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Regio- and Diastereoselective Three-Component Reactions via Trapping of Ammonium Ylides with *N*-Alkylquinolinium Salts: Synthesis of Multisubstituted Tetra- and Dihydroquinoline Derivatives

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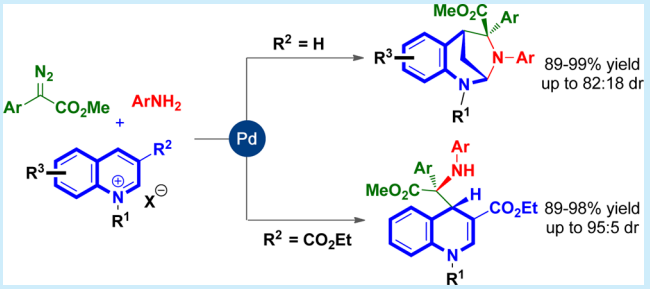
Supporting Information

ABSTRACT: Pd(II)-catalyzed three-component reactions via trapping of ammonium ylides with *N*-alkylquinolinium salts are reported. These reactions provided polyfunctional polycyclic tetrahydroquinolines or 4-substituted 1,4-dihydroquinolines in excellent yields (89−99% and 89−98%, respectively) with high regioselectivities and moderate to good diastereoselectivities (up to 95:5 dr) under mild reaction conditions.



Nitrogen-containing heterocycles are widespread in natural products and constitute core motifs in various biologically active pharmaceutical and agrochemical products as well as in materials science.[1] Hydrogenated (iso)quinoline derivatives, such as dihydro- and tetrahydroquinolines, are particularly important core constituents within this broad family owing to their pharmacological activities.[1c] For example (Figure 1), martinellic acid (**a**) was identified as a nonpeptide

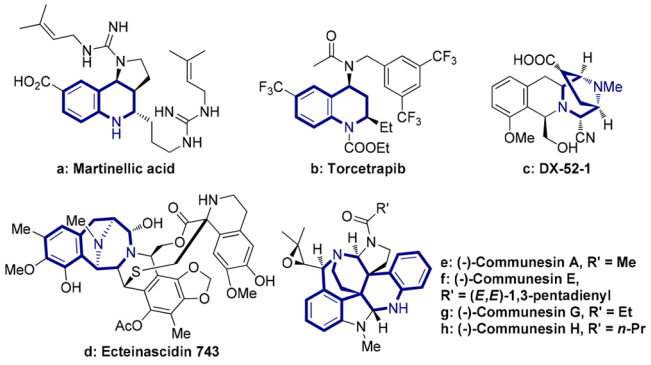


Figure 1. Select examples of biologically active tetrahydroquinolines.

bradykinin receptor antagonist,[2] torcetrapib (**b**) has been implemented in clinical trials as an anti-hypercholesterolemia drug,[3] and quinocarmycin analogue DX-52-1 (**c**) is an inhibitor of epithelial cell migration.[4] On the other hand, bridgehead diazepine cores are also present in naturally occurring and synthetic biologically active heterocycles,[5] including ecteinascidin 743 (**d**), which exhibits good activity against soft tissue sarcomas and ovarian cancer, and communesin alkaloids (**e**−**h**) display cytotoxicity against cultured lymphocytic leukemia cells and insecticidal activity.[6] Considering the significance of these scaffolds, the continued development of efficient methodologies to allow the synthesis of structurally diverse derivatives is of particular importance for drug discovery.

Among the reported methods, nucleophilic addition of *N*-activated quinolines has proved to be one of most straightforward and versatile strategies to afford dihydro- and tetrahydroquinoline derivatives (Scheme 1, a).[7] However, the regioselectivity of this addition may be critical because both the C-2 and C-4 positions of *N*-activated quinolines are active sites. Generally, nucleophilic additions favor the more electron-deficient C-2 position[8a] of N-substituted quinolinium salts,[8] but mixtures of regioisomers have also been observed in many cases.[9] To achieve regioselective additions to the C-4 position, an electron-withdrawing group (EWG) at the C-3 position is required.[10] Regioselective C-4 additions to quinolinium salts without a blocked or induced substituent at the C-2 or C-3 positions are rare.[11] Moreover, the low-face discrimination of aromatic electrophiles creates another challenge in the diastereocontrol over two contiguous stereogenic centers.[10b]

To accomplish nondirect regioselective C-4 additions to quinolinium salts, we turned our attention to transient nucleophilic intermediates with unique reactivities. Onium ylides generated in situ from diazo compounds and alcohols/anilines are transient nucleophilic intermediates and can be trapped by a wide scope of electrophiles with polarized electron-deficient double bonds (C═O, C═N, C═C, etc.)

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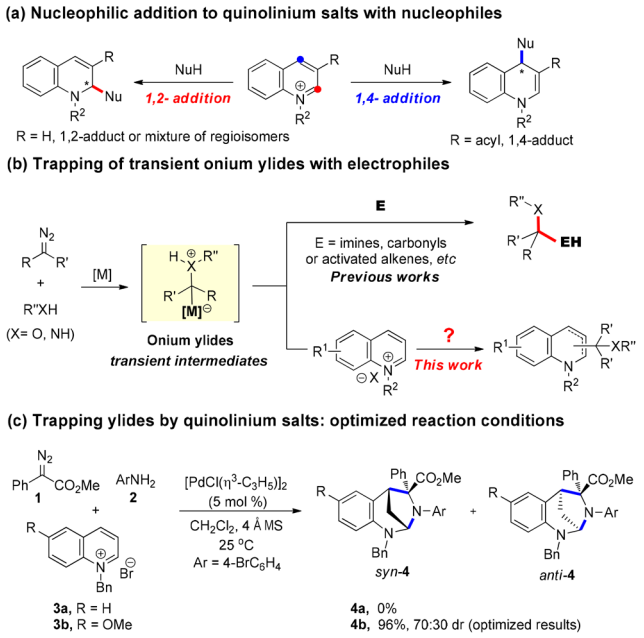
Scheme 1. Nucleophilic Dearomatization of Quinolinium Salts for the Synthesis of Partially Hydrogenated Quinoline Derivatives

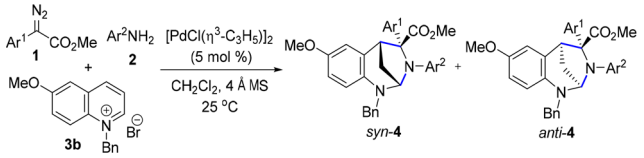


through nucleophilic addition (Scheme 1b). Based on this trapping process, our group has developed a series of novel three-component reactions.[12,13] In view of the unique reactivities of these highly reactive ylide intermediates, we envisioned that they could be utilized as efficient nucleophiles in the dearomatization of cationic quinolinium ions, affording an attractive method to construct multifunctional di- and tetrahydroquinoline derivatives under mild conditions (Scheme 1b). However, owing to the short half-life of transient ylides[14] as well as the low concentration of quinolinium salts in organic solvents, trapping onium ylides with quinolinium salts is challenging not only in the chemoselectivities of 1,2-proton transfer and nucleophilic addition of ylides but also in the regio- and stereocontrol of the desired trapping process.

Herein, we describe a palladium-catalyzed three-component reaction of diazo compounds, anilines, and quinolinium salts with regiospecific C-4 addition (Scheme 1c). In order to avoid the two-component side reaction of anilines and quinolinium ions, bench-stable *N*-alkylquinolinium salts were chosen as substrates. Notably, when *N*-alkylquinolinium salts without a substituent at the C-3 position were employed, the reaction underwent an uncommon regioselective 1,4-conjugate addition/intramolecular cyclization sequence to give bridged medium-ring 1,3-benzodiazepine derivatives. Actually, the construction of medium-ring heterocycles, especially bridged heterocycles, remains a significant synthetic challenge in modern organic synthesis owing to entropy and ring strain.[15] Initially, the reaction using quinolinium salt **3a** as a substrate did not lead to any detectable desired product **4a**, probably due to the poor solubility of **3a** in CH_2Cl_2. After optimizations, the optimal conditions involved the use of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ as a catalyst[12c,13b,16] and the more lipophilic quinolinium salt **3b** as substrate in CH_2Cl_2 at 25 °C, leading to **4b** in 96% yield with 70:30 dr.[17]

We first evaluated the substrate scope of this transformation (Table 1). A series of substituted diazo compounds with electron-withdrawing or electron-donating groups on the

Table 1. Substrate Scope of Diazo Compounds 1 and Anilines 2[a]



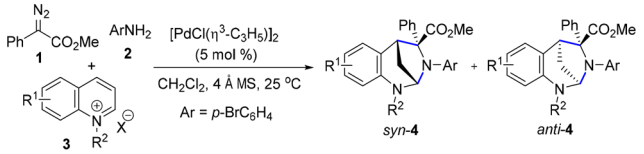
entry	Ar^1, Ar^2	yield[b] (%)	dr[c]
1	Ph, *p*-BrC_6H_4	**4b**: 96	70:30
2	*p*-Tol, *p*-BrC_6H_4	**4c**: 93	62:38
3	*p*-FC_6H_4, *p*-BrC_6H_4	**4d**: 92	71:29
4	*p*-BrC_6H_4, *p*-BrC_6H_4	**4e**: 97	78:22
5	*m*-BrC_6H_4, *p*-BrC_6H_4	**4f**: 97	81:19
6	Ph, *p*-Tol	**4g**: 93	81:19
7	Ph, *p*-FC_6H_4	**4h**: 97	82:18
8	Ph, *m*-BrC_6H_4	**4i**:96	75:25
9	Ph, 3,4-$OMeC_6H_3$	**4j**: 92	76:24
10	Ph, 3,4,5-OMe C_6H_2	**4k**: 94	72:28

[a]Unless otherwise indicated, all reactions were conducted on a 0.2 mmol scale for **3**, **1**/**2**/**3** = 1.5:1.5:1. [b]Combined yields of *anti*- and *syn*-isomers after column chromatography isolation. [c]*Syn*/*anti*, determined by crude ^{1}H NMR.

phenyl ring were evaluated; the reaction afforded three-component products **4** generally in excellent yields (92–97%) with high regioselectivities and moderate diastereoselectivities (62:38–81:19) (entries 1–5). Various substituted anilines were also investigated. Anilines bearing halogen or methyl substituents on the *para*- or *meta*-positions were tolerated and provided the desired products in excellent yields (93–96%) and acceptable diastereoselectivities (75:25–81:19) (entries 6–8). Di- or trisubstituted anilines with substituents at the *meta*- and *para*-positions were also compatible (entries 9 and 10).[18]

With respect to the electrophiles, various substituted quinolinium salts from readily available quinolines were examined (Table 2). *N*-Benzylquinolinium salts bearing various substituents at the C5, C6, and C7 positions, regardless of the electronic properties, were found to be well-tolerated and gave the corresponding products **4** in up to 98% yields with moderate dr value (entries 1–6). *N*-Methylquinolinium salts with 6-CO_2Et or 8-Me also worked and provided the products

Table 2. Substrate Scope of Quinolinium Salts 3 with 1a and 2a[a]



entry	**3**/R^1	R^2/X	yield[b] (%)	dr[c]
1	**3c**/6-Br	Bn/Br	**4l**: 97	60:40
2	**3d**/7-Br	Bn/Br	**4m**: 92	66:34
3	**3e**/6-CO_2Et	Bn/Br	**4n**: 97	73:27
4	**3f**/6-NO_2	Bn/Br	**4o**: 98	56:44
5	**3g**/5-Br	Bn/Br	**4p**: 98	61:39
6	**3h**/6-Me	Bn/Br	**4q**: 96	63:37
7	**3i**/6-CO_2Et	Me/I	**4r**: 99	58:42
8	**3j**/8-Me	Me/I	**4s**: 96	69:31

[a–c]See Table 1.

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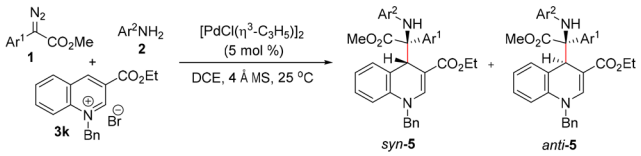
4r or **4s** in excellent yields with selectivities similar to those of their *N*-Bn counterparts (entries 7 and 8). Notably, *N*-Bn-quinolinium salt **3k** (vide infra) containing a 3-CO_2Et substituent provided three-component product **5a** without further intramolecular annulation in **93%** yield with 72:28 dr under the standard reaction conditions (see the SI).

To get high diastereoselectivity of reaction using *N*-Bn-3-ethoxylcarbonylquinolinium salt **3k** as a substrate, extensive optimizations of reaction conditions were conducted,[17] and nonanulated product **5a** was obtained in 96% yield with a remarkably enhanced dr of 93:7 (Table 3, entry 1). The scope

Table 3. Substrate Scope of Three-Component Reaction of 1 and 2 with 3k[a]



entry	Ar^1	Ar^2	yield[b] (%)	dr[c]
1	Ph	*p*-BrC_6H_4	**5a**: 96	93:7
2	Ph	*p*-FC_6H_4	**5b**: 97	93:7
3	Ph	*p*-Tol	**5c**: 96	92:8
4	Ph	PMP	**5d**: 97	90:10
5	Ph	Ph	**5e**: 98	91:9
6	*p*-BrC_6H_4	*p*-BrC_6H_4	**5f**: 97	93:7
7	*p*-ClC_6H_4	*p*-BrC_6H_4	**5g**: 96	91:9
8	*p*-FC_6H_4	*p*-BrC_6H_4	**5h**: 97	93:7
9	*m*-$OMeC_6H_4$	*p*-BrC_6H_4	**5i**: 94	95:5
10	PMP	*p*-BrC_6H_4	**5j**: 89	48:52

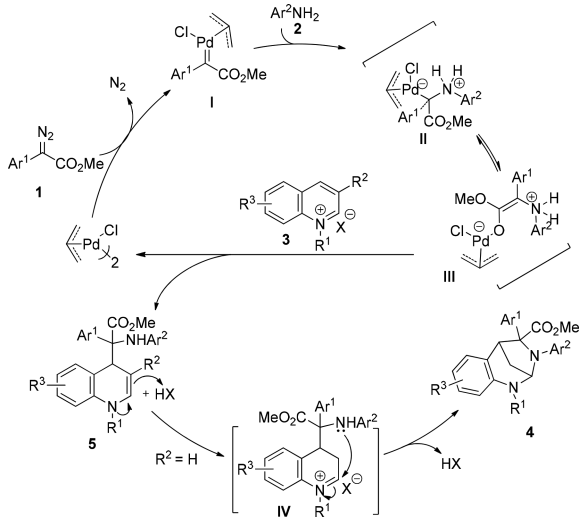
[a−c]See Table 1.

of anilines **2** and diazo compounds **1** was then explored. Anilines with various substituents at the *para*- and *meta*-positions also led to **5b−e** in excellent yields (96−98%) with good dr (entries 2−5). Substituted diazo compounds also proceeded well and provided **5f−i** in 94−97% yields with up to 95:5 dr (entries 6−9), while that with a methoxy group at the *para*-position of the phenyl ring resulted in a considerable decrease in the dr value (48:52) (entry 10).[19]

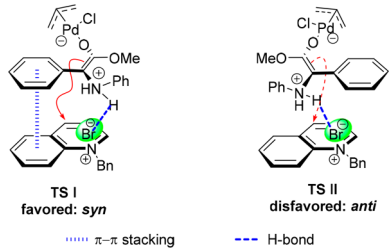
A mechanism for the three-component reaction was proposed (Scheme 2) according to the control experiments (see the SI) and previous investigations.[12,13] First, $[PdCl(\eta^3\text{-}C_3H_5)]_2$ decomposes diazo compounds **1** to form electrophilic palladium carbene intermediates **I**, which react with anilines **2** to give palladium-associated ammonium ylide intermediates **II** and their enolate counterparts **III**. Then the resulting ylide intermediates **II** or **III** are immediately trapped by quinolinium salts **3** via 1,4-conjugate addition to provide 1,4-dihydroquinolines **5**, along with HX (X = Br, I), and regenerate the palladium catalyst. At last, the enamine moiety of 1,4-dihydroquinolines **5** (R^2 = H) are further protonated by the released HX to form iminium intermediates **IV**, which undergo intramolecular nucleophilic cyclization involving the amino group to afford the bridged product **4**. Notably, 1,4-dihydroquinolines **5** (R^2 = CO_2Et) cannot undergo further intramolecular annulation due to the stabilization of the enamine moiety by the electron-withdrawing ester group.

The excellent regioselective outcome of this trapping process, as well as the diastereoselective control, could be rationalized according to the models shown in Scheme 3. It was proposed

Scheme 2. Proposed Mechanism



Scheme 3. Plausible Transition State



that the H-bond between the aniline N−H functionality of ammonium ylides and bromide of quinolinium salts, as well as a $\pi-\pi$ stacking[10b,20] between the aromatic ring of ammonium ylides and that of quinolinium ion, could direct the ylide nucleophilic site to be closer to the C4-position than the C2-position of the quinolinium ion. These interactions result in the more stable transition state **TS-I**, which would lead to the *syn* isomers.

In conclusion, we developed a regiospecific 1,4-conjugate addition of readily available *N*-alkylquinolinium salts with transient ammonium ylides under mild and practical conditions. Multifunctional bridged tetrahydroquinolines and dihydroquinolines derivatives were obtained from simple starting materials in excellent yields with moderate to high diastereoselectivities. This methodology provides a facile access to structurally divergent hydrogenated quinoline derivatives, which is of great potential for the establishment of compound libraries for drug discovery. Exploration of the asymmetric version of this transformation is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01664.

Crystallographic data for *syn*-**4p** (CIF)
Crystallographic data for *anti*-**4p** (CIF)
Crystallographic data for *syn*-**5a** (CIF)
Crystallographic data for *anti*-**5a** (CIF)
Experimental procedures and characterization data for new compounds including NMR spectra (PDF)

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Author Contributions

†Z.K. and D.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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(17) For the detailed optimization of reaction conditions, see the Supporting Information.

(18) For additional examples (**4t−x**), see the Supporting Information.

(19) For additional examples (**5k−n**), see the Supporting Information.

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