Organic LETTERS

Letter

pubs.acs.org/OrgLett

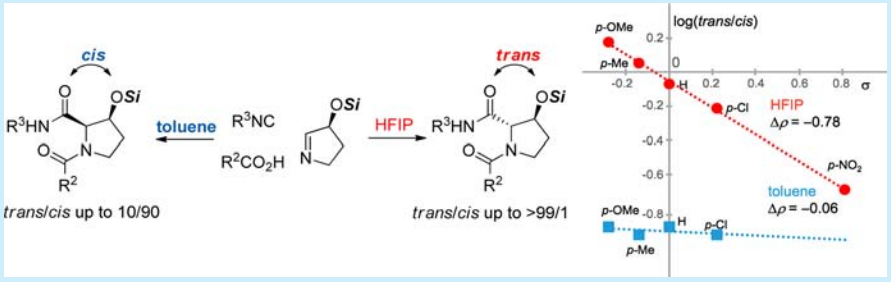
Revisited Mechanistic Implications of the Joullié–Ugi Three-Component Reaction

Akira Katsuyama,[†] Akira Matsuda,[†,‡] and Satoshi Ichikawa*[,†,‡]

[†]Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

[‡]Center for Research and Education on Drug Discovery, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

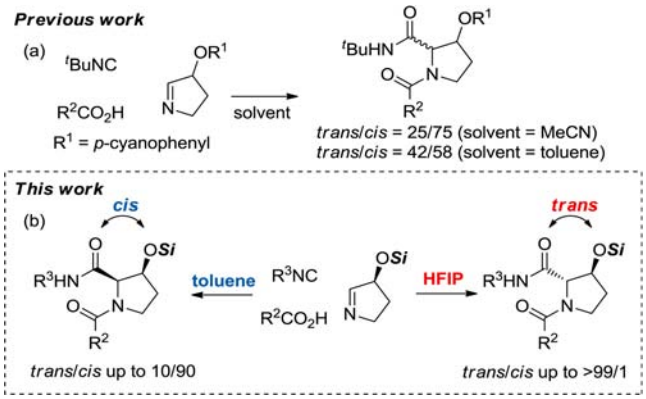
Supporting Information



ABSTRACT: The effect of the solvent on the diastereoselectivity of the Joullié–Ugi three-component reaction (JU-3CR) using an α-substituted five-membered cyclic imine is revisited. The *cis* and *trans* isomers were generated in toluene and HFIP, respectively. Hammett analysis of the JU-3CR suggests the presence of two reaction mechanisms.

The Joullié–Ugi three-component reaction (JU-3CR) is a multicomponent reaction between a cyclic imine, a carboxylic acid, and an isocyanide that yields an *N*-acylpyrrolidine or piperidine carboxamide.[1] The JU-3CR constructs the 3-hydroxyproline derivative in a single step with simultaneous modification at both the C- and N-terminals (Scheme 1). The JU-3CR using a cyclic imine with a substituent at the α-position to the imine affords two diastereomers. However, the reaction of α-aryloxy-Δ^1-pyrrolines typically affords poor selectivity (*trans*/*cis* = 42/58–25/75; Scheme 1a).[2] Moreover, a sterically hindered *cis* isomer is predominant, and the diastereoselectivity is influenced by the solvent polarity. It was suggested by Flanagan and Joullié in their pioneering study[2] that the stereochemical outcome is explained by considering the intermediate "oriented ion pair", which is formed by the carboxylic acid and imine, and that stabilization or destabilization of the intermediate by the solvent is crucial factor for the selectivity. The JU-3CR using an α-siloxy five-membered cyclic imine could be a solvent-dependent diastereodivergent reaction[3−8] if the diastereoselectivity were improved by reinvestigating the solvent effect. Herein we describe a solvent-dependent diastereodivergent JU-3CR using an α-siloxy five-membered cyclic imine (Scheme 1b). During this study, Hammett analysis suggested that another reaction mechanism different from that suggested by Joullié et al. is also involved in the JU-3CR.

Scheme 1



To improve the selectivity, we chose the TIPS group as the protecting group for the α-hydroxy group of the cyclic imine because it is more sterically hindered than the phenyl or benzyl group. Imine **3a** was synthesized from the corresponding γ-lactam **2a** according to a procedure similar to that in Furman's report (Scheme 2).[9,10] Thus, we planned to examine the solvent effect for the reaction. The reaction of imine **3a** with 3-phenylpropionic acid (**5a**) and *tert*-butyl isocyanide (**6a**) in toluene proceeded smoothly to afford 3-hydroxyproline derivatives *trans*-**7a** and *cis*-**7a** in 63% yield (Table 1, entry 1), with the *cis* isomer being favored (*trans*/*cis* = 15/85). The stereochemistry of each isomer was determined by the coupling constant of the α-proton in the ^{1}H NMR spectrum according to the method previously reported by Nutt and Joullié.[1] Then

Received: March 22, 2016
Published: May 23, 2016

DOI: 10.1021/acs.orglett.6b00827
Org. Lett. 2016, 18, 2552–2555

Scheme 2. Synthesis of Cyclic Imine 3

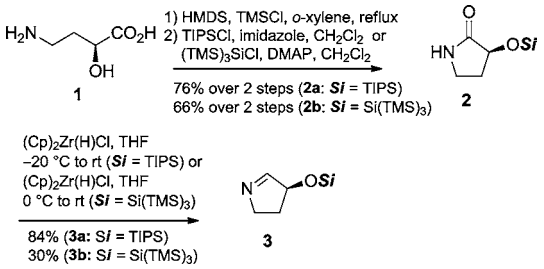
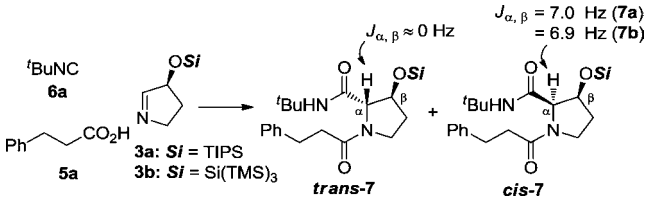


Table 1. Optimization of the Reaction Conditions

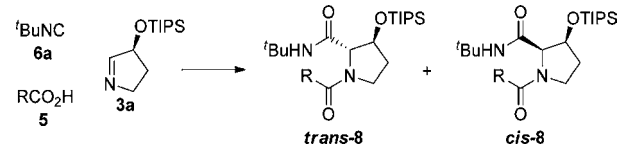


entry	solvent	temp	imine	*trans*/*cis*	yield (%)
1	toluene	rt	**3a**	15/85	63
2	CH_2Cl_2	rt	**3a**	17/83	54
3	MeOH	rt	**3a**	42/58	57
4	^{i}PrOH	rt	**3a**	20/80	57
5	TFE	rt	**3a**	72/28	62
6	HFIP	rt	**3a**	82/18	60
7	toluene	−78 °C	**3a**	15/85	45
8	toluene	70 °C	**3a**	20/80	45
9	HFIP	0 °C	**3a**	85/15	54
10	HFIP	reflux	**3a**	71/29	50
11	toluene	rt	**3b**	27/73	42
12	HFIP	rt	**3b**	>99/1	52

the effect of the solvent on the selectivity was investigated. The reaction in CH_2Cl_2 selectively yielded the *cis* isomer *cis*-**7a** (entry 2), implying that the formation of the *cis* isomer is favored in nonpolar solvents. The *cis* selectivity was reduced when MeOH was used as the solvent, and poor diastereoselectivity was observed (*trans*/*cis* = 42/58; entry 3). The use of ^{i}PrOH, which is more hydrophobic and basic than MeOH, resulted in an increase in *cis* selectivity (*trans*/*cis* = 20/80; entry 4), indicating that the polarity or acidity of the solvent influences the selectivity. Therefore, the JU-3CR in various alcoholic solvents was further investigated. In 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are more polar[11] and acidic alcohols, the *trans* isomer was obtained as the major product (*trans*/*cis* = 72/28−82/18; entries 5 and 6). These experiments indicated that toluene is a suitable solvent for the *cis*-selective reaction and that HFIP is suitable for the *trans*-selective reaction. The reaction temperature was also investigated. However, the reactions at higher or lower temperatures resulted in decreased yield and diastereoselectivity in both toluene and HFIP (entries 7−10). To determine the impact of the bulkiness of the protecting group of the cyclic imine on the diastereoselectivity, imine **3b**, which bears a more hindered tris(trimethylsilyl)silyl group,[12,13] was used for the JU-3CR. The reactions of **3b** with **5a** and **6a** in HFIP yielded the highest *trans* selectivity (*trans*/*cis* ≥ 99/1; entry 12), whereas the *cis* selectivity did not improve in toluene (*trans*/*cis* = 27/73; entry 11).

Because the solvent substantially affected the diastereoselectivity, we determined whether the carboxylic acid and isocyanide influenced the selectivity. First, the effect of the carboxylic acid on the diastereoselectivity was examined, and the results are summarized in Table 2. Imine **3a** was used for

Table 2. Scope of Carboxylic Acids



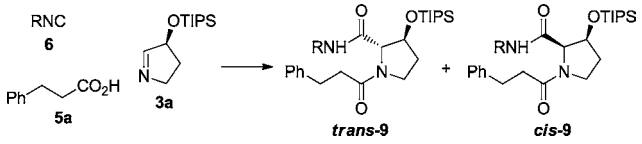
R	entry	solvent = toluene *trans*/*cis*	solvent = toluene yield (%)	entry	solvent = HFIP *trans*/*cis*	solvent = HFIP yield (%)
5b	1	10/90	12	6	88/12	71
5c	2	no reaction		7	85/15	77
5d	3	12/88	75	8	86/14	87
5e	4	10/90	36	9	85/15	90
5f	5	11/89	75	10	71/29	79

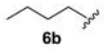
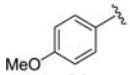
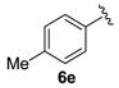
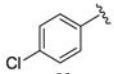
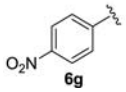
the investigation, and various carboxylic acids were chosen, including sterically hindered aliphatic carboxylic acids **5b** and **5c**, aryl carboxylic acid **5d**, α,β-unsaturated carboxylic acid **5e**, and α-amino acid **5f**. In toluene, the *cis* selectivity was the same as that with **5a** (*trans*/*cis* = 12/88−10/90; entries 1 and 3−5), except for the reaction with **5c**, which resulted in no reaction (entry 2). The reactions with carboxylic acids **5b−f** in HFIP were *trans*-selective (*trans*/*cis* = 71/29−88/12; entries 6−10) and afforded *trans*-**8** in moderate to good yields. These results suggest that the structure of the carboxylic acid does not affect the selectivity of the JU-3CR in toluene and HFIP.

Next, we studied the selectivity of the reaction of imine **3a** and carboxylic acid **5a** with various alkyl and aryl isocyanides **6b−g**,[14,15] and the results are summarized in Table 3. In toluene, a variety of isocyanides **6a−f** selectively afforded *cis* isomers (*trans*/*cis* = 17/83−10/90; entries 1−5). The more electron-deficient isocyanide **6g** did not react under the studied conditions (entry 6). However, in HFIP, the stereochemical outcome of the reaction was influenced by the electronic effect of the isocyanide (entries 7−12). The more electron-rich *tertiary* alkyl isocyanide **6a** yielded the highest *trans* selectivity (*trans*/*cis* = 82/18; Table 1, entry 6), and the *primary* alkyl isocyanide **6b** afforded a slightly lower *trans* selectivity than that using **6a** (*trans*/*cis* = 74/26; Table 3, entry 7). The reactions with more electron-deficient aryl isocyanides **6c−g**, where the isocyano group was attached to the sp^2-hybridized carbon atom, afforded lower *trans* selectivity (*trans*/*cis* = 60/40−17/83; entries 8−12), and the most electron-deficient isocyanide, **6g**, afforded the highest *cis* selectivity (*trans*/*cis* = 17/83; entry 12).

DOI: 10.1021/acs.orglett.6b00827
Org. Lett. 2016, 18, 2552−2555

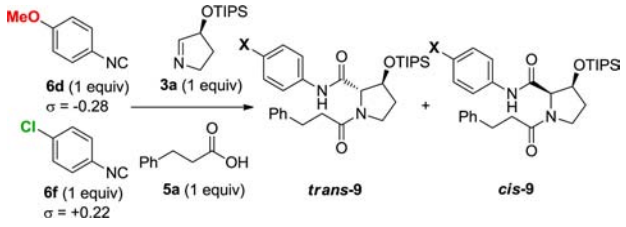
Table 3. Scope of Isocyanides



R	entry	solvent = toluene trans/cis	solvent = toluene yield (%)	entry	solvent = HFIP trans/cis	solvent = HFIP yield (%)
 6b	1	17/83	42	7	74/26	81
 6c	2	11/89	72	8	46/54	93
 6d	3	11/89	77	9	60/40	88
 6e	4	10/90	81	10	53/47	94
 6f	5	10/90	67	11	38/62	93
 6g	6	no reaction		12	17/83	75

These experiments indicate that the diastereoselectivity of the JU-3CR in HFIP is influenced by the electronic properties of the isocyanide. To elucidate the rate- and stereodetermining step of the JU-3CR, competitive reactions between isocyanides **6d** and **6f** in toluene and HFIP were performed (Table 4). In

Table 4. Competitive Experiments



entry	solvent	trans-9f (Cl)	trans-9d (OMe)	cis-9f (Cl)	cis-9d (OMe)
		yield (%)			
1	toluene	1	7	15	62
2	HFIP	7	36	15	27

both cases, the yield of the product from the reaction with the more electron-rich isocyanide **6d** was higher than that with the electron-deficient isocyanide **6f**. The results indicate that electron-donating groups accelerate the reaction because the rate- and stereodetermining step of the JU-3CR involves the addition of isocyanide to the iminium ion, which is discussed below.

To elucidate the effect of the electron density of the isocyanide on the reaction mechanism, Hammett analyses[16] were performed with the data obtained in Table 3 (Figure 1).

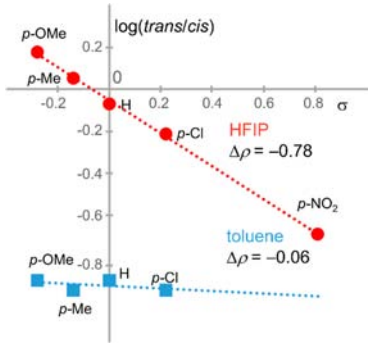


Figure 1. Plots of the value of log(*trans*/*cis*) in toluene (squares) and HFIP (circles) vs the Hammett reaction constant σ.

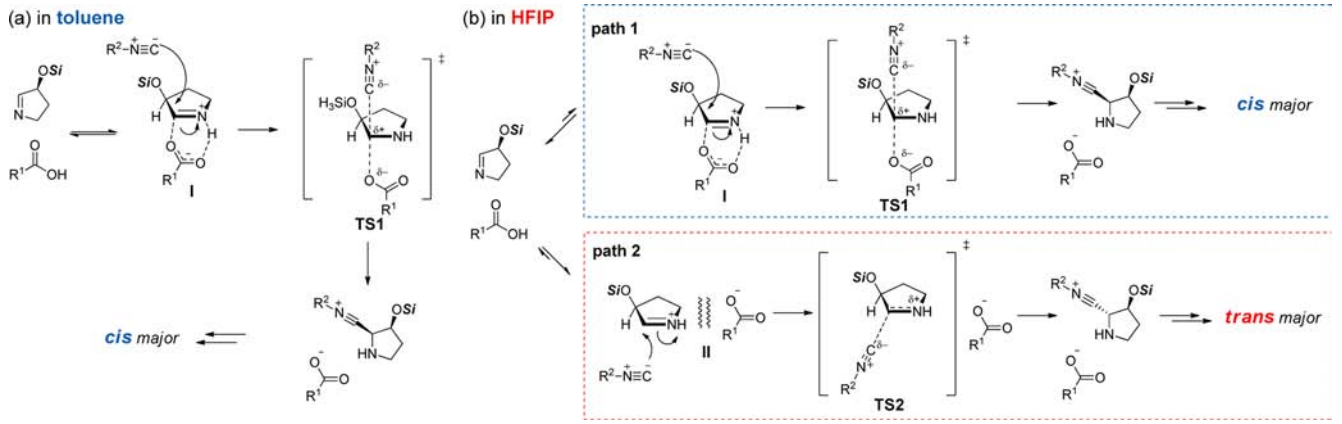
An excellent correlation for log(*trans*/*cis*)[17] as a function of σ was obtained, implying that the log(*trans*/*cis*) values correlate well with the electron density of the isocyanide. The log(*trans*/*cis*) values are assumed to be equal to the difference of the logarithms of the rate constants ($\log k_{trans} - \log k_{cis}$). Therefore, the slope of each plot was equated to the difference in the Hammett reaction constant, $\Delta\rho = \rho_{trans} - \rho_{cis}$. Different $\Delta\rho$ values were obtained for the reactions in toluene (squares) and HFIP (circles) (−0.06 in toluene vs −0.78 in HFIP). On the basis of the results of the competitive reactions, which suggested that ρ_{trans} and ρ_{cis} are negative in both solvents (Table 4), the ρ_{trans} value is more negative than the ρ_{cis} value in HFIP (because $\Delta\rho = -0.78$) and essentially same as the ρ_{cis} value in toluene.

This Hammett analysis provides insights into the reaction mechanism. The small absolute value of $\Delta\rho$ for the reaction in toluene suggests that both diastereomers are produced via the same reaction mechanism in the JU-3CR and that the diastereoselectivity arises from the ratio of the diastereotopic reactions of the common intermediate. In HFIP, however, the more negative value of ρ_{trans} compared with ρ_{cis} implies that the transition state that affords the *trans* isomer is more positively charged than the transition state that affords the *cis* isomer. Therefore, each isomer is produced via a different mechanism in HFIP.

The stereochemical outcome, solvent effect, competition reactions, and results of the Hammett analysis can be rationalized in terms of two different structures of ion pairs as intermediates in the JU-3CR. The results in toluene strongly support Joullié's report.[2] First, the protonation of the imine by the carboxylic acid forms a contact oriented ion pair (I), which is stabilized by the Coulomb force in the nonpolar solvent. Therefore, the isocyanide would react with I, resulting in an S_N2-type transition state (**TS1**) in which the positive charge of the iminium ion is partially stabilized by the carboxylate ion, affording the *cis* isomer selectively. This mechanism may explain the same ρ value of each isomer as well as the stereochemical outcome (*cis*-selective). Because the steric hindrance of the siloxy group restricts the orientation of the carboxylate ion, the *cis* selectivity is improved compared with previous studies. In contrast, this is not the case for the reaction in a polar solvent such as HFIP. The solvent-separated ion pair (II) can exist as a result of the solvation effect of the polar solvent (Scheme 3b). Therefore, the isocyanide could react with the contact oriented ion pair (I) or the solvent-separated ion pair (II). When it reacts with the former, the *cis* isomer is generated, as mentioned above (path 1). In the latter case, the

DOI: 10.1021/acs.orglett.6b00827
Org. Lett. 2016, 18, 2552−2555

Scheme 3. Proposed Reaction Mechanisms of the JU-3CR



isocyanide reacts with the iminium ion on the opposite face of the bulky siloxy group, resulting in an S_N1-type transition state (**TS2**). Here, the positive charge of the iminium ion is not stabilized by the carboxylate ion, resulting in the formation of the *trans* isomer (path 2). On the basis of the balance of these two mechanisms, the diastereoselectivity is affected by the electronic properties of the isocyanides. Therefore, electron-rich isocyanides prefer the more positively charged transition state (**TS2**), and electron-deficient isocyanides prefer the more neutral transition state (**TS1**).

In conclusion, we have developed a diastereodivergent JU-3CR in which the stereochemical outcome can be controlled by the choice of solvent, with *cis* and *trans* isomers being obtained in toluene and HFIP, respectively. We have also revealed differences in the reaction mechanisms in the two solvents. In toluene, the reaction proceeds through an S_N2-type mechanism as previously suggested by Flanagan and Joullié.[2] However, the *trans* isomer is generated selectively via an S_N1-type mechanism in HFIP. The presence of these two mechanisms in the JU-3CR is important for the development of the first asymmetric JU-3CR and Ugi four-component reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00827.

Complete experimental procedures and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ichikawa@pharm.hokudai.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We appreciate the reviewer who pointed out to us the pioneering study by Flanagan and Joullié (ref 2). We thank Ms. S. Oka and Ms. A. Tokumitsu (Center for Instrumental Analysis, Hokkaido University) for measurement of the mass spectra. This research was supported by a JSPS Grants-in-Aid for Scientific Research (B) (Grant 25293026 to S.I.) and Scientific Research on Innovative Areas "Chemical Biology of Natural Products" (Grant 24102502 to S.I.), The Ministry of Education, Culture, Sports, Science and Technology through the Program for Leading Graduate Schools (Hokkaido University "Ambitious Leader's Program"), and the Platform Project for Supporting Drug Discovery and Life Science Research (Platform for Drug Discovery, Informatics and Structural Life Science).

■ REFERENCES

(1) Nutt, R. F.; Joullié, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852.
(2) Flanagan, D. M.; Joullié, M. M. *Synth. Commun.* **1989**, *19*, 1.
(3) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934.
(4) Engl, O. D.; Fritz, S. P.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 5454.
(5) Morgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett.* **2010**, *12*, 4494.
(6) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020.
(7) Li, X.; Lu, M.; Dong, Y.; Wu, W.; Qian, Q.; Ye, J.; Dixon, D. J. *Nat. Commun.* **2014**, *5*, 4479.
(8) Verrier, C.; Melchiorre, P. *Chem. Sci.* **2015**, *6*, 4242.
(9) Szcześniak, P.; Maziarz, E.; Stecko, S.; Furman, B. *J. Org. Chem.* **2015**, *80*, 3621.
(10) Schedler, D. J. A.; Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1993**, *34*, 5035.
(11) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.
(12) Frey, J.; Schottland, E.; Rappoport, Z.; Bravo-Zhivotovskii, D.; Nakash, M.; Botoshansky, M.; Kaftory, M.; Apeloig, Y. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2555.
(13) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.
(14) Guirado, A.; Zapata, A.; Gómez, J. L.; Trabalón, L.; Gálvez, J. *Tetrahedron* **1999**, *55*, 9631.
(15) Stephany, R. W.; de Bie, M. J. A.; Drenth, W. *Org. Magn. Reson.* **1974**, *6*, 45.
(16) Hammett, L. P. *Chem. Rev.* **1935**, *17*, 125.
(17) Lin, C. Y.; Giuliano, M. W.; Ellis, B. D.; Miller, S. J.; Anslyn, E. V. *Chem. Sci.* **2016**, DOI: 10.1039/C5SC04629G.

DOI: 10.1021/acs.orglett.6b00827
Org. Lett. 2016, 18, 2552−2555