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Kinetic resolution of primary allylic amines *via* palladium-catalyzed asymmetric allylic alkylation of malononitriles†

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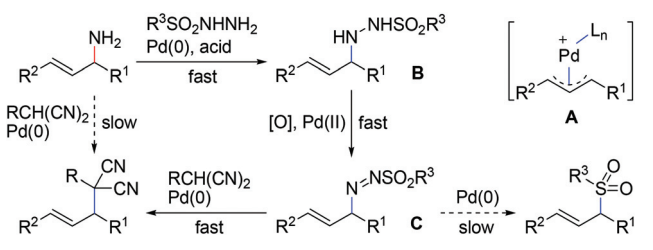
A range of primary allylic amines were resolved with selectivity factors of up to 491 through [Pd(allyl)Cl]$_2$/(*S*)-BINAP-catalyzed and mesitylsulfonyl hydrazide-accelerated asymmetric allylic alkylation of malononitriles involving enantioselective C–N bond cleavage under aerobic conditions. Moreover, the reaction proved useful for the asymmetric synthesis of α-branched allyl-substituted malononitriles with high enantiopurity.

Enantioenriched allylic amines serve as versatile building blocks for the synthesis of important compounds such as azaheterocycles, amino alcohols, amino acids, and therapeutic agents.[1] Moreover, direct substitution of enantioenriched allylic amines has emerged as a powerful approach to afford chiral functionalized alkenes.[2] Enantioenriched allylic amines are generally prepared *via* asymmetric imine additions,[3] allylic amination,[4] Overman rearrangement,[5] and aza-Morita–Baylis–Hillman reaction.[6] Among these approaches, only a few asymmetric allylic amination reactions directly provide enantioenriched primary allylic amines, which are, in fact, limited to terminal or symmetrical ones.[7] Alternatively, direct access to enantioenriched primary allylic amines has been developed *via* resolution of the corresponding racemic mixtures, which, however, has received much less attention relative to that of other primary alkylamines.[8,9] In this regard, classic resolution *via* diastereomeric crystallization with chiral acids proves useful in affording enantioenriched primary allylic amines, albeit the process requires one equivalent of a chiral reagent and frequently suffers from poor yields because of repeated crystallization.[2a,b,10] Moreover, a chiral acylating agent in a stoichiometric amount has enabled kinetic resolution of terminal primary allylic amines with selectivity factors ($s = k_{fast}/k_{slow}$) of up to 34.[11,12] On the other hand, catalytic enantioselective acylation of primary allylic amines has also been disclosed. Enzymatic acylative kinetic resolution has allowed the synthesis of enantioenriched primary allylic amines, mainly α-aryl allylamines, in moderate to excellent ee.[13] In 2011, Seidel and coworkers disclosed a chiral thiourea/aminopyridine-catalyzed acylative kinetic resolution of unsymmetrical primary allylic amines with *s* factors of up to 20.[14] Notably, Itoh and coworkers reported a kinetic resolution of tertiary allylic amines having α-phenyl and γ-trifluoromethyl groups with *s* factors of up to 19 *via* palladium-catalyzed asymmetric α-to-γ isomerization.[15] In connection with our long-standing interest in exploring the synthetic utilities of C–N bond cleavage,[2,16] we have developed a new strategy for the catalytic kinetic resolution of primary allylic amines through enantioselective substitution of the NH_2 group under mild conditions with *s* factors of up to 491.

To develop an efficient kinetic resolution of primary allylic amines, we started our investigation by establishing a set of mild conditions for direct substitution of the NH_2 group. Prompted by our recent studies on the removal of the $NHNH_2$ group from sulfonyl hydrazides,[17] particularly in its oxidative coupling with primary allylic amines,[2d] we proposed a sulfonyl hydrazide-accelerated allylic alkylation reaction of malononitriles with primary allylic amines.[2c] As outlined in Scheme 1, when a primary allylic amine is treated with a malononitrile and a sulfonyl hydrazide in the presence of a palladium catalyst and an acid, the NH_2 group would prefer to be displaced by the sulfonyl hydrazide because of its higher nucleophilicity relative to the malononitrile. The resulting disubstituted



Scheme 1 Proposed sulfonyl hydrazide-accelerated allylic alkylation.

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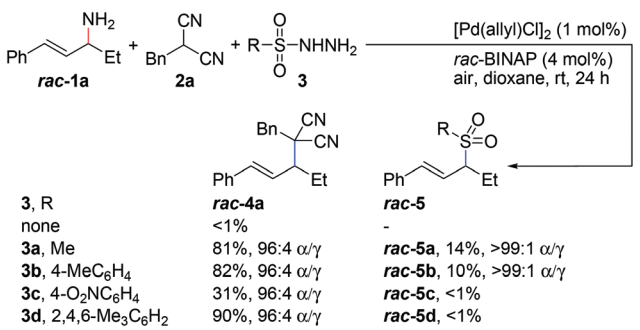
hydrazine **B** would be oxidized quickly to give diazene **C**, which is a highly reactive allylic compound and would undergo palladium-catalyzed substitution with the malononitrile. While a sulfinic acid (R^3SO_2H) would be generated in this step as well as through oxidation of the sulfonyl hydrazide,[2d] its coupling with π-allylpalladium complex **A**, an intermediate generated either in the first step or in the last step, was expected to proceed more slowly due to its lower nucleophilicity relative to the malononitrile.

The allylic alkylation reaction of malononitrile **2a** with racemic primary allylic amine ***rac*-1a** was selected to test our hypothesis (Scheme 2). In the presence of $[Pd(allyl)Cl]_2$ (1 mol%) and racemic BINAP (4 mol%), the reaction proceeded very sluggishly in dioxane under air at room temperature. In sharp contrast, addition of a sulfonyl hydrazide (1.2 equiv.) dramatically accelerated the reaction to yield malononitrile ***rac*-4a**. Moreover, we were able to minimize the formation of sulfone ***rac*-5** by changing the structure of the sulfonyl hydrazide. To our delight, mesitylsulfonyl hydrazide (**3d**) was identified as the best additive, the use of which gave malononitrile ***rac*-4a** in 90% yield with 96 : 4 α/γ selectivity and complete retention of the *E*-alkene geometry.[18]

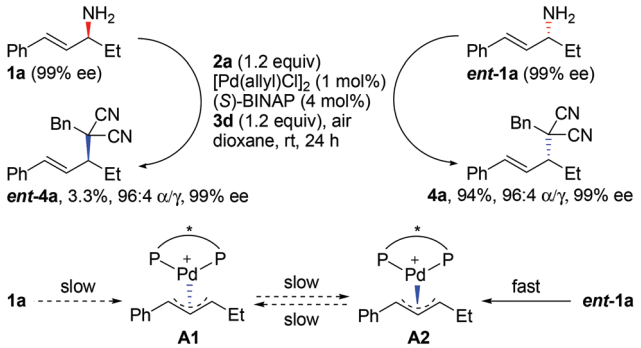
To investigate the stereochemistry, we treated highly enantioenriched primary allylic amine **1a** with malononitrile **2a**, sulfonyl hydrazide **3d**, $[Pd(allyl)Cl]_2$, and optically active (*S*)-BINAP (Scheme 3). The reaction proceeded sluggishly under air at room temperature and gave malononitrile ***ent*-4a** in only 3.3% yield (determined by ^1H NMR) with complete retention of the configuration. In sharp contrast, replacement of amine **1a** with its enantiomer ***ent*-1a** led to the formation of malononitrile **4a** in 94% yield with complete retention of the configuration. These results allowed us to conclude that the stereochemistry was controlled by the substrate rather than by the reagent and that the *in situ*-generated π-allylpalladium complexes, **A1** and **A2**, would not isomerize to each other under the above conditions. Importantly, the dramatically different reaction rates (k_{fast}/k_{slow} = 28) for the two enantiomeric substrates encouraged us to develop an efficient kinetic resolution process for primary allylic amines.

To our delight, the reaction of racemic primary allylic amine ***rac*-1a** with malononitrile **2a** (0.6 equiv.) in the presence



3, R	*rac*-4a	*rac*-5
none	<1%	-
3a, Me	81%, 96:4 α/γ	***rac*-5a**, 14%, >99:1 α/γ
3b, 4-MeC_6H_4	82%, 96:4 α/γ	***rac*-5b**, 10%, >99:1 α/γ
3c, 4-$O_2NC_6H_4$	31%, 96:4 α/γ	***rac*-5c**, <1%
3d, 2,4,6-$Me_3C_6H_2$	90%, 96:4 α/γ	***rac*-5d**, <1%

Scheme 2 Survey of sulfonyl hydrazides.

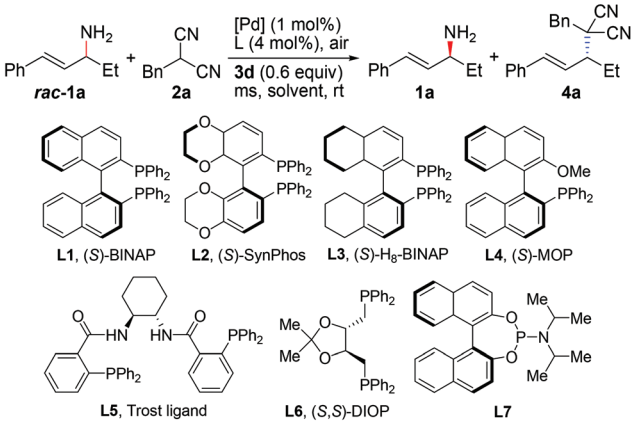


Scheme 3 Allylic alkylation with enantioenriched primary allylic amines.

of sulfonyl hydrazide **3d** (0.6 equiv.), $[Pd(allyl)Cl]_2$ (1 mol%), and (*S*)-BINAP (4 mol%) proceeded smoothly in dioxane under air at room temperature to give malononitrile **4a** in 38% yield and 80% ee together with the recovered enantioenriched primary allylic amine **1a** in 40% yield and 92% ee, corresponding to an *s* factor of 29 for the kinetic resolution (Table 1, entry 1).[19] Addition of 5 Å molecular sieves improved the enantioselectivity of the kinetic resolution with an *s* factor of 42 (entry 2). The use of a palladium(II) source such as $Pd(OAc)_2$, $PdCl_2$, or $Pd(NO_3)_2$ led to lower enantioselectivity for the kinetic resolution, and in contrast, the reaction failed to take place when using a palladium(0) source such as $Pd_2(dba)_3$ (entries 3–6). Chiral phosphorus ligands **L2–7** were evaluated and only axially chiral bisphosphine ligands **L2** and **L3** were capable of promoting the reaction but gave lower enantioselectivity (entries 7–9). Replacing dioxane with some other common organic solvents gave lower enantioselectivity or even led to sluggish reactions (entries 10–13). Finally, portionwise addition of sulfonyl hydrazide **3d** was found to give the best result: *s* = 49 (entry 14).[20]

Under the optimized reaction conditions, we conducted the kinetic resolution of various racemic primary allylic amines with malononitriles (Table 2). In general, the asymmetric allylic alkylation reaction of malononitriles with unsymmetrical primary allylic amines having α-alkyl and γ-aryl groups proceeded with excellent α selectivity and complete retention of the *E*-alkene geometry and the racemic primary allylic amines were efficiently resolved with *s* factors ranging from 32 to 491 (entries 1–6, 8–13, and 17–20).[21] In contrast, moderate enantioselectivity was observed in the kinetic resolution of primary allylic amines when both the α- and γ-substituents are either aryl or alkyl groups (entries 7 and 15). Moreover, the kinetic resolution process was successfully extended to a primary allylic amine having a γ-alkenyl group as well as an α-aryl allylamine with good enantioselectivity (entries 14 and 16). In the above cases, the regioselectivity was determined by the steric and electronic properties of the α- and γ-substituents, and the reaction preferred to occur at the allylic position having less steric hindrance and/or leading to a higher degree of conjugation. Nevertheless, the reaction became sluggish with a

Table 1 Optimization of reaction conditions[a]



Entry	[Pd]	L	Solvent	Yield[b] (%) 1a	Yield[b] (%) 4a	α/γ[c] (4a)	ee[d] (%) 1a	ee[d] (%) 4a	s[e]
1[f]	$[Pd(allyl)Cl]_2$	**L1**	Dioxane	40	38	96 : 4	92	80	29
2	$[Pd(allyl)Cl]_2$	**L1**	Dioxane	42	40	96 : 4	95	84	42
3[g]	$Pd(OAc)_2$	**L1**	Dioxane	72	13	94 : 6	34	87	20
4[g]	$PdCl_2$	**L1**	Dioxane	27	41	95 : 5	99	70	28
5[g]	$Pd(NO_3)_2$	**L1**	Dioxane	34	54	94 : 6	97	73	26
6	$Pd_2(dba)_3$	**L1**	Dioxane	—	0	—	—	—	—
7	$[Pd(allyl)Cl]_2$	**L2**	Dioxane	35	46	96 : 4	99	56	17
8	$[Pd(allyl)Cl]_2$	**L3**	Dioxane	34	41	96 : 4	99	61	20
9	$[Pd(allyl)Cl]_2$	L[h]	Dioxane	—	Trace	—	—	—	—
10	$[Pd(allyl)Cl]_2$	**L1**	THF	47	37	96 : 4	65	84	22
11	$[Pd(allyl)Cl]_2$	**L1**	CH_2Cl_2	48	35	96 : 4	80	66	11
12	$[Pd(allyl)Cl]_2$	**L1**	Toluene	58	26	96 : 4	43	92	37
13	$[Pd(allyl)Cl]_2$	**L1**	Solvent[i]	—	Trace	—	—	—	—
14[j]	$[Pd(allyl)Cl]_2$	**L1**	Dioxane	43	41	96 : 4	95	86	49

[a] Conditions: ***rac*-1a** (0.30 mmol), **2a** (0.18 mmol), **3d** (0.18 mmol), [Pd] (1 mol%), L (4 mol%), ms (30 mg), air, solvent (1.8 mL), rt, 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC. [e] $s = \ln[(1 - C)(1 - ee_{1a})]/\ln[(1 - C)(1 + ee_{1a})]$, where $C = ee_{1a}/(ee_{1a} + ee_{4a})$.[12] [f] Without ms. [g] [Pd] (2 mol%) was used. [h] **L4–7**. [i] MeCN, DMF, DMSO, or EtOH. [j] **3d** was added three times in 8 h.

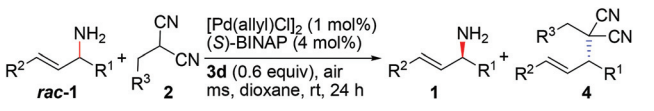
cyclic primary allylic amine, such as 3-aminocyclohexene, and with a primary allylic amine having a β-substituent, such as (*E*)-3-amino-2-methyl-1-phenyl-1-butene.

The enantioenriched primary allylic amines obtained from the above process underwent enantiospecific allylic alkylation of malononitriles under the same reaction conditions but using racemic BINAP instead of (*S*)-BINAP as the ligand (Scheme 4). Such transformation provided facile access to the enantiomers of malononitriles **4** (as listed in Table 2) in good yields with excellent ee. Importantly, the enantioselective kinetic resolution along with the enantiospecific substitution complemented the scope for the asymmetric synthesis of α-branched allyl-substituted malononitriles with high enantiopurity.[2c,19]

When the kinetic resolution process was extended to secondary and tertiary allylic amines, the reaction provided lower enantioselectivity relative to that with primary ones (Scheme 5).[15,22] Furthermore, we found that the enantiopurity of primary allylic amine **1e** (94% ee, Table 2, entry 5) remained unchanged under the standard reaction conditions but without the malononitrile and that, in sharp contrast, significant erosion of enantiopurity was observed for secondary allylic amine **1eb** (from 70% ee to 50% ee). These results indicate that the π-allylpalladium complex generated from an allylic amine having a bulkier leaving amino group would isomerize more readily *via* Pd–Pd-exchange under the standard reaction conditions.[23] Definitely, the isomerization contributes greatly to the lower enantioselectivity for the kinetic resolution of secondary and tertiary allylic amines relative to primary ones. On the other hand, the reaction of a secondary or a tertiary allylic amine would give a primary or a secondary amine, rather than gaseous ammonia in the case of a primary allylic amine, as the byproduct, which would stay in the reaction mixture and decrease the enantioselectivity in the subsequent allylic alkylation through coordination with the palladium atom and/or deprotonation of the malononitrile.[24]

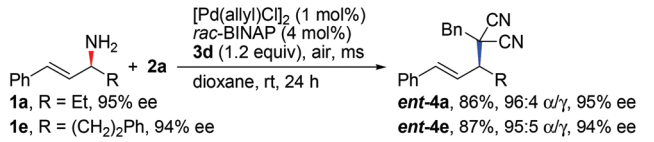
In summary, we have developed a new and efficient strategy for the catalytic kinetic resolution of primary allylic amines *via* enantioselective C–N bond cleavage. A range of primary allylic amines were resolved with *s* factors of up to 491 through

Table 2 Kinetic resolution of primary allylic amines[a]

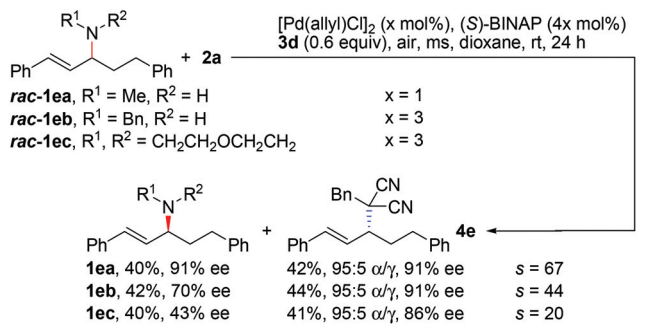


Entry	R^1, R^2, R^3	Yield[b] (%) 1	4	α/γ[c] (4)	ee[d] (%) 1	4	s^e
1	Et, Ph, Ph	43	41	96 : 4	95	86	49
2	Me, Ph, Ph	42	54	>99 : 1	97	79	33
3	$(CH_2)_3Me$, Ph, Ph	39	48	94 : 6	90	94	100
4	$(CH_2)_7Me$, Ph, Ph	44	45	93 : 7	96	94	127
5	$(CH_2)_2Ph$, Ph, Ph	42	44	95 : 5	94	93	98
6	$CH_2CH{=}CH_2$, Ph, Ph	56	21	90 : 10	60	94	60
7[f]	Ph, Ph, Ph	35	57	—	70	60	8.2
8	Et, 4-$MeOC_6H_4$, Ph	51	45	98 : 2	85	96	128
9	Et, 4-FC_6H_4, Ph	42	48	97 : 3	93	88	53
10	Et, 4-ClC_6H_4, Ph	48	49	96 : 4	94	84	40
11	Et, 4-NCC_6H_4, Ph	41	49	97 : 3	91	90	60
12	Me, 2-naphthyl, Ph	41	51	>99 : 1	99	73	32
13	Et, benzo[*b*]thien-2-yl, Ph	42	47	99 : 1	91	95	124
14	Me, (*E*)-PhCH=CH, Ph	40	37	>99 : 1	80	69	13
15	Me, cyclohexyl, Ph	42	41	>99 : 1	70	46	5.4
16[f]	Ph, H, Ph	37	52	<1 : 99	89	—	—
17[g]	$(CH_2)_2Ph$, Ph, 2-furyl	37	50	96 : 4	93	93	94
18[g]	$(CH_2)_2Ph$, Ph, 2-naphthyl	40	36	95 : 5	80	99	491
19[g]	$(CH_2)_2Ph$, Ph, C≡CTMS	30	37	94 : 6	67	94	65
20[g]	$(CH_2)_2Ph$, Ph, $CO_2{}^tBu$	36	45	93 : 7	80	87	35

[a] Conditions: ***rac*-1** (0.30 mmol), **2** (0.18 mmol), **3d** (0.18 mmol), [Pd(allyl)Cl]$_2$ (1 mol%), (*S*)-BINAP (4 mol%), ms (30 mg), air, dioxane (1.8 mL), rt, 24 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC. [e] $s = \ln[(1 - C)(1 - ee_1)]/\ln[(1 - C)(1 + ee_1)]$, where $C = ee_1/(ee_1 + ee_4)$.[12] [f] **3d** (10 mol%) was used and the reaction was run for 4 h. [g] The reaction was run at 50 °C.



Scheme 4 Enantiospecific allylic alkylation.



Scheme 5 Kinetic resolution of secondary and tertiary allylic amines.

[Pd(allyl)Cl]$_2$/(*S*)-BINAP-catalyzed and mesitylsulfonyl hydrazide-accelerated asymmetric allylic alkylation of malononitriles under air at room temperature or at 50 °C. Moreover, the reaction proved useful for the asymmetric synthesis of α-branched allyl-substituted malononitriles with high enantiopurity.

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