **2i** possessing *meta*-tolyl groups proved to be an optimal catalyst in terms of site-selectivity (93% ss) (entries 13–16).

We then thoroughly explored the scope of azlactones **3** in the **2i**-catalyzed asymmetric 1,6-addition to **4**. The results listed in Table 2 show that the incorporation of various alkyl and aryl groups onto the 4-position of **3** was tolerated and 1,6-γ-*Z*,*E*-**5** was predominantly obtained with high stereoselectivity (entries 1–14). It should be noted that lowering the temperature to −40 °C was crucial for the additions of *N*-Ts-tryptophan- and phenylglycine-derived azlactones **3h** and **3i** to proceed with rigorous enantiocontrol (entries 13 and 14).

When an enynyl acceptor has a δ-substituent, the accessibility of the δ-carbon would be considerably reduced, rendering the 1,6-addition process more difficult.[5b] As we assumed, the attempted reaction of δ-methyl enynyl *N*-acyl pyrazole **6a** with azlactone **3e** by the action of DBU (30 mol%) furnished 1,4-adduct of type **(i)** predominantly with concomitant formation of 1,6-γ-*E*,*E*-**7a** and 1,6-γ-*Z*,*E*-**7a** (94% ss). Contrary to this profile, however, 1,6-γ-*Z*,*E*-**7a** was obtained as the major isomer in the **2i**-catalyzed reaction, and the site-selectivity was improved to 86% when the reaction was conducted in *tert*-butyl methyl ether (TBME) (Scheme 2).[20] This protocol appeared to be efficient and applicable to a series of δ-substituted enynyl *N*-acyl pyrazoles **6** and 1,6-γ-*Z*,*E*-**7** was produced with good to high site-selectivity and excellent enantioselectivity. These results emphasize the power of the catalysis of **2i** in achieving multiply selective 1,6-addition by overriding the intrinsic reactivity of the enynyl acceptor.

The synthetic utility of product **5** obtained in the site-selective asymmetric 1,6-addition, which features two differentiated carbonyl functionalities and *Z*,*E*-configured conjugated diene, was demonstrated through straightforward derivatization to a 2-amino-2-deoxy sugar (Scheme 3).[21] 2-Amino-2-deoxy sugar derivatives, such as glucosamine, are biologically relevant molecules, yet their catalytic asymmetric synthesis, particularly selective construction of non-natural

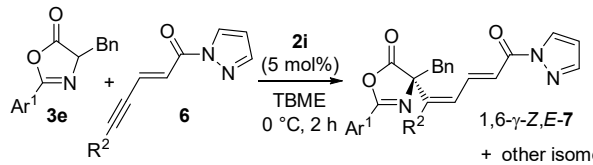
Table 2. *Substrate Scope for* ***2i****-catalyzed 1,6-Selective Michael Addition to Enynyl N-Acyl Pyrazole* ***4****[a]*



entry	R^1 (**3**)	time [h]	yield [%][b]	*1,6-γ-Z,E-**5** (ss)* [%][c]	ee [%][d]	prod.
1	Me (**3a**)	1	99	93	96	**5a**
2	Et (**3j**)	4	>99	95	97	**5j**
3	$Me(CH_2)_3$ (**3k**)	1	95	94	95	**5k**
4	$Me(CH_2)_5$ (**3b**)	4	>99	94	95	**5b**
5	$MeS(CH_2)_2$ (**3c**)	2	98	94	94	**5c**
6	Me_2CHCH_2 (**3d**)	2	98	>95	90	**5d**
7	Me_2CH (**3l**)	2	98	>95	98	**5l**
8	$PhCH_2$ (**3e**)	1	92	94	92	**5e**
9	4-$MeOC_6H_4CH_2$ (**3f**)	2	97	>95	90	**5f**
10	2-$FC_6H_4CH_2$ (**3m**)	3	99	>95	93	**5m**
11	4-$ClC_6H_4CH_2$ (**3g**)	3	99	>95	94	**5g**
12	3,4-$(MeO)_2C_6H_3CH_2$ (**3n**)	2	99	>95	94	**5n**
13[e]	*N*-Ts-3-IndolylCH$_2$ (**3h**)	12	91	>95	92	**5h**
14[e]	Ph (**3i**)	12	88	>95	94	**5i**

Ar^1 = 2,6-$(MeO)_2C_6H_3$

[a] Conditions: 0.10 mmol of ***3****, 0.11 mmol of* ***4****, 5 mol% of* ***2i*** *in Et_2O (1.0 mL) at 0 °C. [b] Isolated yields of the isomeric mixture of* ***5****. [c] Site-selectivity (ss) = percentage of 1,6-γ-Z,E-**5** in the regio- and E/Z-isomeric mixture. [d] Enantiomeric excesses of the major 1,6-γ-Z,E-**5**. See SI for X-ray diffraction analysis of 1,6-γ-Z,E-**5g**.[15] [e] At −40 °C.*



(Ar^1 = 2,6-$(MeO)_2C_6H_3$)

R^2 = Me (**7a**): 99%, 86% ss, 98% ee

Et (**7b**): 91%, 84% ss, 98% ee

$Ph(CH_2)_2$ (**7c**): 92%, 89% ss, 97% ee

$BnOCH_2$ (**7d**): 98%, 93% ss, 96% ee

cf. DBU (30 mol%): 1,4-**7a**/1,6-γ-*E*,*E*-**7a**/1,6-γ-*Z*,*E*-**7a** = 94:5:1

Scheme 2. *1,6-Selective Michael Addition to δ-Substituted Enynyl N-Acyl Pyrazoles* ***6****.*

cores possessing tetrasubstituted stereogenic carbon centers, remains challenging.[8] We anticipated that the geometrically defined diene component of **5** would provide an ideal platform for the assembly of the fully functionalized six-membered ring of the aza-sugar derivatives. The actual synthesis was initiated by quantitative conversion of 1,6-γ-*Z*,*E*-**5a** to hydroxy carboxylic acid **8** via a three-step sequence; *i.e.*, azlactone

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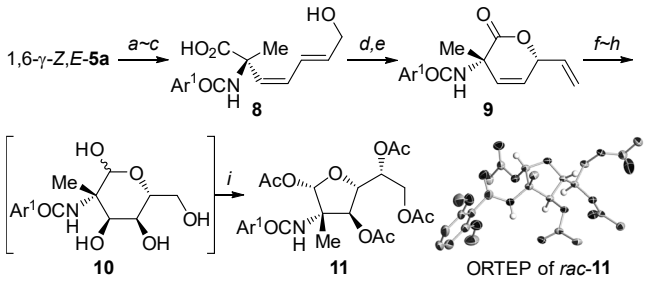
ring-opening with methanol under mildly acidic conditions, reduction of the *N*-acyl pyrazole group with $NaBH_4$, and subsequent saponification of the methyl ester. By taking advantage of the remaining diene moiety in **8**, δ-valerolactone **9**[15] was produced by a diastereoselective selenolactonization followed by the removal of the vicinal hydroxyl and selenenyl groups.[22] Then, selective ozonolysis of the pendant vinyl group was reductively quenched with $NaBH_4$ and, after reduction of the lactone carbonyl, diastereoselective *syn*-dihydroxylation of the endocyclic olefin by the modified Baran's procedure yielded aza-sugar derivative **10**.[23] Finally, acetylation of free hydroxyl groups of **10** with concurrent isomerization of the pyranose core to the furanose form gave rise to a 2-amino-2-deoxy-2-Me-D-altrofuranose derivative **11** in good yield. The relative stereochemistry of **11** was unequivocally assigned by X-ray diffraction analysis of a single crystal of *rac*-**11**.[15]



Scheme 3. *Derivatization to 2-Amino-2-deoxy-2-Me-D-altrofuranose (Ar[1] = 2,6-(MeO)$_2$C$_6$H$_3$). Conditions: a) PPTS, MeOH, 0 °C; b) $NaBH_4$, MeOH, –20 °C; c) KOH, MeOH, 70 °C (>99% in three steps); d) $(PhSe)_2$, $(PhSO_2)_2NF$, CH_2Cl_2, MS 4Å, –20 °C (60%); e) PBr_3, CH_2Cl_2, 0 °C (70%); f) O_3, MeOH/CH_2Cl_2, –78 °C, then $NaBH_4$, –78 °C (87%); g) DIBAH, CH_2Cl_2, –78 °C (>99%, dr = 2.5:1); h) OsO_4, NMO, citric acid, tBuOH/acetone/H_2O, 50 °C; i) AcCl, Et_3N, DMAP, CH_2Cl_2, RT (67% in two steps).*

In conclusion, we established two distinct catalytic systems for achieving a site-divergent, highly diastereo- and enantioselective Michael addition of α-amino acid-derived, prochiral azlactone enolates to enynyl *N*-acyl pyrazoles under mild conditions. The key is the ability of the catalysts to override the intrinsic reactivity preference of the substrates with precise control of multiple selectivity factors. The synthetic value of the structurally and configurationally homogeneous conjugated dienes was highlighted by the concise assembly of a 2-amino-2-deoxy sugar, which substantiates the potential impact of the stereoselective 1,6-addition protocol on the synthesis of complex targets. We believe that the catalyst-directed site-divergent strategy significantly expands the synthetic potential of the Michael reactions with extended conjugate systems.

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Keywords: amino acid • Michael addition • iminophosphorane • hexosamine • organocatalysis

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[15] Crystallographic data (excluding structure factors) for 1,4-**5a**, 1,6-γ-*Z*,*E*-**5g**, **9**, and *rac*-**11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1813740, CCDC-1813741, CCDC-1813742, and CCDC-1813882, respectively. Copies of the data can be obtained free of charge on

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application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[20] The Michael addition of **3e** to **6a** in Et_2O at 0 °C in the presence of **2i** (5 mol%) afforded 1,6-γ-*Z*,*E*-**7a** in 99% yield with 83% ss and 97% ee.

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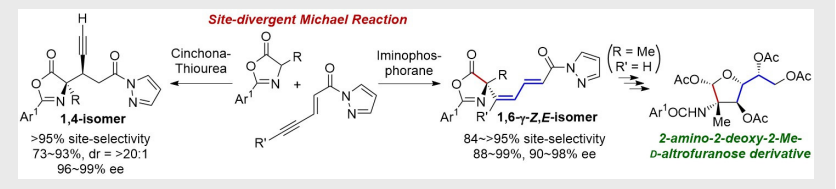

A site-divergent stereoselective Michael reaction system is developed based on the identification of two distinct catalysts. Cinchonidine-derived thiourea catalyzes the 1,4-addition of prochiral azlactone enolates to enynyl *N*-acyl pyrazoles in a highly diastereo- and enantioselective manner to give stereochemically defined alkynes, while *P*-spiro chiral triaminoiminophosphorane catalytically controls the stereoselective 1,6-addition and the consecutive γ-protonation of the vinylogous enolate intermediate to afford *Z*,*E*-configured conjugated dienes. This 1,6-adduct serves as a valuable precursor for the synthesis of a 2-amino-2-deoxy sugar.

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Catalyst-Enabled Site-divergent Stereoselective Michael Reactions: Overriding Intrinsic Reactivity of Enynyl Carbonyl Acceptors