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Choon-Hong Tan (✉ choonhong@ntu.edu.sg)

Nanyang Technological University

Xu Ban

Henan University

Yifan Fan

Henan University

Tuan-Khoa Kha

Nanyang Technological University

Richmond Lee

University of Wollongong

Choon Wee Kee

Institute of Chemical and Engineer Science <https://orcid.org/0000-0003-1843-2189>

Zhiyong Jiang

Henan Normal University

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Pentandium-Catalyzed Direct Assembly of Vicinal All-Carbon Quaternary Stereocenters through C(sp³)-C(sp³) Bond Formation

Xu Ban,^{1,2} Yifan Fan,¹ Tuan-Khoa Kha,² Richmond Lee,^{3,4} Choon Wee Kee,^{2,5} Zhiyong Jiang,^{1*} Choon-Hong Tan^{2*}

¹ International Scientific and Technological Cooperation Base of Chiral Chemistry, Henan University, Kaifeng, Henan, P. R. China 475004

² Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

³ School of Chemistry and Molecular Bioscience, University of Wollongong, Northfields Avenue, Wollongong, NSW 2522, Australia

⁴ Molecular Horizons, University of Wollongong, Northfields Avenue, Wollongong, NSW 2522, Australia

⁵ Process & Catalysis Research, Institute of Chemical and Engineer Science, Singapore 627899

Abstract

The stereoselective construction of vicinal all-carbon quaternary stereocenters has long been a formidable synthetic challenge. Direct asymmetric coupling of a tertiary carbon nucleophile with a tertiary carbon electrophile is the most straightforward approach but it is sterically and energetically disfavored. Herein, we described a catalytic asymmetric substitution, where racemic tertiary bromides directly couple with racemic secondary or tertiary carbanion, creating a series of congested carbon (sp³)-carbon(sp³) bonds, including isolated all-carbon quaternary stereocenters, vicinal tertiary/all-carbon quaternary stereocenters and vicinal all-carbon quaternary stereocenters. This double stereoconvergent process, using pentandium as catalyst, affords substituted products in good enantioselectivities and diastereoselectivities.

Introduction

The use of high-throughput synthetic practices, in tandem with extensive use of Pd-coupling chemistry in medicinal chemistry laboratories world-wide, has led to a propensity of achiral, aromatic compounds in screening libraries.¹ Many secondary metabolites with interesting pharmacological activities contain all-carbon quaternary stereocenters.^{2,3,4} Introducing all-carbon quaternary stereocenters into molecules will improve structural diversities in screening libraries. However, stereoselective construction of all-carbon quaternary stereocenters remains a significant challenge in synthetic chemistry.^{5,6} Amongst the limited

number of strategies, for the formation of this highly congested moiety, double Heck coupling,^{7,8} double Aldol reaction,⁹ and double allylation¹⁰ have been reported to be useful (Figure 1a). Separately, the use of multi-substituted alkenes in [3+2] annulation,^{11,12} Diels-Alder¹³⁻¹⁵ and other cycloadditions^{16,17} is another common approach (Figure 1a). Recent advances include dearomatization addition of β -naphthols on 3-bromooxindoles,¹⁸ Claisen rearrangement of γ,δ -unsaturated carbonyl compounds,¹⁹ dialkylation of bisoxindoles,²⁰ phosphine-catalyzed cyclization of allenes²¹ and a nucleophilic substitution at a quaternary carbon center with concomitant opening of a cyclopropane ring.^{22,23} On the other hand, direct radical coupling of two C(sp³) centers is a promising possibility as it can overcome steric hindrance; but currently it is limited to a narrow substrates scope such as bisoxindoles and chiral auxiliaries need to be deployed if enantioenriched compounds are required (Figure 1b).²⁴⁻²⁷ Thus far, there are no successful reports to prepare vicinal all-carbon quaternary stereocenters through a catalytic asymmetric coupling of two tertiary C(sp³) centers. This will be the most direct and convenient and yet, conceivably, the most sterically challenging approach. Nucleophilic substitution at a quaternary carbon center is difficult and can be made improbable if the nucleophile is also a bulky tertiary carbanion.

We have been developing chiral cationic salts such as pentanidium and bisguanidinium as phase transfer and ion-pair catalysts.²⁸ Using these catalysts, we recently reported an enantioconvergent halogenophilic nucleophilic substitution (S_N2X) to generate enantioenriched quaternary stereocenters using thiols and azides.²⁹⁻³¹ In a conventional S_N2 substitution, the nucleophile displaces a carbon-bound leaving group X, often a halogen, by attacking the carbon face opposite the C-X bond; while in the S_N2X reaction, the nucleophile approach a carbon-bound leaving group X from the front, making it an ideal sterically-immune synthetic approach. Shortly thereafter, a more in-depth investigation of the azide-substitution with tertiary bromide, revealed that it is a dynamic kinetic resolution, modulated by base present in the reaction.³² Herein, we report our recent progress into the use of nucleophilic substitutions to construct vicinal all-carbon quaternary stereocenters, using insights from our previous works, through direct

coupling of racemic tertiary electrophiles with racemic tertiary nucleophiles using chiral cations as catalysts (Figure 1c).

(a) Major previous strategies

(b) Radical dimerizations

(c) This work: direct C(sp³)-C(sp³) coupling

Figure 1 Major Strategies for Construction of Vicinal All-Carbon Quaternary Stereocenters

Results and Discussions

Synthesis of Isolated All-Carbon Quaternary Stereocenters

We began our investigation by extending our previous work on enantioconvergent S_N2X substitution. Instead of thiols and azides, we wanted to demonstrate that carbon nucleophiles can add to racemic tertiary bromides. Firstly, methyl 2-bromo-2-cyanoacetate **1a** was chosen as the model and various carbon pronucleophiles activated by an electron-withdrawing group such as acetophenone, isobutyronitrile and 2-nitropropane, were examined under basic condition (Scheme 1a). We found that only protonated product **1a-H** was obtained via a base-mediated S_N2X debromination process. Further exploration revealed that carbon pronucleophiles with two electron withdrawing groups, such as malononitrile and dialkyl malonate, afforded the desired substituted products (Scheme 1b).

Scheme 1 Investigation of Carbon Pronucleophilities

Subsequently, we found that in the presence of pentanidium **PN1-3** or bisguanidinium **BG1-3** as catalyst, substituted product **2a** was obtained with moderate yields and ee values (Table 1, entries 1-6). Bisguanidinium **BG1**, bearing 3,5-bis(trifluoromethyl)benzyl groups, provided the most promising results (entry 4). Further optimization by investigating various bases (entries 7-8), solvents (entries 9-11) and temperature (entries 12-13) revealed that the ideal condition was using **BG1** as catalyst, 4M aq. KOH (1.5 equiv.) as base in toluene at -30 °C. Lowering the reaction temperature further to -40 °C led to a significant decreased in yield, due to an increase formation of protonated product **1a-H** (entry 13). When methyl ester **1a** is change to ethyl ester **1b**, ee value of adduct **2b** is improved to 84% (entry 14). Further increase in steric bulk of the tertiary bromides led to iso-propyl ester **2c** and *tert*-butyl ester **2d** with even higher ee values (entries 15-16). However, changing dimethyl malonate to diethyl malonate or diisopropyl malonate only led to an increased formation of **1a-H**.

Table 1 Optimization of Reaction Conditions^a

entry	catalyst	base	solvent	1	yield (%) ^b	ee (%) ^c
1	PN1	K ₂ CO ₃	toluene	1a	78	57
2	PN2	K ₂ CO ₃	toluene	1a	80	54
3	PN3	K ₂ CO ₃	toluene	1a	82	46
4	BG1	K ₂ CO ₃	toluene	1a	82	62
5	BG2	K ₂ CO ₃	toluene	1a	80	55
6	BG3	K ₂ CO ₃	toluene	1a	82	45
7	BG1	Cs ₂ CO ₃	toluene	1a	84	62
8	BG1	4M aq. KOH	toluene	1a	85	67
9	BG1	4M aq. KOH	Et ₂ O	1a	84	56
10	BG1	4M aq. KOH	THF	1a	85	25
11	BG1	4M aq. KOH	DCM	1a	78	20
12 ^d	BG1	4M aq. KOH	toluene	1a	85	75
13 ^e	BG1	4M aq. KOH	toluene	1a	47	78
14 ^d	BG1	4M aq. KOH	toluene	1b	84	86
15 ^d	BG1	4M aq. KOH	toluene	1c	80	89
16 ^d	BG1	4M aq. KOH	toluene	1d	78	94

^a Unless otherwise noted, reactions were carried out with catalyst (5 mol %), **1a-d** (0.05 mmol), dimethyl malonate (0.06 mmol), base (0.07 mmol) in solvent (2 mL) at room temperature. ^b Isolated yield of **2a-d**. ^c Determined by HPLC using chiral column. ^d Reactions for 2 days at -30 °C. ^e Reactions for 2 days at -40 °C.

Under the ideal set of conditions developed above, various tertiary bromides **3d-16d** were further evaluated (Figure 2). Both electron-withdrawing group and electron-donating groups of the benzyl-substituted substrates were tolerated (**2e-2i**). Replacing the phenyl group with a naphthyl group, thiophene or pyridine also resulted in good yields and ee values of the adducts **2j** and **2k**, **2l** respectively. Tertiary bromides with alkyl groups can afford the desired substituted adducts in good yields and ee (**2m-2n**). The reaction was also effective for tertiary bromides bearing allylic or alkene substituents (**2o-2q**).

Figure 2 Synthesis of Isolated All-Carbon Quaternary Stereocenters. Unless otherwise noted, the reactions were carried out with **BG1** (5 mol %), 4M aq. KOH (0.07 mmol), tertiary bromides **3d-16d** (0.05 mmol), dimethyl malonate (0.06 mmol) in toluene (2 mL) at -30 °C for 2-3 days. Isolated yields are reported. The *ee* values were determined by HPLC analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of **2l.HCl** (See SI, page 80).

Synthesis of Vicinal Tertiary/All-Carbon Quaternary Stereocenters

Following the success of generating enantioenriched quaternary carbon centers through the addition of dimethyl malonate to racemic tertiary bromides, we wonder if significant diastereoselectivity will be observed when esters groups on malonates were different. Thus, tertiary bromide **1a** was treated with ethyl methyl malonate **18a** (Table 2, entry 1); it was found, after screening our catalyst library, that **PN1** can provide adduct **19a** with moderate enantioselectivity and some diastereoselectivity. By introducing *i*Pr (**18b**), Bn (**18c**) or *t*Bu (**18d**) groups to monomethyl malonates to increase steric discrimination, we found that diastereoselectivities increased correspondingly (entries 2-4). However, using ethyl *iso*-propyl malonate **18e** did not further improve the diastereoselectivity observed and the yield decreased dramatically (entry 5). When ethyl tert-butyl malonate **18f** was used, mostly protonated product **1a-H** was

obtained (entry 6). Thiolate **18g** produced the corresponding adduct but ee and dr values obtained were moderate (entry 7). Amide **18h** was also examined but no desired adduct was observed (entry 8). Further investigations were conducted with methyl *tert*-butyl malonate **18d** (entries 9-11) by varying different bromides and found **1d** gave **19k** the best results with 90% ee and 49:1 dr (entry 11).

Table 2 Optimization of Reaction Conditions^a

entry	1	18	yield (%) ^b	ee (%) ^c	dr ^d
1	1a	18a	87	60	1.2:1
2	1a	18b	82	72	2:1
3	1a	18c	85	55	2:1
4	1a	18d	85	78	4:1
5	1a	18e	60	76	2:1
6	1a	18f	trace	--	--
7	1a	18g	81	54	4:1
8	1a	18h	trace	--	--
9	1b	18d	82	84	8:1
10	1c	18d	80	89	9:1
11	1d	18d	80	90	49:1

^a Unless otherwise noted, reactions were carried out with **PN1** (5 mol %), bromide **1a-d** (0.05 mmol), malonate **18a-h** (0.06 mmol), 4M aq. KOH (0.05 mmol) in toluene (2 mL) at -20 °C for 2 days. ^b Isolated yield of **19**. ^c Determined by HPLC using chiral column. ^d Determined HPLC analysis.

With this optimized reaction conditions in hand, various tertiary bromides were studied (Figure 3). Tertiary bromides with benzylic substitutions, heterocycles, alkyl and allylic substituents that were investigated, afforded their corresponding adducts **19l-19s** in good yields and stereoselectivity.

Figure 3 Synthesis of Vicinal Tertiary and All-Carbon Quaternary Stereocenters. Unless otherwise noted, the reactions were carried out with **PN1** (5 mol %), 4M aq. KOH (0.05 mmol), tertiary bromides (0.05 mmol), malonate **18d** (0.06 mmol) in toluene (2 mL) at -20 °C for 3-4 days. Isolated yields are reported. The *dr* value was determined by HPLC analysis. The *ee* values were determined by HPLC analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of a derivative and DFT calculation (See SI, page 81).

Synthesis of Vicinal All-Carbon Quaternary Stereocenters

As far as we are aware, there are no successful reports to form vicinal all-carbon quaternary stereocenters through the direct catalytic asymmetric coupling of two C(sp³) centers. After our initial success, we are keen to investigate the formation of vicinal all-carbon quaternary stereocenters using this methodology. When tertiary bromide **1a** was treated with 1-ethyl 3-methyl 2-methylmalonate **20** (Scheme 2), we obtained protonated product of **1a-H**. This debromination indicated that the S_N2X occurred between the bromide **1a** and tertiary carbon anion from 1-ethyl 3-methyl 2-methylmalonate **20**, while formation of C-C bond was depressed. Similar results were observed when several other tertiary carbon nucleophiles were investigated.

Scheme 2 Testing of Tertiary Carbon

Table 3 Optimization of Reaction Conditions^a

entry	21	base	yield (%) ^b	ee (%) ^c	dr ^d
1	21a	4M aq.KOH	60	45	2:1
2	21b	4M aq.KOH	50	53	2:1
3	21c	4M aq.KOH	53	62	6:1
4	21c	LiOH	34	60	5:1
5	21c	NaOH	17	56	6:1
6	21c	KOH	23	67	6:1
7	21c	Na ₂ CO ₃	45	70	5:1
8	21c	K ₂ CO ₃	76	70	5:1
9	21c	Cs ₂ CO ₃	84	72	6:1
10	21c	K ₃ PO ₄	78	70	6:1
11 ^e	21c	Cs ₂ CO ₃	83	84	10:1

^a Unless otherwise noted, reactions were carried out with **PN1** (5 mol %), **1a** (0.1 mmol), **21a-c** (0.12 mmol), base (0.15 mmol) in toluene (2 mL) at room temperature for 3-4 days. ^b Isolated yield. ^c Determined by HPLC using chiral column. ^d Determined HPLC analysis. ^e Reaction temperature is -20 °C.

Subsequently, we identified cyclic β-ketone ester **21a** as a suitable model to study this reaction (Table 3).

It allowed the coupling with tertiary bromide **1a** to proceed (entry 1). From our previous studies, we concluded that steric effect played a crucial role in enantioselectivity and diastereoselectivity. When tertiary bromide **1b** was investigated, we found that it led to an increased yield of protonated product and with tertiary bromide **1c**, no desired product was obtained. On the other hand, changing cyclic β-ketone ester **21** led to more interesting results. When tert-butyl ester **21c** was used, both ee and dr values of the corresponding adduct were increased (Table 3, entries 1-3). We hypothesized that the protonated product could be suppressed if we removal of water from the reaction condition. Thus, in order to improve the yield of adduct **22**, we need to choose a more suitable base. We investigated a series of bases ranging

149 from powdered hydroxides salts to carbonates (Table 3, entries 4-10). We found that carbonate salts gave
 150 reproducible results with high yields and stereoselectivities; in particular, Cs₂CO₃ proved to be the more
 151 reliable (entry 9). With Cs₂CO₃ and at a lower reaction temperature, the ideal reaction condition was
 152 found (entry 11).

153
 154 **Figure 4 Synthesis of Vicinal All-Carbon Quaternary Stereocenters.** Unless otherwise noted, the reactions were
 155 carried out with **PN1** (5 mol %), Cs₂CO₃ (0.07 mmol), **1a** (0.05 mmol), **21c** (0.06 mmol) in toluene (2 mL) at -20 °C
 156 for 3-4 days. Isolated yield. The dr value was determined by HPLC analysis. The ee value was determined by HPLC
 157 analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of **22c**
 158 (See SI, page 85).

With the goldilocks zone identified, we expanded investigation of the scope of the tertiary bromides that we can use. We report successful cases, which the reaction proceeded smoothly with good yields and stereoselectivities (Figure 4, **22d-w**). For benzyl substitutions in bromides, both electron-withdrawing and electron-donating groups were tolerated (**22d-k**). Heterocycle such as thiophene was well tolerated (**22l**). Simple alkyl groups also produced good results (**22m-p**). Olefin containing alkyl chains were transformed into the desired product with good yields and stereoselectivities (**22q**). Substitution on cyclic β -ketone ester **21e-f** was also well tolerated (**22r-w**). Attempts to expand to other tertiary carbon nucleophiles such as *tert*-butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate and *tert*-butyl 2-oxocyclopentane-1-carboxylate were not successful. We continue to explore other potential tertiary carbon nucleophiles.

Mechanistic Study

Scheme 3 Control Experiments

In order to gain a better understanding of the mechanism, control experiments were designed accordingly. Firstly, a carbanion-exchange experiment was conducted between tertiary bromide **1a** and cyclic β -ketone ester **21c**. The reaction temperature was lowered from -20 °C to -40 °C and the reaction was quenched using sat. NH₄Cl after 8 hours. The transfer of Br atom from **1a** to **21c** was evident through the significant production bromide **23** (Scheme 3a). However, both protonated product **1a-H** and bromide **23** were obtained as racemic mixtures. Separately, a carbanion-trapping experiment using acrylonitrile, further substantiate the presence of a carbanion intermediate, generated from tertiary bromide **1d** (Scheme 3b). The conjugated addition product **24** was obtained with moderate enantioselectivity, pointing to close ion-pair interaction of the carbanion with bisguanidinium **BG1**. Next, we prepared the enantioenriched tertiary bromide **23** by using preparative high-performance liquid chromatography and subjected them to our conditions separately (Scheme 3c). We found that both enantioenriched tertiary bromides **23** were transformed to the same stereoisomer **22c**. Lastly, a base mediated racemization was observed when treating enantioenriched bromides **23** with Cs₂CO₃, this indicated a Cs₂CO₃ induced dynamic kinetic resolution prior the C-C bond coupling, which contributes to the high stereoselectivity (Scheme 3d). Based on previous investigations (Scheme 4a) and our preliminary studies, we proposed that cyclic β -ketone ester **21c** and tertiary bromide underwent carbanion-exchange through S_N2X (Scheme 4b). Cyclic β -ketone ester bromide **23** that is generated in this step can undergo further racemization through S_N2X that is modulated by base. Finally, S_N2 substitution occurred between the **PN1** paired carbanion generated from tertiary bromide **A** and cyclic β -ketone ester bromide **23** to install the vicinal all-carbon quaternary stereocenters through the coupling of two C(sp³) centers.

Conclusions

In conclusion, we have successfully developed the pentanidium-catalyzed direct coupling of tertiary carbon nucleophiles and tertiary carbon electrophiles through C(sp³)-C(sp³) bond formation. These reactions allowed the direct construction of the challenging vicinal all-carbon quaternary stereocenters in

high efficiencies. This transformation is so far the most efficient approach for assembling this congested C(sp³)-C(sp³) bond. Synthetic application of this new methodology is currently ongoing in our group.

(a) Previous work on S_N2X reaction

S_N2X substitution

Dynamic kinetic resolution

(b) Proposed mechanism for direct C(sp³)-C(sp³) coupling

Scheme 4 Proposed Mechanism

Methods

- General procedure for the synthesis of chiral isolated all-carbon quaternary stereocenters:** the bromide (1.0 equiv.), dimethyl carbonate (1.2 equiv.) and **BG1** (5% mol) were dissolved in toluene, cooling down the reaction mixture to -30 °C, and then 4M aq. KOH was added by a micro syringe. The mixture was stirred at -30 °C for 2-3 days until the completion. TLC monitored the process. The reaction was quenched with NH₄Cl (1 mL) and then water (10 mL) was added. Separate the organic phase and extract aqueous phase with DCM. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash

chromatography (hexane: ether = 5:1 as the eluent) to get the chiral isolated all-carbon quaternary stereocenters.

2. **General procedure for the synthesis of vicinal tertiary and quaternary stereocenters:** the bromide (1.0 equiv.), dimethyl carbonate (1.2 equiv.) and **PN1** (5% mol) were dissolved in toluene, cooling down the reaction mixture to – 20 °C, and then 4M aq. KOH was added by a micro syringe. The mixture was stirred at -20 °C for 3-4 days until the completion. TLC monitored the process. The reaction was quenched with NH₄Cl (1 mL) and then water (10 mL) was added. Separate the organic phase and extract aqueous phase with DCM. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexane: ether = 5:1 as the eluent) to get the chiral vicinal tertiary and quaternary stereocenters. One of the chiral centers which bears an acidic proton is not stable, and can be racemized with excess base. After purification, the sample should be kept in – 20 °C fridge.

3. **General procedure for the synthesis of vicinal all-carbon quaternary stereocenters:** the bromide (1.0 equiv.), dimethyl carbonate (1.2 equiv.) and **PN1** (5% mol) were dissolved in Toluene, cooling down the reaction mixture to – 20 °C, and then Cs₂CO₃ (1.5 equiv.) was added in one portion. The mixture was stirred at -20 °C for 3-4 days until the completion. TLC monitored the process. The reaction was quenched with NH₄Cl (1 mL) and then water (10 mL) was added. Separate the organic phase and extract aqueous phase with DCM. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (hexane: ether = 5:1 as the eluent) to get the chiral vicinal all-carbon quaternary stereocenters.

Data availability

The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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319 **Author contributions**

320 Xu Ban performed the condition optimization, investigated the scope of the substrates, and conducted the
321 experimental mechanistic studies. Yifan Fan and Tuan-Khoa Kha synthesized the bromides and tertiary
322 carbon nucleophiles. Choon Wee Kee and Richmond Lee performed the computational study of the
323 absolute configuration for vicinal tertiary and quaternary all-carbon centers. Zhiyong Jiang participated
324 in the design and discussion of the mechanistic experiments. Choon Hong Tan directed the project and
325 wrote the manuscript. All authors analyzed the results and commented on the manuscript.

326 **Corresponding author**

327 Correspondence to Prof. Choon-Hong Tan

328 **Competing interests**

329 The authors declare no competing interests.

Figures

(a) Major previous strategies

vicinal quaternary
all-carbon
stereocenters

(b) Radical dimerizations

(c) This work: direct C(sp³)-C(sp³) coupling

Figure 1

Major Strategies for Construction of Vicinal All-Carbon Quaternary Stereocenters

Figure 2

Synthesis of Isolated All-Carbon Quaternary Stereocenters. Unless otherwise noted, the reactions were carried out with BG1 (5 mol %), 4M aq. KOH (0.07 mmol), tertiary bromides 3d-16d (0.05 mmol), dimethyl malonate (0.06 mmol) in toluene (2 mL) at -30 °C for 2-3 days. Isolated yields are reported. The ee values were determined by HPLC analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of 2l.HCl (See SI, page 80).

R = benzyl, allylic or alkyl

Figure 3

Synthesis of Vicinal Tertiary and All-Carbon Quaternary Stereocenters. Unless otherwise noted, the reactions were carried out with PN1 (5 mol %), 4M aq. KOH (0.05 mmol), tertiary bromides (0.05 mmol), malonate 18d (0.06 mmol) in toluene (2 mL) at -20 °C for 3-4 days. Isolated yields are reported. The dr value was determined by HPLC analysis. The ee values were determined by HPLC analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of a derivative and DFT calculation (See SI, page 81).

Figure 4

Synthesis of Vicinal All-Carbon Quaternary Stereocenters. Unless otherwise noted, the reactions were carried out with PN1 (5 mol %), Cs₂CO₃ (0.07 mmol), 1a (0.05 mmol), 21c (0.06 mmol) in toluene (2 mL) at -20 °C for 3-4 days. Isolated yield. The dr value was determined by HPLC analysis. The ee value was determined by HPLC analysis on chiral stationary phase. Absolute configuration was determined using an X-ray crystal structure of 22c (See SI, page 85).

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