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Catalytic Kinetic Resolution of Disubstituted Piperidines by Enantioselective Acylation: Synthetic Utility and Mechanistic Insights

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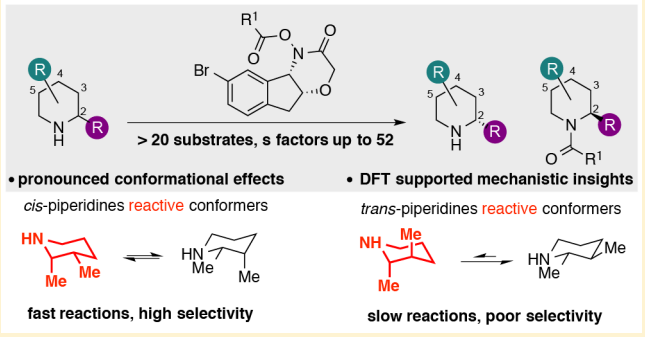
Supporting Information

ABSTRACT: The catalytic kinetic resolution of cyclic amines with achiral N-heterocyclic carbenes and chiral hydroxamic acids has emerged as a promising method to obtain enantioenriched amines with high selectivity factors. In this report, we describe the catalytic kinetic resolution of disubstituted piperdines with practical selectivity factors (*s*, up to 52) in which we uncovered an unexpected and pronounced conformational effect resulting in disparate reactivity and selectivity between the cis- and trans-substituted piperidine isomers. Detailed experimental and computational studies of the kinetic resolution of various disubstituted piperidines revealed a strong preference for the acylation of conformers in which the α-substituent occupies the axial position. This work provides further experimental and computational support for the concerted 7-member transition state model for acyl transfer reagents and expands the scope and functional group tolerance of the secondary amine kinetic resolution.



INTRODUCTION

Disubstituted piperidines are increasingly attractive platforms for drug development, as the precise placement of substituents about the basic, low-molecular weight, three-dimensional scaffold is ideally suited for structure−activity relationship studies.[1] Although the synthesis of such saturated N-heterocycles remains challenging,[2] recent advances including diastereoselective metalation/cross-coupling,[3] conjugate additions of dihydropyridinones,[4] hydrogenation of disubstituted pyridines,[5] and cyclization methods[6] are bringing these once exotic building blocks into the mainstream. Unfortunately, most of the available methods for the preparation of multisubstituted N-heterocycles deliver racemic products, and prospects for enantioselective approaches to many substitution patterns are limited.[7]

For such challenging cases, kinetic resolution can be an efficient and powerful alternative to enantioselective synthesis of chiral N-heterocycles.[8] Although kinetic resolution has the disadvantage of a maximum yield of 50% of a desired stereoisomer, for early stage applications it can be a reliable, effective, and easily implemented tool for the production of enantiopure material. Provided that selectivity factors (*s*) greater than 20 can be obtained, kinetic resolution can be used to separate enantiomers with acceptable yield and outstanding enantiopurity.[9]

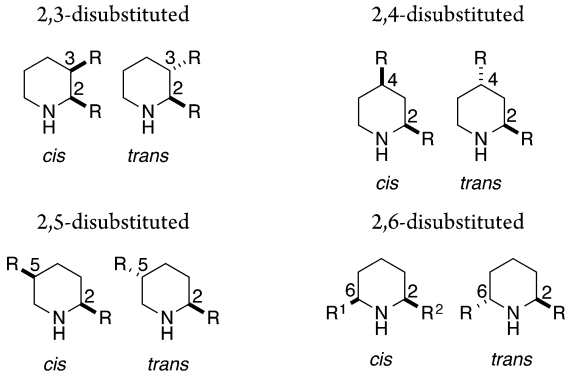
In 2011, our group reported a new approach to the catalytic, kinetic resolution of saturated N-heterocycles consisting of two catalysts working synergistically.[10] Our key advance was the use of a chiral hydroxamic acid, employed in either catalytic or stoichiometric amounts, as highly enantio- and chemoselective acylating agent, which operates by a unique mechanism involving concerted acyl and proton transfer via a seven-member transition state.[11,12] To date, our studies on the kinetic resolution of chiral N-heterocycles using chiral hydroxamic acids have been limited to mono-, α-substituted N-heterocyclic substrates. In contrast to the resolution of α-monosubstituted N-heterocycles, the resolution of disubstituted piperidines requires an enantioselective catalyst that is not affected by the additional ring substituents (Scheme 1).

In this report, we examine the reactivity and selectivity of disubstituted piperidines in the kinetic resolution by means of enantioselective acylation with a chiral hydroxamic acid. Kinetic resolution studies and density functional theory (DFT) calculations exposed remarkable conformational preferences in both reactivity and selectivity, revealing a requirement for axial-α substitution on the reactive form of the N-heterocycle for effective resolution. This preference extends even to substitution patterns where the substituents must occupy bis-axial positions. This work provides, (1) access to valuable enantioenriched disubstituted piperidines, (2) general guidelines for selecting suitable N-heterocycles as substrates for the kinetic resolution via chiral hydroxamic acids, and (3) affirmation of the transition state model involving a high

Received: July 10, 2015

DOI: 10.1021/jacs.5b07201
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 1. Four Possible Positional Isomers of Disubstituted Piperidines That Serve as Targets for Our Study



energy conformation of the substrate that we had previously developed on the basis of DFT calculations.

RESULTS AND DISCUSSION

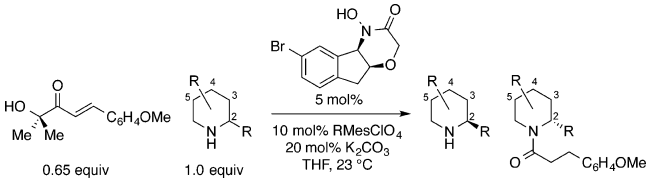
As depicted in Scheme 1, there are four types of disubstituted piperidines that could serve as target substrates for our study. Piperidines without α-substituents, such as 3,5-disubstituted piperidines, undergo acylation in an unselective manner. Further, 2,6-disubstituted substrates were found to be unreactive and were excluded from further studies.

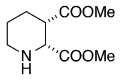
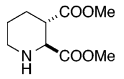
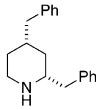
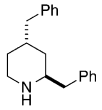
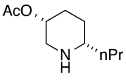
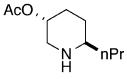
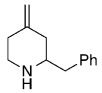
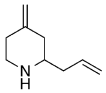
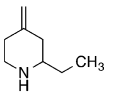
Our work therefore targeted the six isomers arising from 2,3-, 2,4-, and 2,5-disubstitution of piperidine, with cis and trans stereoisomers in each case. Further disubstituted compounds with an exocyclic 4-methylene group were also prepared and evaluated. The results of the catalytic kinetic resolution are summarized in Table 1. Surprisingly, we observed substantial differences in the reactivity and selectivity between the cis isomer and trans isomer of the otherwise identical positional isomers. For the 2,3-disubstituted piperidines (Table 1, entries 1 and 2, entries 7 and 8) and 2,5-disubstituted piperidines (Table 1, entries 5 and 6) the cis isomer underwent faster reactions with higher selectivity, while the trans isomer gave rise to superior outcomes for the 2,4-disubstituted compounds (Table 1, entries 3 and 4). The decahydroquinoline isomers were particularly interesting, as the trans isomer is conformationally locked. These results already hinted at strict stereochemical requirements for effective enantioselective acylation.

In light of these initially confusing results, we undertook an extensive study to assess the role of the positional isomers and their stereoisomers. Our goal was to reliably predict whether a given substrate would undergo a selective kinetic resolution. We elected to evaluate at least three substrate pairs (cis/trans) for each of the three positional isomers, giving 20 substrates in total. Considerations for compound selection included synthetic accessibility, the presence of groups for further functionalization of the products, and ready access to diastereomerically pure forms of the targets (see Supporting Information for experimental procedures and characterization data).

To rule out selectivity arising from the NHC-catalyst in the kinetic resolution, we used our previously reported stoichiometric variant in the resolution of these N-heterocycles.[10] Slightly higher reaction rates and selectivities are observed with this reagent and a recyclable, resin-supported variant makes it an attractive option for practical amine resolution.[13] We first examined the kinetic resolution of the compounds in the 2,3-disubstitution series (Table 2). The data presented in Table 1 implied that substrates with a cis configuration undergo faster reaction with much higher selectivities than those observed for the trans isomers. With *cis*-2-phenylpiperidin-3-ol (Table 2, entry 1) an *s*-factor of 24 and a conversion of 33% could be obtained after 48 h, whereas the trans diastereomer (Table 2, entry 2) reached only 14% conversion after 72 h with essentially no selectivity. This trend could also be observed

Table 1. Catalytic Kinetic Resolution of Disubstituted Piperidines

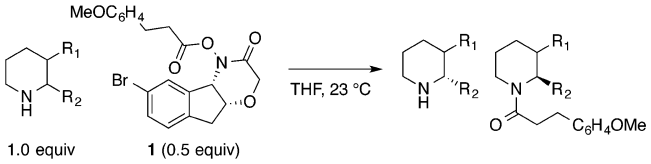


Entry	Substrate	s[a]	Conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e] (%)	er amide[d] yield[e] (%)
1		11	28	72	64:36 (43)	89:11 (25)
2		2	3	72	51:49 (58)	67:33 (5)
3		3	4	48	51:49 (43)	78:22 (4)
4		21	59	20	99:1 (28)	83:17 (26)
5		19	17	20	59:41 (35)	94:6 (20)
6		8	5	48	52:48 (54)	89:11 (9)
7		18	63	48	99:1 (20)	79:21 (40)
8[f]		9	11	65	45:55 (61)	10:90 (9)
9		19	43	20	81:19 (40)	91:9 (42)
10		14	41	20	77:23 (43)	89:11 (40)
11		21	55	20	96:4 (42)	87:13 (43)

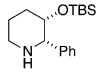
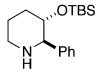
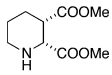
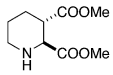
[a]Calculated selectivity.[15] [b]Calculated conversion.[15] [c]Reaction time until the α-hydroxyenone is fully consumed. [d]Determined by SFC or HPLC on a chiral support. [e]Isolated as the Cbz-derivative. Yield after column chromatography. [f]Opposite sense of induction observed. $RMesClO_4$ = (2,4,6-trimethylphenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-*c*][1,2,4]triazol-4-ylium perchlorate.

DOI: 10.1021/jacs.5b07201
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Kinetic Resolution of 2,3-Disubstituted Piperidines with Stoichiometric Reagent 1

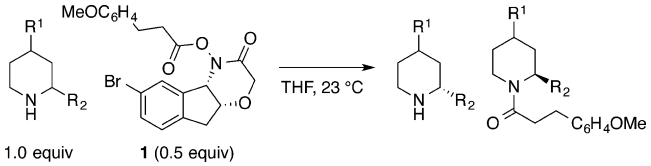


1.0 equiv 1 (0.5 equiv)

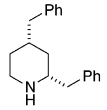
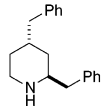
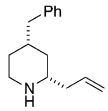
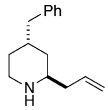
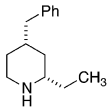
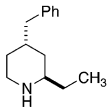
Entry	Substrate	s[a]	Conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e] (%)	er amide[d] yield[e] (%)
1		24	33	48	72:28 (31)	94:6 (30)
2		1	14	72	51:49 (32)	56:44 (5)
3		19	31	72	69:31 (34)	93:7 (28)
4		2	46	96	56:44 (39)	57:43 (7)
5		23	50	72	90:10 (39)	91:9 (50)
6		4	26	96	59:41 (40)	75:25 (21)
7[f]		20	65	15	99:1 (17)	73:27 (50)
8[g]		20	36	48	24:76 (25)	7:93 (30)

[a]Calculated selectivity. [b]Calculated conversion. [c]Reaction time until stoichiometric reagent is fully consumed. [d]Determined by SFC or HPLC on a chiral support. [e]Isolated as the Cbz-derivative. Yield after column chromatography. [f]Stochiometric reagent **1** (0.6 equiv) was used. [g]Opposite sense of induction observed.

Table 3. Kinetic Resolution of 2,4-Disubstituted Piperidines with Stoichiometric Reagent 1



1.0 equiv 1 (0.5 equiv)

Entry	Substrate	s[a]	Conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e] (%)	er amide[d] yield[e] (%)
1		3	22	120	57:43 (39)	78:22 (4)
2[f]		10	65	20	97:3 (15)	75:25 (43)
3		7	32	72	66:34 (56)	84:16 (29)
4		29	52	20	94:6 (46)	91:9 (45)
5		6	38	96	68:32 (46)	80:20 (34)
6[f]		15	62	20	98:2 (19)	80:20 (40)

[a]Calculated selectivity. [b]Calculated conversion. [c]Reaction time until stoichiometric reagent is fully consumed. [d]Determined by SFC or HPLC on a chiral support. [e]Isolated as the Cbz-derivative. Yield after column chromatography. [f]Stochiometric reagent **1** (0.6 equiv) was used.

for the other two sets of substrates (Table 2, entries 3 and 4, entries 5 and 6). Decahydroquinolines showed a similar behavior in terms of reaction rate, although acceptable selectivity was obtain in both cases. In the resolution of *cis*-decahydroquinoline (Table 2, entry 7), 65% conversion was obtained after 15 h, whereas the conformationally locked *trans*-decahydroquinoline (Table 2, entry 8) reacted much slower. Notably, the opposite sense of induction was observed with this substrate, which contradicted a simple stereochemical model based only on the stereochemistry of the acyl transfer reagent (vide infra). The kinetic resolution reactions were stopped once the stoichiometric reagent was fully consumed.[14]

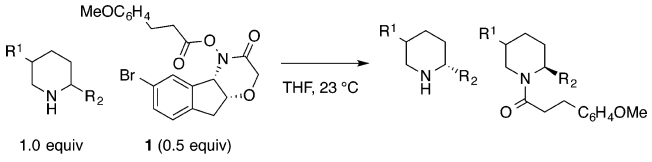
For the 2,4-disubstituted piperidines (Table 3), the trend was reversed in comparison to that observed for the 2,3-disubstituted examples in Table 2. For this series, the cis diastereomers exhibit poor selectivities (s = 3−7) and low reactivity with reaction times between 72 and 120 h (Table 3, entries 1, 3, and 5). In contrast, the trans diastereomers reached full conversion in 20 h or less with high selectivities (s = 10−29) (Table 3, entries 2, 4, and 6).

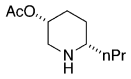
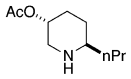
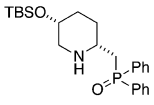
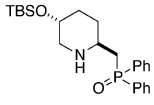
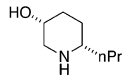
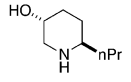
In the case of the 2,5-disubstituted piperidines (Table 4) we observed a similar trend as with the 2,3-disubstituted substrates. Namely, higher s-factors were observed for the cis diastereomers as well as higher reaction rates compared to the corresponding trans diastereomers. The biggest contrast with regards to s factors can be noticed in entry 5; for *cis*-6-propylpiperidin-3-ol an s factor of 52 was obtained while the trans isomer (Table 4, entry 6) afforded an s factor of only 4. Such large differences in selectivity were not evident in entries 1−4; however, the data supports the conjecture that cis isomers in this series are superior to the trans isomers. These substrates also demonstrate the chemoselectivity of the kinetic resolution for N-heterocycles bearing a variety of functional groups suitable for further functionalization.

The divergent reactivity of the diastereomeric pairs in the different series can be rationalized on the basis of our recent DFT calculations of the transition states of α-methylpiperidine reacting with the chiral acylating agent.[12] These studies concluded that acylation occurred via a concerted seven-membered transition state with concomitant proton transfer guided by the hydroxamic acid and with the α-substituent placed in the axial position. In contrast, other work from our group on the resolution of morpholines with stoichiometric chiral acyl donors and achiral hydroxamic acids was most consistent with a stereochemical model featuring an equatorial

DOI: 10.1021/jacs.5b07201
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

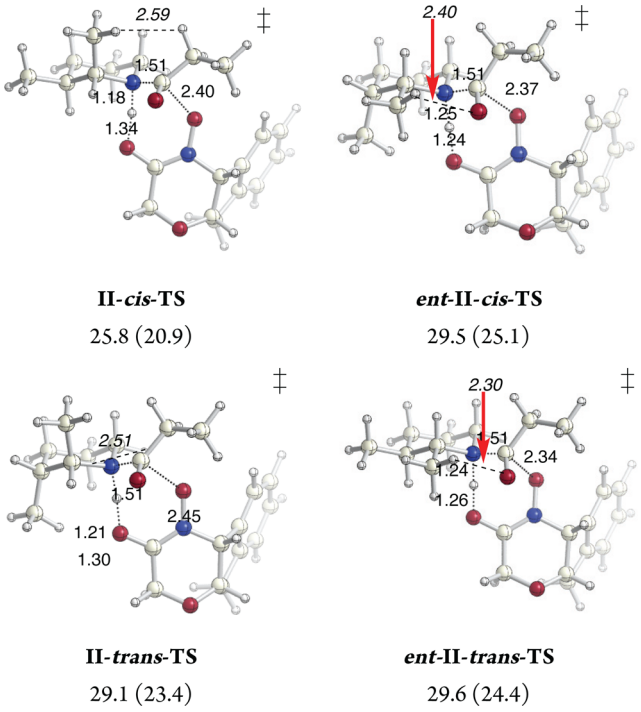
Table 4. Kinetic Resolution of 2,5-Disubstituted Piperidines with Stoichiometric Reagent 1



Entry	Substrate	s[a]	Conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e] (%)	er amide[d] yield[e] (%)
1		22	42	24	81:19 (44)	92:8 (33)
2		20	40	96	78:22 (47)	92:8 (33)
3		13	54	72	90:10 (22)	84:16 (28)
4		9	29	72	65:35 (45)	87:13 (19)
5		52	54	20	99:1 (25)	92:2 (38)
6		4	53	48	74:26 (29)	71:29(51)

[a]Calculated selectivity. [b]Calculated conversion. [c]Reaction time until stoichiometric reagent is fully consumed. [d]Determined by SFC or HPLC on a chiral support. [e]Isolated as the Cbz-derivative. Yield after column chromatography.

Scheme 2. Relative Acyl Transfer Reaction Barriers[a]



II-*cis*-TS
25.8 (20.9)

***ent*-II-*cis*-TS**
29.5 (25.1)

II-*trans*-TS
29.1 (23.4)

***ent*-II-*trans*-TS**
29.6 (24.4)

[a]Relative acyl transfer reaction barriers (free energies are in kcal/mol; gas phase energetics calculated using B3LYP/6-31G(d,p)//(in parentheses IEPCM-CH_2Cl_2-M06-2*X*/6-311+G(d,p)) for the competing diastereomeric transtion states between cis- and trans-2,3-dimethyl substituted piperidines and the acyl transfer agent.

substituent of a morpholine.[16] However, no computational studies were performed on this system and significant conformational differences between morpholine and piperidines can be expected. Both models suggest that the stereoselective step involves a seven-membered transition state with the lone pair of the nitrogen in the equatorial position. This mechanism of acyl transfer was found to be general for a variety of widely used acyl transfer reagents including *N*-hydroxysuccinimide, and HOAt.

To reconcile these two models with the results obtained for the resolution of disubstituted piperidines, we undertook detailed DFT studies on the relevant transition states using the cis and trans geometric isomers of 2,3-dimethylpiperidine as a model system and the chiral hydroxamic acid.[17] All calculations were carried out using the same computational methods previously employed in related systems using Gaussian 09.[18] Structures were optimized with B3LYP/6-31G(d).[19,20] Single-point energy calculations in the condensed phase (CH_2Cl_2; ε = 8.93) were undertaken using the IEPCM solvation model with M06-2*X*/6-311+G(d,p).[21] Scheme 2 shows the lowest energy transition states for acyl transfer to each enantiomer of *cis*- and *trans*-2,3-dimethylpiperidine. As anticipated from our previous work, the concerted seven-membered transition states feature an intramolecular proton shuttle between the secondary amine and the hydroxamate carbonyl. The calculations are in agreement with experimental rates and selectivity trends listed in Table 2 (entries 1−6) in which the cis 2,3-disubstituted piperidines showed significantly faster rates and superior *s* factors (*s* = up to 24) in comparison to the trans 2,3-disubstituted piperidines. For example, the lowest transition state free energy for the **II-*cis*** (25.8 kcal/mol gas phase) is approximately 3 kcal/mol lower in energy than the lowest for **II-*trans*** (29.1 kcal/mol gas phase), which is consistent with the relative rates of these two amine diastereomers.

This finding is in line with our postulate that the lower energy transition states for acyl transfer feature an axial α-substituent, which requires the *trans*-2,3-dimethylpiperidine to adopt an unfavorable diaxial conformation. In contrast, the chair conformation of the *cis*-2,3-dimethylpiperidine with an α-axial substituent is the preferred ground state conformation. Further, our calculations correctly predict the fastest reacting enantiomer via **II-*trans*-TS** and **II-*cis*-TS**, respectively. In agreement with experiment, the quantum mechanical calculations indicate a larger gap between the cis-1,2-disubsituted systems (here modeled as 2,3-dimethylpiperidine **II-*cis*** and ***ent*-II-*cis***) than the trans-1,2-disubsituted systems, which reflects the significant difference in selectivity between cis and trans diastereomers.[22] Notably, the lowest energy diastereomeric transition states place the α-substituent away from both the aromatic ring of the acyl transfer agent and the acyl chain. Exhaustive conformational analysis, including other chair conformations, revealed that all other transition states are much higher in energy (see Figure 1 and Supporting Information). For kinetic resolution, the energy difference between the diastereomeric acylation transition states determines the selectivity. As shown in Figure 1, the significant energy difference (3.7 kcal/mol, *s* = 19−24) between **II-*cis*-TS** and ***ent*-II-*cis*-TS** arises from the additional unfavorable *gauche*

DOI: 10.1021/jacs.5b07201
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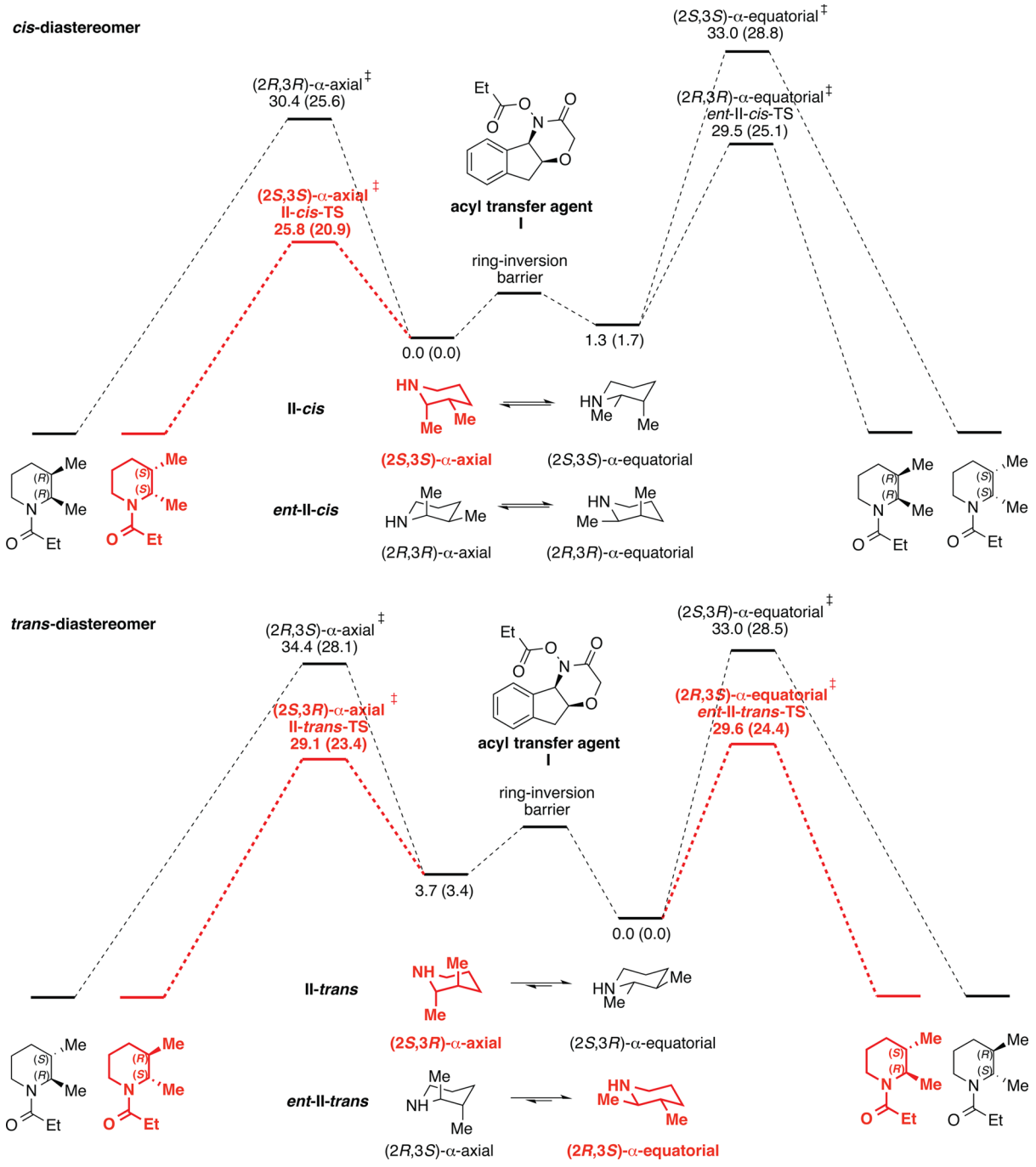

Figure 1. Proposed reaction pathways for possible conformers/enantiomers in the kinetic resolution. Relative acyl transfer reaction barriers (free energies are in kcal/mol; gas phase energetics calculated using B3LYP/6-31G(d,p)//(in parentheses IEPCM-CH_2Cl_2-M06-2X/6-311+G(d,p)) for the competing diastereomeric transtion states between *cis* and *trans* 2,3- dimethyl substituted piperidines and the acyl transfer agent.

interactions between the α-substituent in the equatorial position and the carbonyl group. In addition, ***ent*-II-*cis*-TS** has a further interaction between the axial β-methyl group and the hydroxamate carbonyl.

In contrast, the energy difference between **II-*trans*-TS** and ***ent*-II-*trans*-TS** is small at 0.5 kcal/mol, which is consistent with the poor *s* factors (s = 1−4) observed for the trans substituted systems. It is remarkable, however, that the preferred conformation for the lowest energy transition state is the trans-2,3-bis-axial, which demonstrates again the strong preference for α-axial substituents in the acylation step and offers an excellent example of the Curtin-Hammett principle (Figure 1, bottom). The dimethyl groups are in the axial position in **II-*trans*-TS** and in the equatorial position in ***ent*-II-*trans*-TS**; in this case, the additional 1,3-diaxial interactions in **II-*trans*-TS** raise its energy leading to a smaller energy gap between the two enantiomers and smaller selectivity values.

The disparate results seen for the decahydroquinolines serve to further confirm this model. The *trans*-decahydroquinoline leads to the opposite sense of induction relative to the *cis*-decahydroquinoline even though the same configuration of the chiral acylating reagent is employed. Since the *trans*-decahydroquinoline cannot react in the conformation where the α-substituent is axial, the only transition states that are

DOI: 10.1021/jacs.5b07201
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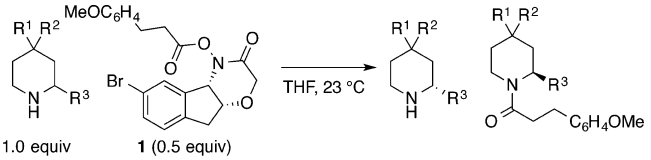
acessible have the α-substituent in the equatorial position (Figure 1, lower right). When only these two transition states are considered, selectivity is expected for the *opposite enantiomer* owing to the large calculated energy gap. Further, the reaction rate of *trans*-decahydroquinoline is expected to be slower, as observed experimentally, since the overall energy of this pathway is higher.

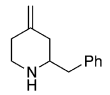
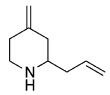
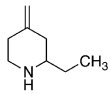
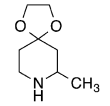
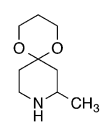
The same results can be applied to 2,5-disubstituted piperidines. Just as with the 2,3-disubstituted compounds, the cis diastereomer consists of two conformers that differ only slightly in energy, whereas the trans diastereomer exists primarily in the diequatorial conformer rather than the higher energy diaxial conformation. An analogous situation occurs for the 2,4-disubstituted compounds; however, it is the trans isomer that always has one axial substituent in the lowest energy conformations, and is more selective. The cis-2,4-disubstituted isomers, in contrast, exist almost exclusively in the more favorable diequatorial conformation and give rise to lower selectivity.

This analysis suggests that disubstituted piperdines with a single chiral center and no large conformational preferences between the axial and equatorial α-substituents should be good substrates for the resolution. This hypothesis is confirmed by the excellent results obtained with substrates bearing an exocyclic 4-methylene and a single α-substituent (Table 5, entries 1−3). In addition 2,4,4-trisubstituted piperidines containing a cyclic ketal were also resolved with modest selectivity (Table 5, entries 4 and 5). All five substrates evaluated show fast reaction rates and useful selectivity, indicating no adverse effect on the resolution of substrates containing additional achiral substitution. The alkene or protected carbonyl in the products provides a means for postresolution derivatization.

Table 5. Kinetic Resolution of 2,4,4-Trisubstituted Piperidines with Stoichiometric Reagent 1



1.0 equiv 1 (0.5 equiv)

Entry	Substrate	s[a]	Conv.[b] (%)	reaction time[c] (h)	er amine[d] yield[e] (%)	er amide[d] yield[e] (%)
1		27	51	20	92:8 (45)	91:9 (43)
2		18	49	20	88:12 (46)	89:11 (43)
3[f]		18	56	20	95: 5 (39)	86:14 (54)
4		8	48	20	79:21 (25)	81:19 (44)
5[f]		9	64	20	94:6 (23)	75:25 (21)

[a]Calculated selectivity. [b]Calculated conversion. [c]Reaction time until stoichiometric reagent is fully consumed. [d]Determined by SFC or HPLC on a chiral support. [e]Isolated as the Cbz-derivative. Yield after column chromatography. [f]Stochiometric reagent **1** (0.6 equiv) was used.

In summary we have examined the kinetic resolution of disubstituted piperidines using a chiral hydroxamic acid catalyst and its corresponding stoichiometric reagent. For most cases, synthetically useful relative rates and outstanding functional group tolerance were observed. The exceptions—stereoisomeric substrates that gave poor reactivity and selectivity—revealed a pronounced conformational preference in which the lowest energy transition states require that the α-substituent populates the axial position. This conjecture was fully supported by DFT calculations on the transition states for all of the relevant stereoisomers and ring conformations. These findings rationalized the initially unexpected differences in reactivity and selectivity between cis and trans stereoisomers and strengthen our stereochemical model.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07201.

Experimental procedures and spectroscopic data for all new compounds. Transition state structures of all minimized TSs (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the European Research Council (ERC Starting Grant No. 306793-CASAA) and National Institutes of Health (GM-112684 to M.C.K.) and the National Science Foundation (CHE1464778 to M.C.K.). Computational support was provided by XSEDE on SDSC Gordon (TG-CHE120052). We thank LOC MS Service (ETH Zürich) for analyses and Dr. Nils Trapp and Dr. Bernd Schweizer for the acquisition of X-ray structures. We are also grateful to Dr. Kimberly Geoghegan, Sheng-Ying Hsieh, and Dr. Hidetoshi Noda for helpful discussions.

■ REFERENCES

(1) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(2) For reviews on the a functionalization of unsubstituted heterocycles see: (a) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoal, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092−10142. (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084. (c) Vo, C. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809−2815.

(3) (a) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241−2247. (b) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946−10949. (c) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114−1117.

(4) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315−4319. (b) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153−9156.

DOI: 10.1021/jacs.5b07201
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(5) (a) Cai, W.; Colony, J. L.; Frost, H.; Hudspeth, J. P.; Kendall, P. M.; Krishnan, A. M.; Maskowski, T.; Mazur, D. J.; Phillips, J.; Brown Ripin, D. H.; Gut Ruggeri, S.; Stearns, J. F.; White, T. D. *Org. Process Res. Dev.* **2005**, *9*, 51−56. (b) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 10181−10184. (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557−2590. (d) Iimuro, A.; Yamaji, K.; Kandula, S.; Nagano, T.; Kita, Y.; Mashima, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2046−2050. (e) Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892−8895.

(6) (a) Pablo, O.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2013**, *78*, 9181−9189. (b) Launay, G. G.; Slawin, A. M. Z.; OHagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, 41.

(7) (a) Chen, S.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2015**, *80*, 6660−6668. (b) Duttwyler, S.; Chen, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3877−3880. (c) Ischay, M.; Takase, M. K.; Bergma, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 2478−2481. (d) Duttwyler, S.; Chen, S.; Takase, M. K.; Wiberg, K. B.; Bergman, R. G.; Ellman, J. A. *Science* **2013**, *339*, 678−682.

(8) (a) Mittal, N.; Lippert, K. M.; De, C. K.; Klauber, E. G.; Emge, T. J.; Schreiner, P. R.; Seidel, D. *J. Am. Chem. Soc.* **2015**, *137*, 5748−5758. (b) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060−17061. (c) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624−13626. (d) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605−17612. (e) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412−420. (f) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547. (g) Fowler, B. S.; Mikochick, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870−2871. (h) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226−12227. (i) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836−13837. (j) Brown, M. K.; Blewett, M. M.; Colombe, J. R.; Corey, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 11165−11170. (k) Larionov, E.; Mahesh, M.; Spivey, A. C.; Wei, Y.; Zipse, H. *J. Am. Chem. Soc.* **2012**, *134*, 9390−9399.

(9) (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem.* **2004**, *116*, 806−843; *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824.

(10) Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698−19701.

(11) Hsieh, S.-Y.; Binanzer, M.; Kreituss, I.; Bode, J. W. *Chem. Commun.* **2012**, *48*, 8892−8894.

(12) Allen, S. E.; Hsieh, S.-Y.; Gutierrez, O.; Bode, J. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11783−11791.

(13) Kreituss, I.; Murakami, Y.; Binanzer, M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10660−10663.

(14) For the purposes of method development and study, we performed the kinetic resolutions under conditions that allow for accurate calculations of the relative rates. At longer reaction times, the hydroxyenone and stochiometric reagent can undergo side reactions. This protocol explains the low conversion even with full consumption of the reagent with slow-reacting substrates. For preparative work, the resolutions are allowed to proceed to higher conversion, which affords virtually enantiopure recovered amines. As a guideline, s = 20 can deliver > 99% ee at 62% conversion. See Vedejs, E.; Jure, M. *Angew. Chem.* **2005**, *117*, 4040−4069; *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001 for a discussion.

(15) Calculated according to: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249−330.

(16) Hsieh, S.-Y.; Wanner, B.; Wheeler, P.; Beauchemin, A. M.; Rovis, T.; Bode, J. W. *Chem.—Eur. J.* **2014**, *20*, 7228−7231.

(17) All calculations were carried out using Gaussian 09, revision D.01.

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford CT, 2013.

(19) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.

(20) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724−728. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265−3269.

(21) (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032−3041. (b) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(22) Additional calculations using *cis*- and *trans*-2-phenyl-3-hydroxypiperidine showed a similar trend as the model, *cis*- and *trans*-2,3-dimethylpiperidine. For instance the enthalpic energy difference (in solvent) between *cis*-2-phenylpiperidin-3-ol was computed to be 1.7 kcal/mol vs only 0.4 kcal/mol for the corresponding trans diastereomer. This calculation is in excellent agreement with experiment for kinetic resolution of the *cis*- and *trans*-2- phenylpiperidin-3-ol systems (Table 2, entries 1 and 2) which exhibited s values of 24 and 1, respectively.

DOI: 10.1021/jacs.5b07201
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