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

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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 pentanidium 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,\textsuperscript{7,8} double Aldol reaction,\textsuperscript{9} and double allylation\textsuperscript{10} have been reported to be useful (Figure 1a). Separately, the use of multi-substituted alkenes in [3+2] annulation,\textsuperscript{11,12} Diels-Alder\textsuperscript{13-15} and other cycloadditions\textsuperscript{16,17} is another common approach (Figure 1a). Recent advances include dearomatization addition of β-naphthols on 3-bromooxindoles,\textsuperscript{18} Claisen rearrangement of γ,δ-unsaturated carbonyl compounds,\textsuperscript{19} dialkylation of bisoxindoles,\textsuperscript{20} phosphine-catalyzed cyclization of allenes\textsuperscript{21} and a nucleophilic substitution at a quaternary carbon center with concomitant opening of a cyclopropane ring.\textsuperscript{22,23} On the other hand, direct radical coupling of two C(sp\textsuperscript{3}) 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).\textsuperscript{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(sp\textsuperscript{3}) 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.\textsuperscript{28} Using these catalysts, we recently reported an enantioconvergent halogenophilic nucleophilic substitution (S\textsubscript{N}2X) to generate enantioenriched quaternary stereocenters using thiols and azides.\textsuperscript{29-31} In a conventional S\textsubscript{N}2 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\textsubscript{N}2X 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.\textsuperscript{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 Sₙ2X 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 Sₙ2X 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).
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.

**Scheme 1 Investigation of Carbon Pronucleophilies**
Table 1 Optimization of Reaction Conditions

| entry | catalyst | base | solvent | 1 | yield (%) | ee (%) |
|-------|----------|------|---------|---|-----------|--------|
| 1     | PN1      | K₂CO₃| toluene | 1a| 78        | 57     |
| 2     | PN2      | K₂CO₃| toluene | 1a| 80        | 54     |
| 3     | PN3      | K₂CO₃| toluene | 1a| 82        | 46     |
| 4     | BG1      | K₂CO₃| toluene | 1a| 82        | 62     |
| 5     | BG2      | K₂CO₃| toluene | 1a| 80        | 55     |
| 6     | BG3      | K₂CO₃| toluene | 1a| 82        | 45     |
| 7     | BG1      | Cs₂CO₃| toluene | 1a| 84        | 62     |
| 8     | BG1      | 4M aq. KOH| toluene | 1a| 85        | 67     |
| 9     | BG1      | 4M aq. KOH| Et₂O | 1a| 84        | 56     |
| 10    | BG1      | 4M aq. KOH| THF  | 1a| 85        | 25     |
| 11    | BG1      | 4M aq. KOH| DCM  | 1a| 78        | 20     |
| 12d   | BG1      | 4M aq. KOH| toluene | 1a| 85        | 75     |
| 13e   | BG1      | 4M aq. KOH| toluene | 1a| 47        | 78     |
| 14d   | BG1      | 4M aq. KOH| toluene | 1b| 84        | 86     |
| 15d   | BG1      | 4M aq. KOH| toluene | 1c| 80        | 89     |
| 16d   | BG1      | 4M aq. KOH| toluene | 1d| 78        | 94     |

*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. *Isolated yield of 2a-d. *Determined by HPLC using chiral column. †Reactions for 2 days at -30 °C. ‡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 iPr (18b), Bn (18c) or tBu (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

| entry | 1   | 18   | yield (%) | ee (%) | dr  |
|-------|-----|------|-----------|--------|-----|
| 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 |

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 8).

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.
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*   | \(21c\) | 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 \(^\circ\)C.

Subsequently, we identified cyclic \(\beta\)-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 \(\beta\)-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...
from powdered hydroxides salts to carbonates (Table 3, entries 4-10). We found that carbonate salts gave reproducible results with high yields and stereoselectivities; in particular, Cs$_2$CO$_3$ proved to be the more reliable (entry 9). With Cs$_2$CO$_3$ and at a lower reaction temperature, the ideal reaction condition was found (entry 11).
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**

(a) Carbanion-exchange experiment

(b) Carbanion-trapping experiment

(c) Reactions with enantioenriched tertiary bromides

(d) Base-mediated racemization

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 S₈2X (Scheme 4b). Cyclic β-ketone ester bromide 23 that is generated in this step can undergo further racemization through S₈2X that is modulated by base. Finally, S₈2 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

$$
\begin{array}{c}
\text{R} - \text{Br} + \text{Ar} - \text{S} \rightarrow S_N2X \\
\text{S} \rightarrow \text{Ar} - \text{S} - \text{CO}_2\text{Me}
\end{array}
$$

Dynamic kinetic resolution

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

**Scheme 4 Proposed Mechanism**

**Methods**

1. **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 $-30^\circ C$, and then 4M aq. KOH was added by a micro syringe. The mixture was stirred at $-30^\circ C$ for 2-3 days until the completion. TLC monitored the process. The reaction was quenched with NH$_4$Cl (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 Na$_2$SO$_4$, 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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Author contributions

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

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Competing interests

The authors declare no competing interests.