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Pentanidium-Catalyzed Direct Assembly of Vicinal All-Carbon Quaternary Stereocenters through C(sp^3)–C(sp^3) Bond Formation

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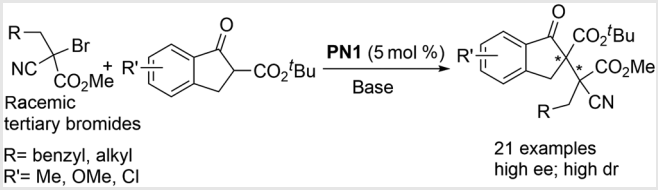
The stereoselective construction of vicinal all-carbon quaternary stereocenters has long been a formidable synthetic challenge. Direct asymmetric coupling of a tertiary carbon nucleophile with a tertiary carbon electrophile is the most straightforward approach, but it is sterically and energetically disfavored. Herein, we describe a catalytic asymmetric substitution, where racemic tertiary bromides coupled directly with racemic secondary or tertiary carbanion, creating a series of congested C(sp^3)–C(sp^3) bonds, including isolated all-carbon quaternary stereocenters, vicinal tertiary/all-carbon quaternary stereocenters and vicinal all-carbon quaternary stereocenters. Using pentanidium as a catalyst, this double stereoconvergent process afforded substituted products in good enantioselectivities and diastereoselectivities.



Keywords: **ion-paired catalyst, asymmetric substitution, S_N2 substitution, S_N2X substitution, all-carbon quaternary stereocenters**

Introduction

The use of high-throughput synthetic practices in tandem with extensive use of Pd-coupling chemistry in medicinal chemistry laboratories worldwide 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.[2–4] Introducing all-carbon quaternary stereocenters into molecules will improve structural diversities in screening libraries. However, the stereoselective construction of all-carbon quaternary stereocenters remains a significant challenge in synthetic chemistry.[5,6] Among the limited number of strategies employed in forming this highly congested moiety, double Heck coupling,[7,8] double Aldol reaction,[9] and double allylation[10] have been reported to be useful (Figure 1a). In contrast, using multisubstituted alkenes in [3+2] annulation,[11,12] Diels–Alder,[13–15] 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 allenes,[21] and a nucleophilic substitution at a

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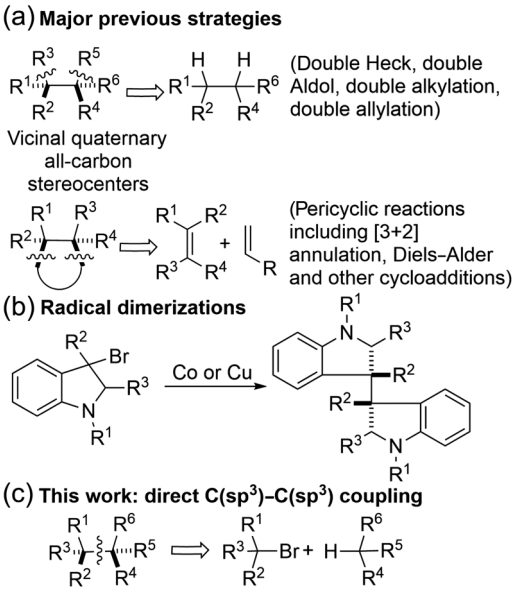

Figure 1 | *(a–c) Major strategies for the construction of vicinal all-carbon quaternary stereocenters.*

quaternary carbon center with the concurrent opening of a cyclopropane ring.[22,23] On the other hand, direct radical coupling of two C(sp^3) centers is a promising possibility as it could 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 on the preparation of vicinal all-carbon quaternary stereocenters through a catalytic asymmetric coupling of two tertiary C(sp^3) centers, which should be the most direct and convenient, and yet, conceivably, the most sterically challenging approach. Nucleophilic substitution at a quaternary carbon center is difficult and improbable to achieve if the nucleophile is also a bulky tertiary carbanion.

We have been developing chiral cationic salts such as pentanidium (**PN1**) and bisguanidinium (**BG1**) 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. Soon afterward, a more in-depth investigation of the azide substitution with tertiary bromide revealed a dynamic kinetic resolution modulated by a base present in the reaction.[32] Herein, we report our recent progress into using nucleophilic substitutions to construct vicinal all-carbon quaternary stereocenters, using insights from our previous reports, through direct coupling of racemic tertiary electrophiles with racemic tertiary nucleophiles using chiral cations as catalysts (Figure 1c).

Experimental Methods

General procedure for the synthesis of chiral isolated all-carbon quaternary stereocenters

The racemic tertiary bromide **1d** (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 4 M aq. KOH was added using a microsyringe. The mixture was stirred at –30 °C for 2–3 days until reaction completion. Thin-layer chromatography (TLC) monitored the process. The reaction was quenched with NH_4Cl (1 mL), and then water (10 mL) was added. The organic phase was separated from the aqueous phase using dichloromethane (DCM) extraction. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_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.

General procedure for the synthesis of vicinal tertiary and quaternary stereocenters

The racemic tertiary 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 4 M aq. KOH was added using a microsyringe. The mixture was stirred at –20 °C for 3–4 days until reaction completion. TLC was utilized to monitor the process. The reaction was quenched with NH_4Cl (1 mL), and then water (10 mL) was added. Separate the organic phase and extract the aqueous phase with DCM. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane: ether = 5:1 as the eluent) to obtain the chiral vicinal tertiary and quaternary stereocenters. One of the chiral centers which bore an acidic proton was not stable and readily racemized with excess base. After purification, the sample should be kept at –20 °C.

General procedure for the synthesis of vicinal all-carbon quaternary stereocenters

The racemic tertiary bromide **1d** (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 Cs_2CO_3 (1.5 equiv) was added in one portion. The mixture was stirred at –20 °C for 3–4 days until reaction completion. TLC was utilized to monitor the

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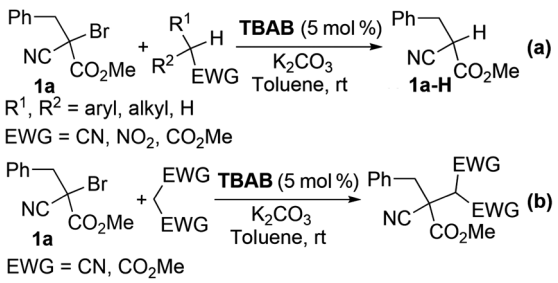
process. The reaction was quenched with NH_4Cl (1 mL), and then water (10 mL) was added. The organic phase was separated from the aqueous phase by DCM extraction. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and membrane filtered to concentrate. The residue was purified by flash chromatography (hexane:ether = 5:1 as the eluent) to obtain the chiral vicinal all-carbon quaternary stereocenters.

Results and Discussion

Synthesis of isolated all-carbon quaternary stereocenters

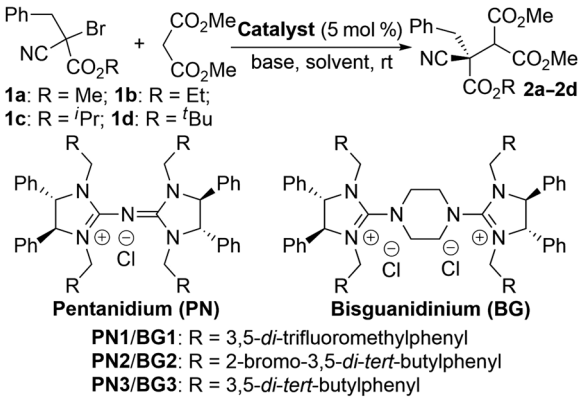
We began our investigation by extending our previous work on enantioconvergent S_N2X substitution. Instead of thiols and azides, we embarked on demonstrating that carbon nucleophiles could add to racemic tertiary bromides. First, methyl 2-bromo-2-cyanoacetate **1a** was chosen as the model, and various carbon pronucleophiles were activated by an electron-withdrawing group such as acetophenone isobutyronitrile and 2-nitropropane, were examined under basic conditions (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).

Subsequently, we found that in the presence of pentanidium **PN1-3** or bisguanidinium **BG1-3** as a 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 and 8), solvents (entries 9–11), and temperature (entries 12 and 13) revealed that the ideal reaction conditions involved 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 significantly decreased yield due to the formation of increased protonated product **1a-H** (entry 13). When methyl ester **1a** was changed to ethyl ester **1b**, the ee value of adduct **2b** improved to 84% (entry 14). Further increase in steric bulk of the tertiary bromides led to the formation of isopropyl ester **2c** and *tert*-butyl ester **2d** with even higher ee values (entries 15 and 16; 89% and 95%, respectively). However, changing dimethyl malonate to diethyl malonate or diisopropyl malonate only led to an increased formation of **1a-H**, thereby decreasing the yield.



Scheme 1 | *(a and b) Investigation of carbon pronucleophilies addition to racemic tertiary bromides.*

Table 1 | *Optimization of Reaction Conditions for Isolated all-carbon Quaternary Stereocenters*[a]



Entry	Catalyst	Base	Solvent	1	Yield (%)[b]	ee (%)[c]
1	**PN1**	K_2CO_3	Toluene	**1a**	78	57
2	**PN2**	K_2CO_3	Toluene	**1a**	80	54
3	**PN3**	K_2CO_3	Toluene	**1a**	82	46
4	**BG1**	K_2CO_3	Toluene	**1a**	82	62
5	**BG2**	K_2CO_3	Toluene	**1a**	80	55
6	**BG3**	K_2CO_3	Toluene	**1a**	82	45
7	**BG1**	Cs_2CO_3	Toluene	**1a**	84	62
8	**BG1**	4M aq. KOH	Toluene	**1a**	85	67
9	**BG1**	4M aq. KOH	Et_2O	**1a**	84	56
10	**BG1**	4M aq. KOH	Tetra-hydrofuran	**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–1d** (0.05 mmol), dimethyl malonate (0.06 mmol), base (0.07 mmol) in the solvent (2 mL) at room temperature.
[b] Isolated yield of **2a–2d**.
[c] Determined by HPLC using a chiral column.
[d] Reactions for 2 days at −30 °C.
[e] Reactions for 2 days at −40 °C.

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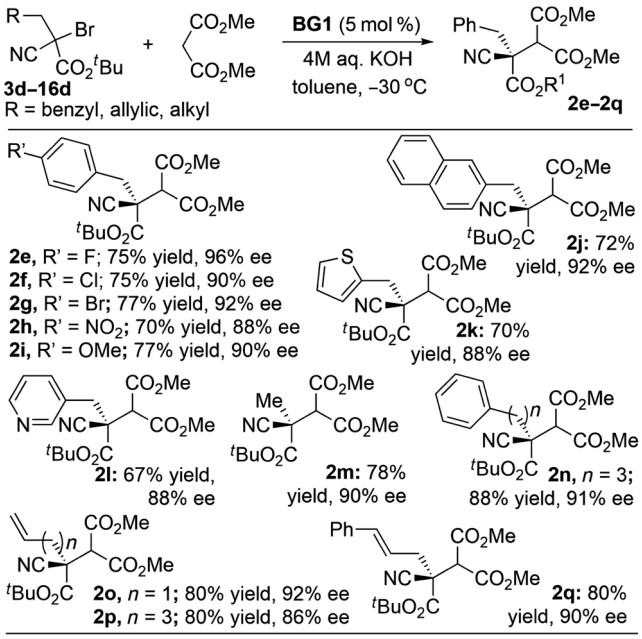
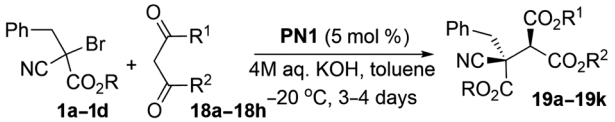


Figure 2 | *Synthesis of isolated all-carbon quaternary stereocenters. Unless otherwise noted, the reactions were carried out with* ***BG1*** *(5 mol %), 4M aq. KOH (0.07 mmol), tertiary bromides* ***3d–16d*** *(0.05 mmol), dimethyl malonate (0.06 mmol) in toluene (2 mL) at –30 °C for 2–3 days. Isolated yields are reported. The ee values were determined by HPLC analysis on the chiral stationary phase. The absolute configuration was determined using an X-ray crystal structure of* ***2l***·*HCl (see Supporting Information, page S80).*

Table 2 | *Optimization of Reaction Conditions for Vicinal Tertiary and all-carbon Quaternary Stereocenters*[a]



1a: R = Me
1b: R = Et
1c: R = ^{i}Pr
1d: R = ^{t}Bu

18a, R^1 = OMe, R^2 = OEt; **18b**, R^1 = OMe, R^2 = O^{i}Pr; **18c**, R^1 = OMe, R^2 = OBn; **18d**, R^1 = OMe, R^2 = O^{t}Bu; **18e**, R^1 = OEt, R^2 = O^{i}Pr; **18f**, R^1 = OEt, R^2 = O^{t}Bu; **18g**, R^1 = OMe, R^2 = S^{t}Bu; **18h**, R^1 = OMe, R^2 = NH^{t}Bu.

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–1d** (0.05 mmol), malonate **18a–18h** (0.0.06 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 a chiral column.
[d] Determined HPLC analysis.

Under the ideal set of conditions developed above, various tertiary bromides **3d–16d** were further evaluated (Figure 2). Both electron-withdrawing and -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**, (88%, 92%, and 88%, respectively. Tertiary bromides with alkyl groups can afford the desired substituted adducts in good yields and ee (**2m** and **2n**, 42% yield, 88% ee, respectively). The reaction was also effective for tertiary bromides bearing allylic or alkene substituents (**2o–2q**, 13% yield, 74% ee, respectively).

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 wondered if significant diastereoselectivity could be observed if the ester 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 improve the diastereoselectivity further, 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 the 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).

With these 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.

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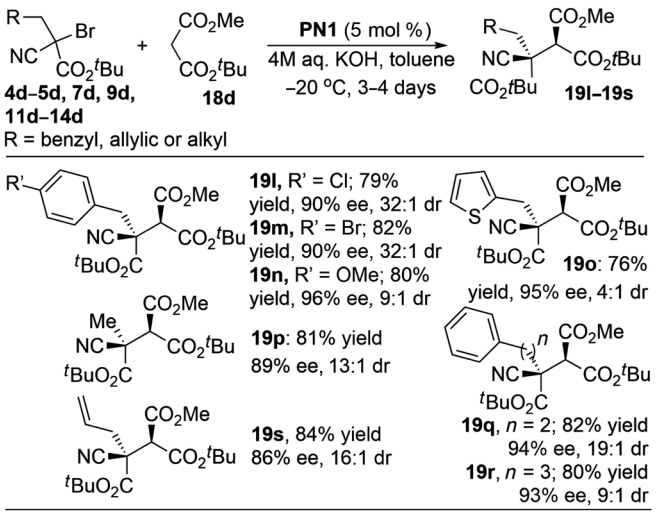
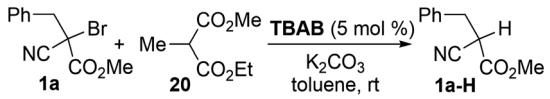


Figure 3 | *Synthesis of vicinal tertiary and all-carbon quaternary stereocenters. Unless otherwise noted, the reactions were carried out with* ***PN1*** *(5 mol %), 4M aq. KOH (0.05 mmol), tertiary bromides (0.05 mmol), malonate* ***18d*** *(0.06 mmol) in toluene (2 mL) at –20 °C for 3–4 days. Isolated yields are reported. The dr value was determined by HPLC analysis. The ee values were determined by HPLC analysis on the chiral stationary phase. The absolute configuration was determined using an X-ray crystal structure of a derivative and density functional theory (DFT) calculation (see Supporting Information, page S81).*

Synthesis of vicinal all-carbon quaternary stereocenter

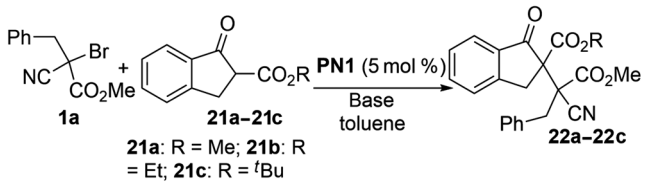
As far as we know, there are no successful reports regarding the formation of vicinal all-carbon quaternary stereocenters through the direct catalytic asymmetric coupling of two C(sp^3) centers. After our initial success, we were keen on investigating the formation of vicinal all-carbon quaternary stereocenters using this methodology. When we treated tertiary bromide **1a** 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 the C–C bond formation was depressed. Similar results were observed when several other tertiary carbon nucleophiles were investigated.

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



Scheme 2 | *Testing of tertiary carbon nucleophiles for vicinal all-carbon quaternary stereocenters.*

Table 3 | *Optimization of Reaction Conditions for Vicinal all-carbon Quaternary Stereocenters*[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_2CO_3	45	70	5:1
8	**21c**	K_2CO_3	76	70	5:1
9	**21c**	Cs_2CO_3	84	72	6:1
10	**21c**	K_3PO_4	78	70	6:1
11[e]	**21c**	Cs_2CO_3	83	84	10:1

[a] Unless otherwise noted, reactions were carried out with **PN1** (5 mol %), 1a (0.1 mmol), **21a–21c** (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 a chiral column.
[d] Determined HPLC analysis.
[e] Reaction temperature is –20 °C.

allowed the coupling with tertiary bromide **1a** to proceed (entry 1). Based on our previous studies, we concluded that the steric effect played a crucial role in enantioselectivity and diastereoselectivity. When we investigated tertiary bromide **1b**, we found that it led to an increased yield of protonated product, while 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 the ee and dr values of the corresponding adduct were increased (Table 3, entries 1–3). We hypothesized that the protonated product could be suppressed by water removal from the reaction condition. Thus, to improve the yield of adduct **22**, we needed 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_2CO_3 proved to be more reliable (entry 9), yielding ideal reaction conditions at a lower reaction temperature (-20 °C, entry 11).

With the goldilocks zone identified, we expanded our investigation on the scope of the tertiary bromides that could be used. We reported successful cases in which the

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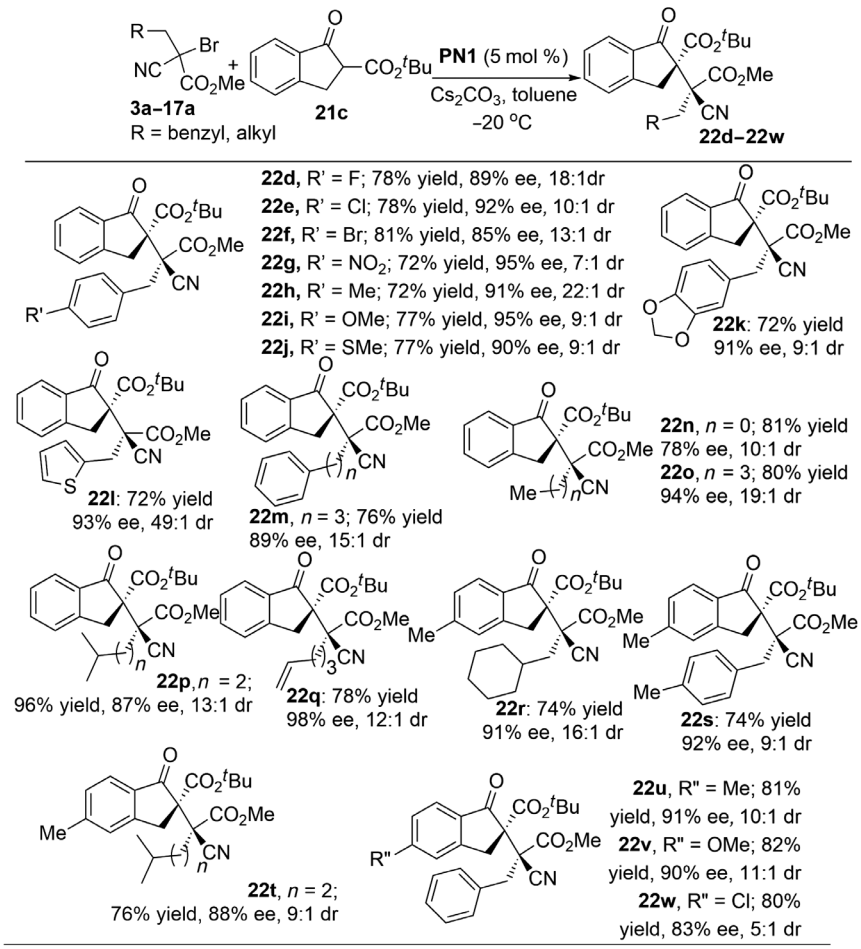

Figure 4 | *Synthesis of vicinal all-carbon quaternary stereocenters. Unless otherwise noted, the reactions were carried out with **PN1** (5 mol %), Cs_2CO_3 (0.07 mmol), **1a** (0.05 mmol), **21c** (0.06 mmol) in toluene (2 mL) at –20 °C for 3–4 days. Isolated yield. The dr value was determined by HPLC analysis. The ee value was determined by HPLC analysis on the chiral stationary phase. The absolute configuration was determined using an X-ray crystal structure of **22c** (see Supporting Information, page S85).*

reaction proceeded smoothly with good yields and stereoselectivities (Figure 4, **22d–22w**). For benzyl substitutions in bromides, both electron-withdrawing and -donating groups were tolerated (**22d–22k**). Heterocycle such as thiophene was well tolerated (**22l**). Also, simple alkyl groups produced good results (**22m–22p**). Olefins containing alkyl chains were transformed into the desired product with good yields and stereoselectivities (**22q**). Substitution on cyclic β–ketone ester **21e** and **22f** was also well tolerated (**22r–22w**). 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 unsuccessful. We continued to explore other potential tertiary carbon nucleophiles, including bearing less electron donating groups and linear vicinal all-carbon quaternary stereocenters.

To gain a better understanding of the mechanism, control experiments were designed accordingly. First, a carbanion-exchange experiment was conducted between tertiary bromide **1a** and cyclic β-ketone ester **21c**. The reaction temperature was lowered from –20 to –40 °C and quenched using saturated NH_4Cl after 8 h. The transfer of Br atom from **1a** to **21c** was evident through the significant production of bromide **23** (Scheme 3a). However, both protonated product **1a-H** and bromide **23** were obtained as racemic mixtures. Moreover, a carbanion-trapping experiment using acrylonitrile further substantiated 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** using preparative high-performance liquid chromatography (HPLC) and subjected them to our conditions independently (Scheme 3c). We found that both enantioenriched

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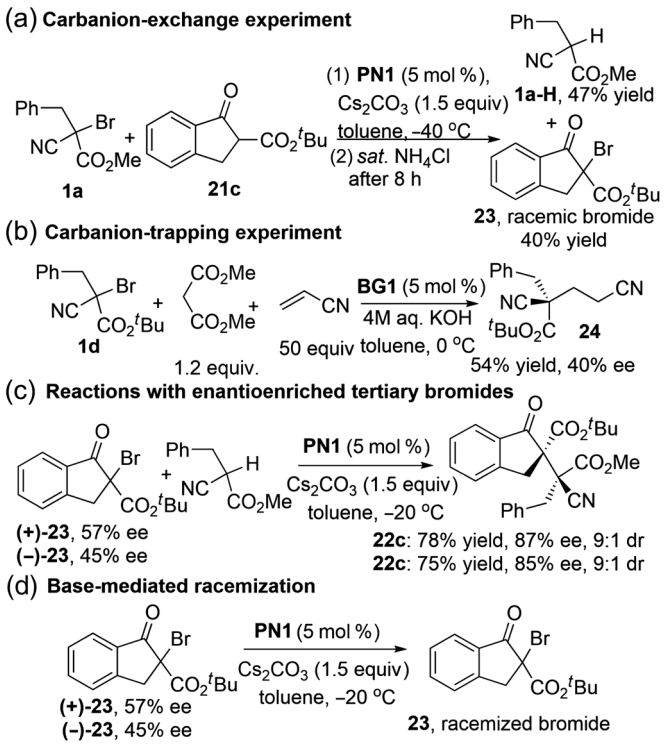
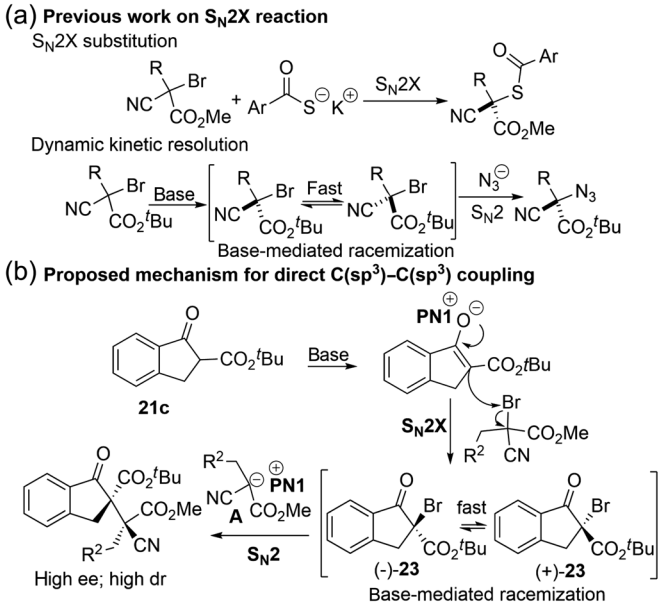


Scheme 3 | *(a–d) Control experiments performed to understand the mechanism of formation of vicinal all-carbon quaternary stereocenters.*



Scheme 4 | *(a and b) Proposed mechanism for construction of vicinal all-carbon quaternary stereocenters.*

tertiary bromides **23** were transformed to the same stereoisomer **22c**. Finally, base-mediated racemization was observed when treated enantioenriched bromides **23** with Cs_2CO_3, indicating that the Cs_2CO_3 induced dynamic kinetic resolution before the C–C bond coupling thereby contributing to the high stereoselectivity (Scheme 3d).

To gain a better understanding of the mechanism, control experiments were designed accordingly. First, a carbanion-exchange experiment was conducted between tertiary bromide **1a** and cyclic β-ketone ester **21c**. The reaction temperature was lowered from –20 to –40 °C, and the reaction was quenched using saturated NH_4Cl after 8 h. The transfer of Br atom from **1a** to **21c** was evident through the significant production of bromide **23** (Scheme 3a). However, both protonated product **1a-H** and bromide **23** were obtained as racemic mixtures. Further, a carbanion-trapping experiment using acrylonitrile substantiated 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 the bisguanidinium **BG1**. Next, we prepared the enantioenriched tertiary bromide **23** using preparative HPLC and subjected them to our conditions independently (Scheme 3c). We found that both enantioenriched tertiary bromides **23** were transformed to the same stereoisomer **22c**. Finally, base-mediated racemization was observed when enantioenriched bromide **23** was treated with Cs_2CO_3; this indicated that Cs_2CO_3 induced dynamic kinetic resolution prior to the C–C bond coupling, contributing 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**, generated at this step, could undergo further racemization through S_N2X, modulated by a 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(sp^3) centers.

Conclusion

We have successfully developed a pentanidium-catalyzed direct coupling of tertiary carbon nucleophiles and tertiary carbon electrophiles through C(sp^3)–C(sp^3) bond formation. These reactions allowed the direct construction of the challenging vicinal all-carbon quaternary stereocenters at high efficiencies. This transformation is so far the most efficient approach for assembling this congested C(sp^3)–C(sp^3) bond. Synthetic application of this new methodology is currently ongoing in our group.

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Supporting Information

Supplementary Information is available and include X-ray crystallographic data.

Conflict of Interest

The authors declare no competing interests.

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References

1. Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success *J. Med. Chem.* **2009**, *52*, 6752–6756.
2. Steven, A.; Overman, L. E. Total Synthesis of Complex Cyclotryptamine Alkaloids: Stereocontrolled Construction of Quaternary Carbon Stereocenters. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488–5508.
3. Quasdorf, K. W.; Overman, L. E. Catalytic Enantioselective Synthesis of Quaternary Carbon Stereocenters. *Nature* **2014**, *516*, 181–191.
4. Li, C.; Ragab, S.; Liu, G.; Tang, W. Enantioselective Formation of Quaternary Carbon Stereocenters in Natural Product Synthesis: A Recent Update. *Nat. Prod. Rep.* **2020**, *37*, 276–292.
5. Peterson, E. A.; Overman, L. E. Contiguous Stereogenic Quaternary Carbons: A Daunting Challenge in Natural Products Synthesis. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11943–11948.
6. Long, R.; Huang, J.; Gong, J.; Yang, Z. Direct Construction of Vicinal All-Carbon Quaternary Stereocenters in Natural Product Synthesis. *Nat. Prod. Rep.* **2015**, *32*, 1584–1601.
7. Overman, L. E; Panone, D. V.; Stearns, B. A. Direct Stereo- and Enantiocontrolled Synthesis of Vicinal Stereogenic Quaternary Carbon Centers. Total Syntheses of Meso- and (-)-Chimonanthine and (+)-Calycanthine. *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703.
8. Overman, L. E.; Watson, D. A. Diastereoselection in the Formation of Contiguous Quaternary Carbon Stereocenters by the Intramolecular Heck Reaction. *J. Org. Chem.* **2006**, *71*, 2600–2608.
9. De, S.; Das, M. K.; Roy, A.; Bisai, A. Synthesis of 2-Oxindoles Sharing Vicinal All-Carbon Quaternary Stereocenters via Organocatalytic Aldol Reaction. *J. Org. Chem.* **2016**, *81*, 12258–12274.
10. Trost, B. M; Osipov, M. Palladium-Catalyzed Asymmetric Construction of Vicinal All-Carbon Quaternary Stereocenters and Its Application to the Synthesis of Cyclotryptamine Alkaloids. *Angew. Chem. Int. Ed.* **2013**, *52*, 9176–9181.
11. Trost, B. M.; Malhotra, S.; Chan, W. H. Exercising Regiocontrol in Palladium-Catalyzed Asymmetric Prenylations and Geranylation: Unifying Strategy toward Flustramines A and B. *J. Am. Chem. Soc.* **2011**, *133*, 7328–7331.
12. Ohmatsu, K.; Imagawa, N.; Ooi, T. Ligand-Enabled Multiple Absolute Stereocontrol in Metal-Catalysed Cycloaddition for Construction of Contiguous All-Carbon Quaternary Stereocentres. *Nat. Chem.* **2014**, *6*, 47–51.
13. Toro, A.; Nowak, P.; Deslongchamps, P. Transannular Diels-Alder Entry into Stemodanes: First Asymmetric Total Synthesis of (+)-Maritimol. *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703.
14. Kim, A. I.; Rychnovsky, S. D. Unified Strategy for the Synthesis of (-)-Elisapterosin B and (-)-Colombiasin A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1267–1270.
15. Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. Efficient Total Syntheses of (-)-Colombiasin A and (-)-Elisapterosin B: Application of the Cr-Catalyzed Asymmetric Quinone Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2005**, *44*, 6046–6050.
16. Gao, L.; Hwang, G. S.; Ryu, D. H. Oxazaborolidinium Ion-Catalyzed Cyclopropanation of α-Substituted Acroleins: Enantioselective Synthesis of Cyclopropanes Bearing Two Chiral Quaternary Centers. *J. Am. Chem. Soc.* **2011**, *133*, 20708–20711.
17. Jolit, A.; Walleser, P. M.; Yap, G. P. A.; Tius, M. A. Catalytic Enantioselective Nazarov Cyclization: Construction of Vicinal All-Carbon-Atom Quaternary Stereocenters. *Angew. Chem. Int. Ed.* **2014**, *53*, 6180–6183.
18. Liu, X.; Wang, P.; Bai, L.; Wang, L.; Yang, D.; Wang, R. Construction of Vicinal All-Carbon Quaternary Stereocenters Enabled by a Catalytic Asymmetric Dearomatization Reaction of β-Naphthols with 3-Bromooxindoles. *ACS Catal.* **2018**, *8*, 10888–10894.
19. Zheng, H.; Wang, Y.; Xu, C.; Lin, L.; Liu, X.; Feng, X. Stereodivergent Synthesis of Vicinal Quaternary-Quaternary Stereocenters and Bioactive Hyperolactones. *Nat. Commun.* **2018**, *9*, 1968–1973.
20. Chen, S. K.; Ma, W. Q.; Yan, Z. B.; Zhang, F. M.; Wang, S. H.; Tu, Y. Q.; Zhang, X. M.; Tian, J. M. Organo-Cation Catalyzed Asymmetric Homo/Heterodialkylation of Bisoxindoles: Construction of Vicinal All-Carbon Quaternary

Stereocenters and Total Synthesis of (-)-Chimonanthidine. *J. Am. Chem. Soc.* **2018**, *140*, 10099–10103.
21. Chan, W. L.; Tang, X.; Zhang, F.; Quek, G.; Mei, G. J.; Lu, Y. Phosphine-Catalyzed (3+2) Annulation of Isoindigos with Allenes: Enantioselective Formation of Two Vicinal Quaternary Stereogenic Centers. *Angew. Chem. Int. Ed.* **2019**, *58*, 6260–6264.
22. Lanke, V.; Marek, I. Nucleophilic Substitution at Quaternary Carbon Stereocenters. *J. Am. Chem. Soc.* **2020**, *142*, 5543–5548.
23. Pierrot, D.; Marek, I. Synthesis of Enantioenriched Vicinal Tertiary and Quaternary Carbon Stereogenic Centers within an Acyclic Chain. *Angew. Chem. Int. Ed.* **2020**, *59*, 36–49.
24. Movassaghi, M.; Schmidt, M. A. Concise Total Synthesis of (-)-Calycanthine, (+)-Chimonanthine, and (+)-Folicanthine. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725–3728.
25. Kim, J.; Ashenhurst, J. A.; Movassaghi, M. Total Synthesis of (+)-11,11′-Dideoxyverticillin A. *Science* **2009**, *324*, 238–241.
26. Liang, K.; Deng, X.; Tong, X.; Li, D.; Ding, M.; Zhou, A.; Xia, C. Copper-Mediated Dimerization to Access 3a,3a-Bispyrrolidinoindoline: Diastereoselective Synthesis of (+)-WIN 64821 and (–)-Ditryptophenaline. *Org. Lett.* **2015**, *17*, 206–209.
27. Shen, X.; Zhou, Y.; Xi, Y; Zhao, J.; Zhang, H. Copper Catalyzed Sequential Arylation.Oxidative Dimerization of o-Haloanilides: Synthesis of Dimeric HPI Alkaloids. *Chem. Common.* **2015**, *51*, 14873–14876.
28. Zong, L.; Tan, C. H. Phase-Transfer and Ion-Pairing Catalysis of Pentanidiums and Bisguanidiniums. *Acc. Chem. Res.* **2017**, *50*, 842–856.
29. Zhang, X.; Ren, J.; Tan, A. M.; Tan, D.; Lee, R.; Tan, C. H. An Enantioconvergent Halogenophilic Nucleophilic Substitution (SN2X) Reaction. *Science* **2019**, *363*, 400–404.
30. Zefirov, N. S.; Makhonkov, D. I. X-Philic Reactions. *Chem. Rev.* **1982**, *82*, 615–624.
31. Sazonov, P. K. Nucleophilic Substitution at the Halogen Atom (Halogenophilic Reactions). Russ. *Chem. Rev.* **2012**, *81*, 317–337.
32. Ren, J.; Ban, X.; Zhang, X.; Tan, S. M.; Lee, R.; Tan, C. H. Kinetic and Dynamic Kinetic Resolution of Racemic Tertiary Bromides by Pentanidium-Catalyzed Phase-Transfer Azidation. *Angew. Chem. Int. Ed.* **2020**, *59*, 9055–9058.

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